KMJ
KUWAIT MEDICAL JOURNAL
The Official Journal of The Kuwait Medical Association

## REVIEW ARTICLE



## ORIGINAL ARTICLES



## CASE REPORTS



## BRIEF COMMUNICATION



KU ISSN 0023-5776

Continued inside

**Open access for articles at**

***http: www.kmj.org.kw***

**Indexed and abstracted in:**

**SCOPUS**

**EMBASE**

**(*The Excerpta Medica Database*)**

**Science Citation Index Expanded**

**(**also known as **SciSearch®)**

**Journal Citation Reports/Science Edition**

**IMEMR Current Contents**

(*Index Medicus* for the Eastern Mediterranean Region)

available online at: www.emro.who.int/EMRJorList/online.aspx

Vol. 55 No. 4 DECEMBER 2023

# KUWAIT MEDICAL JOURNAL

## CONTENTS

Continued from cover

## LETTER TO THE EDITOR



***



**PUBLISHER:** The Kuwait Medical Journal (KU ISSN-0023-5776) is a quarterly publication of THE KUWAIT MEDICAL ASSOCIATION. Address: P.O. Box 1202, 13003 Safat, State of Kuwait; Telephone: 1881181 Fax: 25317972, 25333276. E-mail : kmj@kma.org.kw



**INSTRUCTIONS FOR AUTHORS:** Authors may submit manuscripts prepared in accordance with the Uniform Requirements for Manuscripts Submitted to Biomedical Journals. These Requirements are published in each issue of the Kuwait Medical Journal.

**CHANGE OF ADDRESS:** Notice should be sent to the Publisher six weeks in advance of the effective date. Include old and new addresses with mail codes.

**KUWAIT MEDICAL JOURNAL** (previously The Journal of the Kuwait Medical Association) is added to the list of journals adhering to the "Uniform Requirements for Manuscripts Submitted to Biomedical Journals", American College of Physicians, Independence Mall West, Sixth Street at Race, Philadelphia, PA 19106-1572, USA, and can be located at http://www.icmje.org/jrnlist.html

# Kuwait Medical Journal

Published by the Kuwait Medical Association
***Previously known as The Journal of the Kuwait Medical Association (Est. 1967)***



## EDITORIAL ADDRESS

P.O. Box: 1202, 13003-Safat, Kuwait
Telephone: (00-965) 1881181(Ext. 114, 115) - Fax: (00-965) 25317972, 25333276
E-mail: kmj@kma.org.kw
Website: www.kmj.org.kw

# Guidelines for Authors

Formerly known as 'The Journal of the Kuwait Medical Association', the Kuwait Medical Journal (KMJ) was established in the year 1967. It is the official publication of the Kuwait Medical Association and is published quarterly and regularly every March, June, September and December.

KMJ aims to publish peer-reviewed manuscripts of international interest. Submissions on clinical, scientific or laboratory investigations of relevance to medicine and health science come within the scope of its publication. Original articles, case reports, brief communications, book reviews, insights and letters to the editor are all considered. Review articles are solicited. Basic medical science articles are published under the section 'Experimental Medicine'.

The Kuwait Medical Journal follows the guidelines set down in "Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals" developed by the International Committee of Medical Journal Editors (ICMJE). The official and most recent version of the recommendations are available at *www.icmje.org*.

## Journal Policies

### Ethics in Publishing

Where human investigations are part of the study, the research must be conducted ethically in accordance with the Declaration of Helsinki, and the design of the work has to be approved by a local ethics committee and informed written consent must be obtained from all subjects. Documented review and approval from the Institutional Review Board or Ethics Committee must be submitted along with any studies involving people, medical records and human tissues. A relevant statement of approval should be added in the 'Subjects and Methods' section of the manuscript.

Authors should also consult guidelines for the reporting of specific study types (*e.g.*, the CONSORT guidelines for the reporting of randomized trials); see *http://equator-network.org*.

### Copyright

The publisher reserves copyright on the Journal's contents. No part may be reproduced, translated or transmitted in any form by any means, electronic or mechanical, including scanning, photocopying, recording or any other information storage and retrieval system without prior permission from the publisher. The publisher shall not be held responsible for any inaccuracy of the information contained therein.

### Conflict of Interest

Potential conflicts of interest for all authors must be identified in a 'Conflict of interest' statement at the end of the manuscript. An electronic cover letter from the corresponding author is acceptable. Authors of research articles should disclose any affiliation with any organization with a financial interest, direct or indirect, in the subject matter or materials discussed in the manuscript (*e.g.*, consultancies, employment, expert testimony, honoraria, retainers, stock) that may affect the conduct or reporting of the work submitted. If uncertain as to what might be considered a potential conflict of interest, authors should err on the side of full disclosure. Because reviews and editorials are based on selection and interpretation of the literature, the Journal expects that authors of such articles will not have any financial interest in a company (or its competitor) that makes a product discussed in the article. Information about potential conflict of interest will be made available to reviewers and will be published with the manuscript at the discretion of the editors. If there is no conflict of interest, please state: "The authors declare no conflicts of interest."

### Peer Review

All submitted manuscripts are reviewed by the editorial staff to ensure adherence to the guidelines of the Journal. Manuscripts that are considered suitable for review are sent to a peer in the relevant field of study as part of a double- blinded peer review. The reviewer may recommend the manuscript be accepted as is, undergo revision, or be rejected. If a reviewer recommends revision of a manuscript, the revised version must be re-submitted to the Journal within 3 months from the date when the review report is sent to the corresponding author.

### Authors

To be named as an author on a submission, the following 4 criteria are followed:

1. Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
2. Drafting the work or revising it critically for important intellectual content; AND
3. Final approval of the version to be published; AND
4. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

In addition to being accountable for the parts of the work he/she has done, an author should be able to identify which co-authors are responsible for specific other parts of the work. Authors should also have confidence in the integrity of the contributions of their co-authors. Specific contributions made by each author to the article must be clearly stated at the end of the document. Those who do not meet all four criteria should be mentioned in the Acknowledgment section of the submission.

Once a paper has been accepted, the Journal does not consider requests to add, delete or rearrange the sequence of the authors. If the corresponding author requests to add, remove or rearrange the authors' names after manuscript submission, the journal will seek justification for the requested change. Written confirmation signed by all authors, attesting that they agree to the addition, removal, or rearrangement of names is required. In the case of the addition or removal of authors, the author being added or removed must confirm assent. Requests that are not sent by the corresponding author will not be considered.

The corresponding author is responsible for communication with the journal during the manuscript submission, peer review, and publication process, and must ensure that all the journal's administrative requirements are properly completed. He/she should also be available throught out the submission and peer review process to respond to editorial queries in a timely manner. It is also the corresponding authors responsibility to ensure all the co-authors are made aware of the most recent status of their submission.

### Fees

Publication in the Kuwait Medical Journal is free of charge.

### Plagiarism

The Journal defines plagiarism as the use of others' published and unpublished ideas or words without prior consent, and presenting them as new and original, whether intentional or not. If an accepted or published paper is found to

be plagiarised, the manuscript will be retracted and the author will be blacklisted from submitting to the journal.

## Preparing your manuscript

### Article types

*Original Articles:* Original Articles include laboratory and clinical investigations as well as research not previously published or being considered for publication elsewhere. The text should contain a Title page, Abstract (in structured format) of not more than 250 words, Key Words (no more than five), Introduction, Subjects (or Materials) and Methods, Results, Discussion, Conclusion, Acknowledgment/s (if any) and References, Figure Legends, Tables, and Figures in this order. Details of the section contents are explained below for further adherence.

*Review Articles (solicited only):* Review articles should contain separate sections such as Title Page, Abstract (preferably in structured format) of no more than 250 words, Key Words (no more than five), Introduction, Methods/History (if applicable), Literature Review, Conclusion, Acknowledgment/s (if any) and References followed by (if relevant), Legends to figures, Tables, and Figures.

*Case Reports:* These should contain separate sections such as Title page, Abstract (a short summary of not more than 200 words), Key Words (no more than five), Introduction, Case history/report, Discussion, Conclusion, Acknowledgment/s (if any) and References followed by (if relevant), Legends to figures, Tables, and Figures.

*Short Communications:* Short communications are concise articles that aim to report new ideas, significant improvements to existing methods, a new practical application, or a new tool or resource. Short communications do not cover in detail background information about the problems treated, rather they provide key pointers to the reader. The work reported needs to be technically sound, innovative and significantly unique, advancing the state of the art. Short communication is not intended to publish preliminary results. Short communications should be similar to a research article, but with briefer Materials and Methods and Discussion.

*Letters to the Editor:* Letters may comment on recently published KMJ articles, novel cases or topics of current interest to the public. They should be concise and to the point, with a maximum of 1000 words and 2 authors. Letters commenting on previously published articles must be received within 6 months of publication of the relevant article.

### Title Page

The title page of the submitted manuscript should provide a clear title of the study followed by full names of all authors, the highest academic degree and affiliations if any, the name and address of the institution(s) where the work was done including the department, the name and complete address of the corresponding author to whom proofs and correspondences shall be sent, duly supported with contacts such as telephone, mobile and the e-mail address. This page must also contain any disclaimers, sources of support and a conflict of interest declaration.

### Structured abstract

A structured abstract (no more than 250 words) is required for studies under the section "Original Articles". It must provide an overview of the entire paper, and should contain succinct statements on the following, where appropriate: Objective(s), Design, Setting, Subjects, Intervention(s), Main Outcome Measure(s), Result(s), and Conclusion(s). (See: Haynes RB, Mulrow CD, Huth AJ, Altman DG, Gardner MJ. More informative abstracts revisited. Annals of Internal Medicine 1990; 113:69-76). Abstracts for all other category of submissions shall be a short summary followed by Key words and the report or review.

### Preparation of the manuscript

The manuscript should be typed as 'normal text' with no hyphenation and no hard-returns within paragraphs (use automatic wordwrap) on A4 size (29.7 x 21 cm) paper in single column format, preferably in font size 12. Cell format for paragraphs, artwork and/or special effects for the text and/or table(s) are not acceptable. Italics shall be used only for foreign/ Latin expressions and/or special terminologies such as names of micro-organisms. Maintain a minimum of 2 cm margin on both sides of the text and a 3 cm margin at the top and bottom of each page. No part of the manuscript other than abbreviations and/or subtitles should be written in upper case. Header/foot notes, end notes, lines drawn to separate the paragraphs or pages *etc*. are not acceptable. Do not submit articles written/saved in 'Track-change' mode.

More than six authors are not appreciated for a research article and if listed, the authors may be asked to justify the contribution of each individual author. For case reports, not more than three authors are acceptable. Regarding contributions of authors over the limit mentioned above, please read the 'Acknowledgment' section.

### Key words

Key Words (maximum five) should be preferably MeSH terms, and shall not duplicate words already in the manuscript title. MeSH terms can be checked at: *http://www.nlm.nih.gov/mesh/.*

### Tables

Tables typed on separate pages using table format (MS Word or Excel) should follow the list of references. Tables must be numbered consecutively using Arabic numerals and provided with appropriate titles. Contents of the table should be simple, and information therein not duplicated, but duly referred to, in the main text. Tables recording only a few values are not appreciated, since such information can be more accurately, usefully and concisely presented in a sentence or two in the manuscript.

### Design of the work

This should be stated clearly. The rationale behind the choice of sample size should be given. Those about to begin randomized controlled studies may wish to study the CONSORT statement (JAMA 1996; 276:637-639).

### Illustrations

All illustrations including figures should be numbered as Fig 1, Fig 2, *etc* in running sequence and submitted as separate attachments along with the manuscript. Photographs should fit within a print area of 164 x 235 mm. In the case of figures where patient's identity is not concealed, authors need to submit a written consent of the patient or of the patient's guardian, in case of minors. Figure legends should be listed separately after the 'References' section. If any of the tables, illustrations or photomicrographs have been published elsewhere previously, a written consent for re-production is required from the copyright holder along with the manuscript. When charts are submitted, the numerical data on which they were based should be supplied.

**Abbreviations**

Except for units of measurement, abbreviations should be defined on their first use in the abstract and in the text and then applied consistently throughout the article. Non-standard abbreviations or those appearing fewer than three times are not accepted. Use abbreviated units of measure, only when used with numbers. Abbreviations used as legends in Tables and/or figures should be duly defined below the respective item.

**Numbers and units**

Measurements of length, height, weight and volume must be reported in metric units (meter, kilogram, liter *etc.*) or their decimal multiples. Temperature should be given in degrees Celsius, Blood pressure in mmHg, and hematological and biochemical measurements in Système International (SI) units. For decimal values, use a point, and not a comma, *e.g.*, 5.7. Use a comma for numbers > 10,000 (*i.e.*, $10^3$) and do not use a comma for numbers < 9999, (*e.g.*, 6542).

**Drug names**

Non-proprietary (generic) names of product should be employed. If a brand name for a drug is used, the British or international non-proprietary (approved) name should be given in parentheses. The source of any new or experimental preparation should also be given.

**Acknowledgment**

Contributors who meet fewer than all 4 of the aforementioned criteria for authorship should only be listed in this section. Contributions of others who have involved in the study, such as statisticians, radiologists *etc*. and/or those who have assisted in the preparation of the manuscript being submitted could also be included in this section. The corresponding author must obtain written permission to be acknowledged from all acknowledged individuals.

**References**

Indicate references in the text in sequence using Arabic numerals within square brackets and as superscripts (*e.g.*,[1, 3-5] *etc*). Do not quote additional data (like part of the title, year of publication *etc*.) from the references, with citations in the text, unless very important. In the References section, list them in the same sequence as they appeared in the text. Include the names and initials of all authors if not more than six (< 6). Write the last name of authors followed by the initials with no punctuation other than a comma to separate the names. In references where authorship exceeds six, use *et al* after six author names. Do not use automatic numbering, end notes or footnotes for references. References to manuscripts either in preparation or submitted for publication, personal communications, unpublished data, *etc*. are not acceptable.

References should be limited to those relating directly to the contents of the paper and should be set out in the style outlined by the International Committee of Medical Journal Editors (ICMJE), as shown in the examples below. Additional examples are in the ICMJE sample references. *https://www.nlm.nih.gov/bsd/uniform_requirements.html*

**Examples**

***Article***: Rose ME, Huerbin MB, Melick J, Marion DW, Palmer AM, Schiding JK, ***et al***. Regulation of interstitial excitatory amino acid concentrations after cortical contusion injury. Brain Res. 2002;935(1-2):40-6.

***Book***: Murray PR, Rosenthal KS, Kobayashi GS, Pfaller MA. Medical microbiology. 4th ed. St. Louis: Mosby; 2002.

***Book chapter***: Meltzer PS, Kallioniemi A, Trent JM. Chromosome alterations in human solid tumors. In: Vogelstein B, Kinzler KW, editors. The genetic basis of human cancer. New York: McGraw-Hill; 2002. p. 93-113.

***Weblinks***: eatright.org [Internet]. Chicago: Academy of Nutrition and Dietetics; c2016 [cited 2016 Dec 27]. Available from: http://www.eatright.org/.

**Manuscript submission**

To present your original work for consideration, one complete set of the manuscript written in English, accompanied by tables and one set of figures (if applicable) should be submitted to the Editor by e-mail to "kmj@kma.org.kw" as attachment files.

The manuscript submitted by e-mail should be in MS Word document (.doc) format, together with a scanned copy or PDF version of the signed consent letter of the author(s) (see the section 'Authorship and Consent Form' for details). Figures or photographs, if any, need to be presented as separate attachments in JPG or BMP format with a resolution of 300 dpi and illustrations such as graphs, charts *etc*., as Excel format files. Incomplete/improper submissions will not be processed, and will be returned. Author(s) will receive a formal acknowledgment letter with a permanent reference number towards each successful submission.

Following a peer review process, the corresponding author will be advised of the status; acceptance or recommendation for revision or rejection of the paper, in a formal letter sent through e-mail. A galley proof will be forwarded to the corresponding author by e-mail at the time of publication of the accepted paper, which must be returned to the journal office within 48 hours with specific comments or corrections, if any. Such corrections in the galley proof must be limited to typographical errors or missing contents from the finally accepted version.

**Authorship and consent form**

All authors must give their signed consent for publication in a letter of submission, which should accompany the manuscript. This letter should contain the following statement:

*"This manuscript (write the title) is an unpublished work which is not under consideration elsewhere and the results contained in this paper have not been published previously in whole or part, except in abstract form. In consideration of the KMJ accepting my/our submission for publication, the author(s) undersigned hereby assign all copyrights ownership to the KMJ and shall have no right to withdraw its publication. It is expressly certified that I/we, have done/actively participated in this study and agree to the accuracy of contents of this manuscript. It was conducted in accordance with current ethical considerations and meets with the committee's approval. I/all of us agree to its publication in KMJ and to the authorship as expressed in this declaration and in the title page of our manuscript".*

The consent form must also contain the names of all authors, along with their signatures.

Manuscripts should be submitted to:
The Editor,
Kuwait Medical Journal
P.O. Box: 1202
Code-13003-Safat
Kuwait.
Telephone: (965) 1881181, 25333920 extn. 114
E-mail: kmj@kma.org.kw
Website: www.kma.org.kw/KMJ

Review Article

# Liver dysfunction and COVID-19: what we know so far

Abdelhamid Hachimi[1,4], Adil ait-Errami[2], Moulay Abdelmonaim el Hidan[3], Mohamed Merzouki[4]
[1]Medical ICU, Mohammed VI[th] University Hospital of Marrakech, Cadi Ayyad University, Marrakech, Morocco
[2]Department of Gastroenterorology, Mohammed VI[th] University Hospital of Marrakech, Cadi Ayyad University, Marrakech, Morocco
[3]Bioresources and Applied Sciences Team, Laboratory of Biotechnologies and Valorization of Natural Resources, Faculty of Applied Sciences Ait Melloul, Ibn Zohr University, Morocco
[4]Laboratory of Biological Engineering, Faculty of Sciences and Techniques of Beni Mellal (FST BM), Sultan Moulay Slimane University, Morocco

Kuwait Medical Journal 2023; 55 (4): 279 - 291

## ABSTRACT

SARS-CoV-2 is a new zoonotic coronavirus. The disease was named Coronavirus Disease 2019 (COVID-19) by the World Health Organization. Since December 2019, it has spread through the globe and infected more than two hundred fifty-seven million persons worldwide (as of Nov 20, 2021). It involves many organs and systems; respiratory symptoms predominate the clinical presentation in COVID-19. Gastrointestinal dysfunction is increasingly reported. The occurrence of liver damage worsens the prognosis. It can occur de novo or in a setting of chronic liver disease. Its pathophysiological mechanisms are multifactorial. Herein, we review the liver dysfunction in COVID-19 through a literature search in multiple databases dedicated to the literature about COVID-19. This review provides an overview of the epidemiology of liver impairments, genetic predispositions for COVID-19, and liver dysfunction and COVID-19 in subgroups. This study has highlighted the need for more studies to understand the pathogenic components of liver dysfunction, especially the liver involvement with or without underlying chronic disease.

**KEY WORDS:** coronavirus, COVID-19, histopathological lesions, liver dysfunction, SARS-CoV-2

## INTRODUCTION

Of the coronaviridae family, coronaviruses include six strains. The first human CoV (HCoV), named B814, was identified in 1965 in nasal swabs in patients with cold[1]. Since then, more HCoVs have been isolated: HCoV-229E (229E), HCoV-OC43 (OC43), HCoV-NL63 (NL63), and HCoV-HKU1 (HKU1); besides severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus[2]. They primarily cause upper respiratory and gastrointestinal infections, which vary from mild (common cold) to severe acute respiratory syndrome with possible multiorgan failure[3]. SARS-CoV was discovered during the SARS epidemic that started from Guangdong Province in southern China in November 2002 and spread to other countries in Asia, North America and Europe[4,5]. Middle East respiratory syndrome coronavirus, on the other hand, has been responsible for a progressing outbreak in the Middle East since 2012[6].

After these viruses, novel Coronavirus (2019-nCoV) has spread from Wuhan, China, and infected more than two hundred fifty-seven million persons worldwide (as of Nov 20, 2021) since December 2019[7]. The International Committee on Taxonomy of Viruses named 2019-nCoV as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The World Health Organization titled the disease caused by SARS-CoV-2 as coronavirus disease 2019 (COVID-19)[8]. Chan *et al*[9], Hui *et al*[10], Zhou *et al*[11] and Wu *et al*[12] suggested that the origin of SARS-CoV-2 was bats since their genomes are identical in 96%[13], but the intermediate host remains unknown.

The COVID-19 clinical presentation, since the first case, was not a simple lung disease. It can cause severe cardiovascular or renal impairment, peripheral/central

***Address correspondence to:***
*Prof. Mohamed Merzouki, Laboratory of Biological Engineering, Faculty of Sciences and Techniques of Beni Mellal (FST BM), Sultan Moulay Slimane University (USMS), Campus Mghilla, BP 523, 23000 Béni Mellal, Maroc. Tel: +212 (0)5234-85112; E-mail: m.merzouki@usms.ma*

neurologic disorders, thromboembolic events[14,15], and acute liver dysfunction, which was overlooked at the pandemic, can worsen the prognosis. COVID-19 is a life-threatening condition with decreased hepatic function, infection, renal injury, encephalopathy/ increased intracranial pressure and coagulopathy, even without underlying chronic liver disease[4,11-15]. The acute liver dysfunction can occur de novo or in a setting of chronic liver disease. Its pathophysiological mechanisms are multifactorial.

This review aimed to set out the liver dysfunction in COVID-19.

## LITERATURE SEARCH

We performed a literature search in multiple databases dedicated to the literature about COVID-19: New England Journal of Medicine database (https://www.nejm.org/coronavirus?query=RP), European Society of Intensive Care Medicine database (https://www.esicm.org/resources/coronavirus-public-health-emergency/), Elsevier information center (https://www.elsevier.com/connect/coronavirus-information-center?fbclid=IwAR11-XRVRxDQjjiIq6JEjNsf_x64JQ-BEL74iw7PDLibVQTmatBFqt4xUlI), National Center for Biotechnology Information database (Pubmed) (https://www.ncbi.nlm.nih.gov/sars-cov-2/), and Medscape center (https://www.medscape.com/resource/coronavirus).

The keywords used in the research were SARS-CoV-2, COVID-19, gastrointestinal, liver, hepatic, biliary and jaundice. The references cited in these papers were also explored for more data.

We defined liver dysfunction as any test more than the upper limit of the normal value of alanine transaminase (ALT), aspartate transaminase (AST) and total bilirubin[16].

### Epidemiology of the liver dysfunction

Zhang *et al*[17] observed that 2-11% of COVID-19 patients had preexisting chronic liver disease (CLD) and 16.1-53.1% had abnormal levels of AST and ALT. Meta-analysis of 128 studies of 22,257 patients showed an acute hepatic injury in 23.7%, and an underlying CLD in 2.64% of patients with an elevation of ALT, AST, alkaline phosphatase, and gamma-glutamyl transferase (GGT) in 23.28%, 23.41%, 7.48% and 27.94%, respectively; as well as hypoalbuminemia in 61.27% of cases[18]. In another meta-analysis of 21 studies enrolling 3366 patients, parameters of hepatic function were increased in severe and fatal COVID-19[19]. In the same way, Parohan *et al*[20], in a systematic review and meta-analysis including 20 retrospective studies with 3428 patients, announced that severe cases had higher serum AST values (weighted mean difference: 8.84U/L; 95%CI: 5.97-11.71; *P*<0.001), ALT (mean difference: 7.35 U/L; 95%CI: 4.77-9.93; *P*<0.001), total bilirubin (mean difference: 2.30 mmol/L; 95% CI: 1.24-3.36; *P*<0.001), and lower serum levels of albumin (mean difference: − 4.24 g/L; 95% CI: −6.20 to −2.28; *P*<0.001), compared to mild cases; of note, the risk factors were older and male patients, with higher body mass index and previous CLD, and, in another study, in multivariate logistic regression analysis: male gender (OR: 2.038; 95% CI: 1.443-2.879; *P*<0.001), hs C-reactive protein ≥10 mg/L (OR: 1.733; 95% CI: 1.118-2.687; *P*=0.014), neutrophil-to-lymphocytes ratio ≥5 (OR: 2.154; 95% CI: 1.486-3.124; *P*<0.001)[21], high D-dimer level (OR: 1.48; 95% CI: 1.19-1.85; *P*<0.001), and neutrophil percentage (OR: 1.004; 95% CI: 1.01-1.06; *P*=0.003)[22]. Similarly, in an international cohort including two online registries SECURE-cirrhosis (co-ordinated by University of North Carolina, Chapel Hill, USA) and COVID-Hep.net (co-ordinated by the University of Oxford and supported by The European Association for the Study of the Liver), the fatality predictors were age (OR: 1.02; 95% CI: 1.01-1.04; *P*=0.011), Child-Pugh class A (OR: 1.90; 95% CI: 1.03-3.52; *P*=0.040), Child-Pugh class B (OR: 4.14; 95% CI: 2.4-7.65; *P*<0.001), Child-Pugh class C (OR: 9.32; 95% CI: 4.80-18.08; *P*<0.001), and alcohol-related liver disease (OR: 1.79; 95% CI: 1.03-3.13; *P*=0.040)[23].

In Table 1, among 49,441 patients, the overall mortality was 16.2% (range 0-61.5%) of cases[24-27]. Acute hepatic injury was also present in 40.78% (range 3.75-79.7%)[26] with CLD in 2.5% (range 0-18%)[28].

### Genetic predispositions for COVID-19

Several factors make some people susceptible to the coronavirus (Figure 1). COVID-19 presents phenotypes ranging from asymptomatic to severe forms with acute respiratory distress syndrome and possible multiorgan failure. Firstly, Gralinski *et al*[29] suggested altering the innate-immune modulatory gene *Ticam2* function makes rodents highly susceptible to the coronavirus. This gene codes for a helper protein that activates the toll-like receptor involved in innate immunity. Secondly, Zhao *et al*[30] showed that blood group A is linked to a higher risk of acquiring COVID-19 (OR: 1.279; 95% CI: 1.136-1.440; *P*<0.001) and death (OR: 1.482; 95%CI: 1.113-1.972; *P*=0.008) compared with other blood groups. Jokela *et al*[31] expressed the same findings for SARS-CoV in 2005. Recently, Goel *et al*[32] and Hernández Cordero *et al*[33] suggested that group A may be linked with a high risk of COVID-19 and its severity. Thirdly, the susceptibility to SARS-CoV-2 is associated with HLA-B*46:01[34], as previously expressed by Lin *et al*[35] for SARS-CoV. Fourthly, ACE2 is the functional receptor of SARS-CoV[36]. Effectively, Hamming *et al*[37] reported that this receptor is plenteous in the lung and small intestine's human epithelia and the vascular endothelium.

**Table 1:** Characteristics of liver disorder in COVID-19

| References | Sample size, n | Patients with ALI, n (%) | Patients with previous chronic liver disease, n (%) | Overall mortality, n (%) |
|---|---|---|---|---|
| Sun *et al*[90] | 83 | 15 (18.1) | NR | 40 (48.2) |
| Zhang *et al*[22] | 218 | 76 (36.2) | 3 (1.4) | NR |
| Chen *et al*[91] | 99 | 43 (43.4) | NR | 11 (11) |
| Wang *et al*[92] | 69 | 42 (60.9) | 1 (1) | 5 (7.24) |
| Cai *et al*[93] | 298 | 44 (14.8) | 8 (2.7) | 3 (1) |
| Zhang *et al*[28] | 82 deaths | 64 (78) | 2 (2.4) | -- |
| Wang *et al*[94] | 138 | 55 (39.9) | 4 (2.9) | 6 (4.3) |
| Li *et al*[95] | 85 | 33 (38.8) | 6 (7) | NR |
| Yang *et al*[24] | 52 | 15 (29) | NR | 32 (61.5) |
| Fan *et al*[96] | 148 | 55 (37.16) | NR | 1 (0.7) |
| Huang *et al*[67] | 41 | 15 (36.6) | 1 (2.4) | 6 (15) |
| Zhou *et al*[97] | 191 | 59 (30.9) | NR | 53 (27.7) |
| Hu *et al*[98] | 322 | NR | 5 (1.5) | 35 (10.8) |
| Zhang *et al*[62] | 115 | 28 (24.3) | NR | 1 (0.87) |
| Yang *et al*[22] | 149 | 45 (30.2) | NR | 0 |
| Fu *et al*[99] | 354 | 101 (28.5) | 16 | 34 (9.6) |
| Cao *et al*[100] | 199 | 120 (60.3) | NR | 44 (22.11) |
| Shi *et al*[101] | 81 | 43 (53.1) | 7 (8.6) | 3 (4) |
| Wu *et al*[64] | 80 | 3 (3.75) | 1 (1.25) | 0 |
| Xu *et al*[46] | 62 | 10 (16.1) | 7 (11) | 0 |
| Liu *et al*[102] | 32 | 11 (34.3) | 1 (3.13) | NR |
| Xie *et al*[103] | 79 | 29 (36.7) | NR | NR |
| Zhang *et al*[104] | 140 | NR | 8(5.7) | NR |
| Wu *et al*[64] | 201 | 59 (29.8) | 7 (3.5) | 44 (21.9) |
| Arentz *et al*[105] | 21 | NR | 10 (4.8) | 11 (52.4) |
| Chen *et al*[106] | 274 | 144 (52.5) | 11 (4) | 113 (41.2) |
| Xu *et al*[107] | 354 | 193 (54.3) | NR | NR |
| Cholankeril *et al*[108] | 116 | 65 (56) | 3 (2.6) | 1 (0.9) |
| Tabata *et al*[109] | 104 | 18 (17.3) | NR | 0 |
| Luan *et al*[110] | 117 | 54 (46.2) | NR | 2 (1.7) |
| Wang *et al*[54] | 156 | 64 (41) | NR | 4 (2.5) |
| Guo *et al*[111] | 187 | 19 (15.4) | 0 | 43 (23) |
| Zhang *et al*[112] | 194 | 30 (15.4) | NR | 9 (4.6) |
| Yang *et al*[113] | 200 | 74 (37) | 2 (1) | 15 (7.5) |
| Pan *et al*[114] | 204 | 49 (24) | 5 (2.4) | 36 (17.6) |
| Zhang *et al*[115] | 221 | NR | 7 (3/2) | 12 (5.4) |
| Webb *et al*[116] | 299 | 100 (33.4) | 41 (13.7) | 25 (8.3) |
| Cai *et al*[117] | 417 | 90 (21.6) | 21 (5.04) | 10 (24) |
| Shi *et al*[118] | 416 | NR | 4 (1) | 57 (13.7) |
| Qin *et al*[119] | 452 | NR | 6 (1.3) | NR |
| Mushtaq *et al*[120] | 589 | 318 (54) | 10 (1.7) | 34 (5.8) |
| Guisado-Vasco *et al*[121] | 607 | NR | 24 (4.08) | 141 (23.2) |
| Jin *et al*[122] | 651 | 64 (9.8) | 25 (3.8) | NR |
| Wang *et al*[21] | 657 | 303 (46.1) | 52 (8) | 82 (12.5) |
| Zhang *et al*[123] | 663 | 322 (48.6) | NR | 25 (3.77) |
| Chen *et al*[124] | 830 | 37 (4.5) | 24 (2.9) | 98 (11.8) |
| Zhao *et al*[65] | 1000 | 64 (6.4) | 29 (2.9) | 119 (11.9) |
| Hajifathalian *et al*[66] | 1059 | 844 (79.7) | 32 (3) | 96 (9.1) |
| Guan *et al*[125] | 1099 | 326 (29.6) | 23 (2.1) | 15 (1.4) |
| Luo *et al*[126] | 1141 | 183 (16) | NR | 7 (3.8) |
| Liu *et al*[127] | 1190 | NR | 40 (3.4) | 157 (13.2) |
| Grasselli *et al*[128] | 1591 | NR | 28 (3) | 405/1581 (25.6) |
| Elmunzer *et al*[129] | 1992 | 480 (24) | 55 (2.8) | 375 (18.8) |
| Pun *et al*[130] | 2088 | NR | 48 (2.3) | 601 (28.8) |
| Phipps *et al*[131] | 2273 | 1022 (45) | 114 (5) | 517 (23) |
| Price-Haywood *et al*[132] | 3481 | 1351 (38.8) | 59 (1.7) | 326 (9.3) |
| Mikami *et al*[133] | 3708 | 1924 (55.1) | NR | 806 (21.7) |
| Richardson *et al*[134] | 5700 | 3263 (58.4) | 30 (0.5) | 553/2634 (21) |
| Lei *et al*[135] | 5771 | NR | 81 (1.4) | NR |
| Kalyanaraman Marcello *et al*[136] | 6248 | NR | 190 (3) | 1724 (28) |
| Total | 49441 | 12366 (40.78) | 1060 (2.5) | 6744 (16.2) |

ALI: acute liver injury; NR: not reported

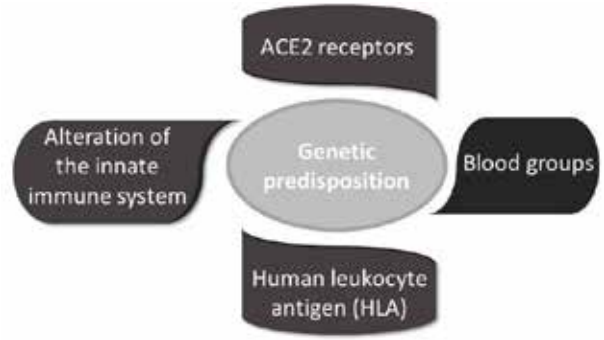


**Figure 1:** Described mechanisms involved in the genetic predisposition for liver dysfunction in COVID-19.

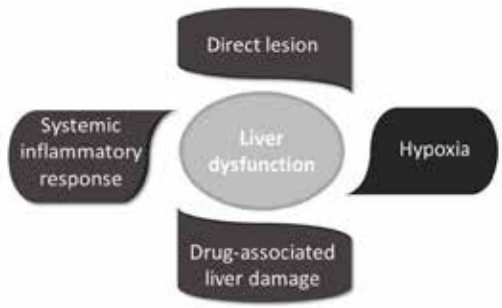


**Figure 2:** Suggested mechanisms for liver dysfunction in COVID-19.

Experimentally, Kuba *et al*[38] outlined that the infected ACE2 knockout mice are resistant to virus infection. The virus titers are $10^5$-fold lower than those isolated from the lung of SARS-CoV-infected wild-type mice, without evidence of inflammation in the lung histology. Similarly, ACE2 is involved in the SARS-CoV-2 infection pathogenesis[39-40] since it is expressed in multiple tissues, including the digestive system, such as the liver[41, 42] and the transmembrane protease serine type 2 that is highly exhibited in hepatocytes[43,44].

**Pathophysiology of the liver impairment in COVID-19**

Consistently, the liver injury is likely of multifactorial origin: direct lesion of the SARS-CoV-2, systemic inflammatory response, hypoxia and drug-associated liver damage (Figure 2).

**Direct lesion**

Given that the expression of ACE2 is abundant in the gastrointestinal system, including the liver, the SARS-CoV-2 can be replicated in different liver cells, especially in cholangiocytes in the bile duct[45]. As a result, damage of bile duct cells triggered hepatocyte dysfunction and consequent liver injury[46]. Pathological findings showed spike structures in the cytoplasm of hepatocytes in the ultrastructural examination, substantial hepatic apoptosis, and vascular damage with dilatation, thrombosis and fibrosis of the portal system[47]. In the past, Chau *et al*[48] found positive reverse transcription polymerase chain reaction (RT-PCR) for SARS-CoV in the hepatic tissue. Recently, in a series of 40 cases, Lagana *et al*[49] noted macrovesicular steatosis in 75%, mild lobular necroinflammation and portal inflammation in 50%, and sinusoidal microthrombi in 15% of cases; of note, the RT-PCR was positive in 55% of cases (11 of 20 patients tested). However, we still need more studies to understand the pathogenesis of SARS-CoV-2-related impairment.

**Systemic inflammatory response**

In response to SARS-CoV-2 invasion, the immune system releases various cytokines such as tumor necrosis factor-$\propto$, IL-1$\beta$, IL-2, IL-6, IL-8, CCL2, CCL3, CCL5, by activation of both natural and cellular immunity[50], via TLR receptors and activation of killer T lymphocytes[51]. This release can be uncontrolled and cause multiorgan failure[52]. Biologically, this storm is reflected by elevated inflammatory serum indicators (e.g., C-reactive protein, serum ferritin, lactate dehydrogenase), which are significantly elevated in severe COVID-19 patients[53].

**Hypoxia**

The principal characteristic of respiratory failure is hypoxia that can induce anoxia-associated hepatitis, especially with severe symptoms[54]. Furthermore, it might be attendant to heart failure by low perfusion[55], and hepatic venous congestion due to the increased central venous pressure in mechanically ventilated patients with high positive end-respiratory pressure[56,57].

**Drug-associated liver damage**

Drugs used off-label in treating COVID-19 (chloroquine associated or not with azithromycin, baricitinib, imatinib, tocilizumab, interferon beta, lopinavir /ritonavir, remdesivir, uminefovir, darunavir, traditional Chinese medicines), and acetaminophen could be hepatotoxic[58-59]. Additionally, they and corticoids might reactivate previous viral hepatitis, particularly biological medications prescribed to fight the hyperactive immune response[60]. This statement is consolidated by the presence of microvesicular steatosis with mild inflammation[61].

**Liver dysfunction de novo in COVID-19 patients**

**Liver test abnormalities in COVID-19 patients**

A meta-analysis enrolling 22,257 patients showed an elevation of ALT, AST and GGT in 23.28%, 23.41% and 27.94%, respectively; as well as hypoalbuminemia

**Table 2:** Liver function tests in COVID-19 patients with liver dysfunction

| References | Sample size, n | Abnormal liver tests, % | Note |
|---|---|---|---|
| Zhang *et al*[22] | 218 | - abnormal ALT >35 U/L, 33%<br>- abnormal AST >40 U/L, 45.6%<br>- elevated GGT, 57.0%<br>- abnormal TBIL, 15.2%<br>- hypoalb<32 g/L, 50% | Liver injury is more prevalent in severe cases than in mild cases of COVID-19. |
| Chen *et al*[91] | 99 | - abnormal ALT >41 U/L, 8%<br>- abnormal AST >40 U/L, 11.3%<br>- hypoalbuminaemia<32 g/L, 12.77% | Values of ALT, AST and albumin were markedly higher in deceased patients than in recovered patients. |
| Wang *et al*[54] | 69 | - abnormal ALT >35 U/L, 33%<br>- abnormal AST >40 U/L, 28% | |
| Cai *et al*[117] | 298 | - abnormal ALT >40 U/L, 13.1%<br>- abnormal AST >40 U/L, 8.4%<br>- increased TBIL 8.1%<br>- abnormal GGT 17.1% | The peak value of ALT, AST, TBIL and GGT was increased significantly among severe patients compared with non-severe patients. |
| Zhang *et al*[62] | 82 deaths | - abnormal ALT >35 U/L, 30.6%<br>- abnormal AST >40 U/L, 61%<br>- TBIL >20.5mmol/L, 30.6%<br>- hypoalb<32 g/L, 77.8% | There is a significant association between AST, ALT and time from initial symptoms to death. |
| Li *et al*[95] | 85 | - abnormal ALT >35 U/L, 38.8%<br>- abnormal AST >40 U/L, 38.8% | |
| Fan *et al*[96] | 148 | - abnormal ALT >41 U/L, 18%<br>- abnormal AST >37 U/L, 21%<br>- abnormal TBIL, 6%<br>- abnormal GGT, 17.5% | |
| Huang *et al*[67] | 41 | - abnormal AST >37 U/L, 37% | |
| Zhou *et al*[97] | 191 | - abnormal ALT >41 U/L, 31% | |
| Hu *et al*[98] | 322 | - abnormal ALT >41 U/L, 18%<br>- abnormal AST >35 U/L, 27.6% | Concentrations of ALT, AST were markedly higher in patients with unfavorable outcomes. |
| Zhang *et al*[63] | 115 | - abnormal ALT >40 U/L, 12%<br>- abnormal AST >35 U/L, 18%<br>- increased TBIL, 2.6%<br>- hypoalb<30g/L, 6%<br>- elevated GGT, 13% | ALT, AST and TBIL showed significant elevation in severe COVID-19 cases compared with mild cases. |
| Yang *et al*[113] | 149 | - abnormal ALT >50 U/L, 9%<br>- abnormal AST >35 U/L, 14%<br>- abnormal TBIL, 6%<br>- hypoalb< 30 g/L, 4%<br>- elevated GGT, 13% | |
| Fu *et al*[99] | 354 | - abnormal ALT >50 U/L, 39%<br>- abnormal AST >35 U/L, 39%<br>- abnormal TBIL, 6%<br>- hypoalb<30g/L, 62%<br>- increased GGT, 42% | TBIL, ALT and AST, and GGT were higher in critically ill patients than those in mild cases. |
| Cao *et al*[100] | 199 | - abnormal ALT >41 U/L, 41%<br>- abnormal AST >35 U/L, 20.5% | |
| Shi *et al*[101] | 81 | - abnormal AST >35 U/L, 55% | |
| Wu *et al*[41] | 80 | - abnormal ALT >40 U/L, 3.75%<br>- abnormal AST >35 U/L, 3.75%<br>- abnormal TBIL, 1.25%<br>- hypoalb<30g/L, 2.5% | Patients with COVID-19 infection are prone to exhibit liver dysfunction. |
| Xu *et al*[107] | 62 | - abnormal AST >35 U/L 16.1% | |
| Xie *et al*[103] | 79 | - abnormal ALT >40 U/L, 31.6%<br>- abnormal AST >35 U/L, 35.4%<br>- abnormal TBIL, 5.1% | - Liver injury is prevalent in COVID-19 patients.<br>- Severe lung lesions on CT might be related to higher incidence of ALI. |
| Wu *et al*[12] | 201 | - abnormal ALT >40 U/L, 29.8%<br>- abnormal AST >40 U/L, 21.7%<br>- hypoalb<30g/L, 98.5% | |
| Arentz *et al*[105] | 21 | - abnormal ALT >40 U/L, 38%<br>- abnormal AST >35 U/L, 38% | |
| Tabata *et al*[109] | 104 | - abnormal ALT >40 U/L 12%<br>- abnormal AST >35 U/L 9% | |

| | | | |
|---|---|---|---|
| Wang *et al*[54] | 156 | - abnormal ALT >40 U/L, 41%<br>- abnormal AST >40 U/L, 41% | The liver enzyme abnormality was associated with disease severity. |
| Zhang *et al*[112] | 194 | - abnormal ALT >50 U/L, 15.46%<br>- abnormal AST >35 U/L, 15.46%<br>- increased TBIL, 1.9% | |
| Yang *et al*[113] | 200 | - abnormal ALT >40 U/L, 22%<br>- abnormal AST >35 U/L, 37%<br>- hypoalb<40g/L, 72% | |
| Cai *et al*[93] | 417 | - abnormal ALT >50 U/L, 58.8%<br>- abnormal AST >35 U/L, 43%<br>- increased TBIL, 1.5%<br>- increased GGT, 48% | Patients with abnormal liver tests were at higher risk of severe disease. |
| Wang *et al*[94] | 657 | - abnormal AST >35 U/L, 26.8%<br>- hypoalb<40g/L, 57%<br>- increased GGT, 16.6% | |
| Zhang *et al*[115] | 663 | - abnormal ALT >40 U/L, 22.8%<br>- abnormal AST >40 U/L, 25.8% | |
| Chen *et al*[106] | 830 | - abnormal ALT >50 U/L, 41.9%<br>- abnormal AST >35 U/L, 48.5%<br>- increased TBIL, 21%<br>- elevated GGT, 50.7% | Patients with COVID-19 frequently exhibit liver abnormalities. |
| Hajifathalian *et al*[137] | 1059 | - abnormal ALT >50 U/L, 62%<br>- abnormal AST >40 U/L, 62% | |
| Zhao *et al*[138] | 1000 | - abnormal ALT >150U/L, 1.7%<br>- abnormal AST >120U/L, 1.5% | The older group had more patients with liver dysfunction on admission. |
| Guan *et al*[125] | 1099 | - abnormal ALT >40 U/L, 21.3%<br>- abnormal AST >35 U/L, 22.2%<br>- increased TBIL, 10.5% | |
| Elmunzer *et al*[129] | 1992 | - abnormal ALT >50 U/L, 28%<br>- increased TBIL, 28% | |
| Pun *et al*[130] | 2088 | - abnormal ALT >40 U/L, 2.3%<br>- abnormal AST >40 U/L, 2.3% | |
| Phipps *et al*[131] | 2273 | - abnormal ALT >50 U/L, 31%<br>- abnormal AST >35 U/L, 14%<br>- increased TBIL, 1.9% | |
| Price-Haywood *et al*[132] | 3481 | - AST >40 U/l:<br>white patients (55.2%)<br>black patients (62.0%)<br>- ALT >40 U/l:<br>white patients (38.6%)<br>black patients (37%)<br>- Tbil ≥1.2 mg/dl:<br>white patients (13.5%)<br>black patients (11.9%) | |
| Mikami *et al*[133] | 3708 | - abnormal ALT >40 U/L, 34.2%<br>- abnormal AST >35 U/L, 53.4% | |
| Richardson *et al*[134] | 5700 | - abnormal ALT >40 U/L, 39%<br>- abnormal AST >35 U/L, 58.4% | |
| Marcello *et al*[136] | 6248 | - abnormal ALT >40 U/L, 50 %<br>- abnormal AST >40 U/L, 3% | |

AST: aspartate aminotransferase; ALT: alanine aminotransferase; GGT: γ-glutamyl transferase; Hypoalb: hypoalbuminemia; TBIL: total bilirubin; ALI: acute liver injury; CT: computed tomography.

in 61.27% of cases[18]. In our review, the occurrence of elevated ALT, AST, bilirubin and GGT is in 1.7-62%, 1.5-62%, 1.25-30.6%, and 13-57%, respectively; plus hypoalbuminemia in 2.5-98.5%[62-66] (Table 2).

**Histopathological findings in biopsy/autopsy in COVID-19 patients**

At the beginning of the pandemic, though the autopsy is the cornerstone to determine the cause of death, pathological features were scarce due to difficult access to perform biopsy/autopsy[67] and the risk of contamination. Gradually, researchers started to biopsy/autopsy respecting safety recommendations proposed by the World Health Organization[68] and the American Centers of Disease Control and Prevention[69]. The liver damages were mostly non-specific and indicated an acute disease or previous illness, including steatosis, congestion, dilation of sinusoids, lobular lymphocytic infiltrates, hepatitis, necrosis, venous obstruction, thrombi and hemophagocytosis[70-72].

**Table 3:** Synthesis of histopathological findings in biopsied/autopsied COVID-19 patients with hepatic dysfunction

| Reference | Sample size, n | Main histopathological findings, n (%) |
|---|---|---|
| Zhao *et al*[138] | 17 | - Thrombi, 12 (70.6)<br>- Steatosis, 12 (70.6)<br>- Megakaryocytes in sinusoids, 11 (64.7)<br>- Portal inflammation, 8 (47)<br>- Zone 3 hemorrhage/necrosis, 8 (47)<br>- Lobular inflammation, 5 (29.4)<br>- Histiocytic hyperplasia, 5 (29.4)<br>- Ischemia/necrosis, 2 (11.8) |
| Bradley *et al*[71] | 14 | - Congestion, 11 (78.6)<br>- Steatosis, 9 (64.3)<br>- Portal inflammation, 4 (28.6)<br>- Centrilobularnecrosis, 4 (28.6)<br>- Lobular inflammation, 1 (7.1)<br>- Toxic/metabolic disease, 1 (7.1) |
| Xu *et al*[139] | 1 | - Steatosis, 1 (100)<br>- Lobular inflammation, 1 (100)<br>- Portal inflammation, 1 (100) |
| Rapkiewicz *et al*[140] | 7 | - Steatosis, 7 (100)<br>- Thrombi, 6 (85.7)<br>- Ischemic necrosis, 2 (28.6)<br>- Zone 3 necrosis, 1 (14.3) |
| Bösmüller *et al*[141] | 4 | - Congestion, 1 (25)<br>- Hemophagocytosis, 1 (25)<br>- Centrilobular necrosis, 1 (25) |
| Remmelink *et al*[72] | 17 | - Steatosis, 10 (59)<br>- Congestion, 7 (41.2)<br>- Centrilobular necrosis, 1 (5.9) |
| Tian *et al*[142] | 4 | - Portal inflammation, 2 (50)<br>- Centrilobular necrosis, 2 (50)<br>- Zone 3 sinusoidal dilatation, 2 (50),<br>- Steatosis, 1(25)<br>- Portal necrosis, 1 (25) |
| Bryce *et al*[141] | 93 | - Congestion, 41/92 (45)<br>- Steatosis, 28/92 (30)<br>- Thrombi in portal venules, 37/92 (40)<br>- Hemophagocytosis, (some cases)<br>- Zone 3 ischemic necrosis, 11/92 (12) |
| Schaller *et al*[144] | 12 | - Portal inflammation, 12 (100) |
| Duarte-Neto *et al*[145] | 10 | - Congestion, 10 (100)<br>- Portal inflammation, 9 (90)<br>- Steatosis, 6 (60)<br>- Lobular inflammation, 6 (60)<br>- Ischemic necrosis, 3 (30)<br>- Hemophagocytosis, 3 (30) |
| Lacy *et al*[146] | 1 | - Steatosis, 1 (100)<br>- Congestion, 1 (100)<br>- Centrilobulor pallor, 1 (100) |
| Edler *et al*[147] | 80 | - Shock changes, 40 (50) |
| Menter *et al*[148] | 17 | - Steatosis, 7 (41.2)<br>- Necrosis, 5 (29.4) |
| Aguiar *et al*[149] | 1 | - Micro abscesses, 1 (100) |
| Zerehpoosh *et al*[150] | 5 | - Sinusoidal dilatation, 5 (100)<br>- Portal inflammation, 5 (100)<br>- Steatosis, 5 (100) |
| Takahashi *et al*[151] | 1 | - Micro abscesses, 1 (100) |
| Buja *et al*[152] | 23 | - Steatosis, 3 (13) |
| Fiel *et al*[153] | 2 | - Portal inflammation, 2 (100)<br>- Lobular inflammation, 2 (100)<br>- Bile duct damage, 2 (100)<br>- Endotheliitis, 2 (100)<br>- Centrilobular necrosis, 2 (100)<br>- Apoptotic bodies, 2 (100)<br>- Thrombi, 1 (50) |
| Total | 238 | - Steatosis, 77 (32.3)<br>- Portal inflammation, 43 (18)<br>- Shock changes, 40 (16.8)<br>- Necrosis, 36 (15.1)<br>- Thrombi, 34 (14.3)<br>- Congestion, 32 (13.4)<br>- Lobular inflammation, 15 (6.3)<br>- Hemophagocytosis, 12 (5)<br>- Megakaryocytes in sinusoids, 11 (4.6)<br>- Sinusoidal dilatation, 7 (3)<br>- Histiocytic hyperplasia, 5 (2.1)<br>- Apoptotic bodies, 2 (0.8)<br>- Bile duct damage, 2 (0.8)<br>- Endotheliitis, 2 (0.8)<br>- Microabscesses, 2 (0.8)<br>- Portal necrosis, 1 (0.4)<br>- Centrilobulor pallor, 1 (0.4)<br>- Toxic/metabolic disease, 1 (0.4) |

Through 18 studies, Table 3 summarized the principal following histological features: steatosis (32.3%), portal inflammation (18%), shock changes (16.8%), necrosis (15.1%), thrombi (14.3%), and congestion (13.4%).

**Radiological findings in COVID-19 patients**

Radiological explorations play a crucial role in managing COVID-19 patients, especially chest computed tomography (CT). Furthermore, it can provide essential information about changes in the abdominal organs. Indeed, Guler *et al*[73] remarked that the liver-to-spleen ratio was decreased in high lung CT score, plus the lowering of the hepatic CT attenuation rates[74]. In a retrospective study with 316 patients (204 RT-PCR positives; 112 RT-PCR negative and chest CT negative), Medeiros *et al*[75] revealed a higher prevalence of steatosis in COVID-19 patients (31.9% vs. 7.1%; $P<0.001$), compared to controls, after matching to age and sex. Also, the sonography can be performed at the bedside, particularly in critically ill COVID-19 patients. It can demonstrate vascular, cholestatic or inflammatory complications[76] and be a secure option to the autopsy[77].

**Liver dysfunction and COVID-19 in subgroups**

**Chronic liver disease**

The American Centers of Disease Control and Prevention declared that CLD is a potential risk for severe COVID-19 infection[78]. Among an American multicenter research network study with 2780 patients[79], 9% had preexisting CLD. The CLD group

patients were older (55.2±14.6 vs 51.6±17.8 years; *P*<0.01), had more comorbidities such as nicotine dependence (24% vs 7.5%; *P*<0.01), hypertension (68% vs 40.3%; *P*<0.01), diabetes mellitus (48% vs 14.8%; *P*<0.01), chronic respiratory disease (40% vs 11%; *P*<0.01), chronic kidney disease (32% vs 7.2%; *P*<0.01), and heart failure (24% vs 8.7%; *P*<0.01). These patients had significant high risk of hospitalization (RR: 1.3; 95% CI: 1.1-1.6; *P*=0.006), and mortality (RR: 3.0; 95% CI: 1.5-6.0; *P*=0.001), especially with cirrhosis. These complications resulted from the immune dysfunction in this type of patient[80]. On the other hand, in a pooled analysis, Lippi *et al*[81] suggested that CLD was not linked with severity or mortality. Nevertheless, with COVID-19, cirrhosis is a high-risk condition for severe infection and decompensation and could induce acute-on-chronic liver failure[82,83]. An international multicenter cohort study of patients with CLD showed that the mortality rate was 12.2% of CLD patients without cirrhosis, 23.9% of Child-Pugh class A, 43.3% of Child-Pugh class B, and 63% of Child-Pugh class C cirrhotic patients[84]. In the same line, the 30-day fatality rate was elevated in COVID-19 patients with cirrhosis[85]. Equivalent, the fatality rate was 32% of cases with cirrhosis compared to 8% in those without (*P*<0.001), and it was associated with the Child-Pugh class: 19% in class A, 35% in class B, and 51% in Class C[23].

**Liver transplant recipients**

Owing to the immunosuppressive therapy, the American Association for the Study of Liver Diseases considered these patients as a high-risk population for severe COVID-19 and have priority for the PCR examination[86].

In an 18-country international registry (COVID-Hep and SECURE-Cirrhosis), comparing 151 liver transplant recipients to 627 patients who had not undergone liver transplantation, the first group was more admitted to the intensive care unit (28% vs 8%; *P*<0.0001), more mechanically ventilated (20% vs 5%; *P*<0.0001); and in the multivariable logistic regression analysis age (OR: 1.06; 95% CI: 1.01-1.11; *P*=0.03), serum creatinine concentration (OR: 1.57; 95% CI: 1.05-2.36; *P*=0.02), and non-liver cancer (OR: 18.30; 95% CI: 1.96-170.75; *P*=0.01) were predictors of death[87].

Managing the immunosuppressive and anti-infective medications is difficult since infection lasts over time, and the viral load is proportional to the dose of immunosuppressive therapy[88].

A Swiss multicenter study including 21 solid organ transplant patients concluded that the clinical progression and the stage of severity did not vary from the general population, through temporary discontinuation or reduction of anti-metabolite medications and maintaining the dose of corticosteroids and calcineurin inhibitors[89].

## CONCLUSION

This review is not final and conclusive to help clinicians in their practice. The pathogenic components of liver dysfunction are still misunderstood. Likely, they are multifactorial. More studies are needed to clarify the other aspects of COVID-19, especially the liver involvement with or without the underlying chronic disease (e.g., viral hepatitis, primary biliary cholangitis, autoimmune hepatitis, autoimmune cholangitis, cirrhosis, hepatocellular carcinoma).

## ACKNOWLEDGMENT

**Authors' contributions:** All authors have participated in the conception and design of the study, acquisition of data, analysis, interpretation of data, drafting the article, revising it critically for important intellectual content, and final approval of the version to be submitted.

## REFERENCES

1. Tyrrell DA, Bynoe ML. Cultivation of a novel type of common-cold virus in organ cultures. Br Med J 1965; 1(5448):1467-70.
2. Daqqaq TS. Radiological findings from patients with COVID-19: A meta-analysis of clinical studies. Kuwait Med J 2021; 53(2):117-23.
3. Wevers BA, van der Hoek L. Recently discovered human coronaviruses. Clin Lab Med 2009; 29(4):715-24.
4. Peiris JSM, Lai ST, Poon LLM, Guan Y, Yam LYC, Lim W, *et al.* Coronavirus as a possible cause of severe acute respiratory syndrome. Lancet 2003; 361(9366):1319-25.
5. World Health Organization. Severe Acute Respiratory Syndrome (SARS). Accessed November 20, 2021. https://www.who.int/health-topics/severe-acute-respiratory-syndrome#tab=tab_1
6. Raj VS, Osterhaus ADME, Fouchier RAM, Haagmans BL. MERS: emergence of a novel human coronavirus. Curr Opin Virol 2014; 5:58-62.
7. Worldometer. COVID Live Update. Accessed November 20, 2021. https://www.worldometers.info/coronavirus/
8. Gorbalenya AE, Baker SC, Baric RS, *et al*. The species Severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. Nat Microbiol 2020; 5:536-44.
9. Chan JF, Kok K, Zhu Z, Chu H, To KK, Yuan S, *et al.* Genomic characterization of the 2019 novel human-pathogenic coronavirus isolated from a patient with atypical pneumonia after visiting Wuhan. Emerg Microbes Infect 2020; 9(1):221-36.
10. Hui DS, Azhar EI, Madani TA, Ntoumi F, Kock R, Dar O, *et al.* The continuing 2019-nCoV epidemic threat of novel coronaviruses to global health - The latest 2019 novel coronavirus outbreak in Wuhan, China. Int J Infect Dis 2020; 91:264-66.

11. Zhou P, Yang X-L, Wang X-G, Hu B, Zhang L, Zhang W, *et al.* A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature 2020; 579(7798):270-3.
12. Wu F, Zhao S, Yu B, Chen Y-M, Wang W, Song Z-G, *et al.* A new coronavirus associated with human respiratory disease in China. Nature 2020; 579(7798):265-9.
13. Chen Y, Liu Q, Guo D. Emerging coronaviruses: Genome structure, replication, and pathogenesis. J Med Virol 2020; 92(4):418-23.
14. Pathak N. The Great Invader: How COVID-19 attacks every organ. Medscape. Accessed November 20, 2021. https://www.medscape.com/ viewarticle/ 929284? spon=32&uac=84305D V&impID=2363351 &sso=true&faf=1& nlid=13522 1_530&src= WNL_ mdplsfeat_200428_mscpedit_ccmd
15. Dong X, Cao Y, Lu X, Zhang J, Du H, Yan Y, *et al*. Eleven faces of coronavirus disease 2019. Allergy 2020; 75(7):1699-709.
16. Qi X, Liu C, Jiang Z, Gu Y, Zhang G, Shao C, *et al.* Multicenter analysis of clinical characteristics and outcomes in patients with COVID-19 who develop liver injury. J Hepatol 2020; 73(2):455-8.
17. Zhang C, Shi L, Wang FS. Liver injury in COVID-19: management and challenges. Lancet Gastroenterol Hepatol 2020; 5(5):428-30.
18. Kumar-M P, Mishra S, Jha DK, Shukla J, Choudhury A, Mohindra R, *et al.* Coronavirus disease (COVID-19) and the liver: a comprehensive systematic review and meta-analysis. Hepatol Int 2020; 14(5):711-22.
19. Henry BM, Santos de Oliveira MH, Benoit S, Plebani M, Lippi G. Hematologic, biochemical and immune biomarker abnormalities associated with severe illness and mortality in coronavirus disease 2019 (COVID-19): a meta-analysis. Clin Chem Lab Med 2020; 58(7):1021-8.
20. Parohan M, Yaghoubi S, Seraji A. Liver injury is associated with severe coronavirus disease 2019 (COVID-19) infection: A systematic review and meta-analysis of retrospective studies. Hepatol Res 2020; 50(8):924-35.
21. Wang M, Yan W, Qi W, Wu D, Zhu L, Li W, *et al.* Clinical characteristics and risk factors of liver injury in COVID-19: a retrospective cohort study from Wuhan, China. Hepatol Int 2020; 14(5):723-32.
22. Zhang H, Liao Y-S, Gong J, Liu J, Zhang H. Clinical characteristics and risk factors for liver injury in COVID-19 patients in Wuhan. World J Gastroenterol 2020; 26(31):4694-702.
23. Marjot T, Moon AM, Cook JA, Abd-Elsalam S, Aloman C, Armstrong MJ, *et al.* Outcomes following SARS-CoV-2 infection in patients with chronic liver disease: An international registry study. J Hepatol 2021; 74(3):567-77.
24. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, *et al*. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med 2020; 8(5):475-81.
25. Yang W, Cao Q, Qin L, Wang X, Cheng Z, Pan A, *et al*. Clinical characteristics and imaging manifestations of the 2019 novel coronavirus disease (COVID-19): A multicenter study in Wenzhou city, Zhejiang, China. J Infect 2020; 80(4):388-93.
26. Wu J, Liu J, Zhao X, Liu C, Wang W, Xi W, *et al.* Clinical characteristics of imported cases of coronavirus disease 2019 (COVID-19) in Jiangsu Province: A multicenter descriptive study. Clin Infect Dis 2020; 71(15):706-12.
27. Xu XW, Wu XX, Jiang XG, Xu KJ, Ying LJ, Ma CL, *et al*. Clinical findings in a group of patients infected with the 2019 novel coronavirus (SARS-Cov-2) outside of Wuhan, China: Retrospective case series. BMJ 2020; 368:1-7.
28. Dreher M, Kersten A, Bickenbach J, Balfanz P, Hartmann B, Cornelissen C, *et al*. The characteristics of 50 hospitalized COVID-19 patients with and without ARDS. Dtsch Arztebl Int 2020; 117(16):271-8.
29. Gralinski LE, Menachery VD, Morgan AP, Totura AL, Beall A, Kocher J, *et al.* Allelic variation in the toll-like receptor adaptor protein Ticam2 contributes to SARS-coronavirus pathogenesis in mice. G3 (Bethesda) 2017; 7(6):1653-63.
30. Zhao J, Yang Y, Huang H, *et al.* Relationship between the ABO blood group and the coronavirus disease 2019 (COVID-19) susceptibility. Clin Infect Dis 2021; 73:328-31.
31. Jokela M, Virtanen M, David Batty G, Kivimaki M. ABO blood group and susceptibility to severe acute respiratory syndrome. JAMA 2005; 292:1447.
32. Goel R, Bloch EM, Pirenne F, Al-Riyami AZ, Crowe E, Dau L, *et al.* ABO blood group and COVID-19: a review on behalf of the ISBT COVID-19 working group. Vox Sang 2021; 116(8):849-61.
33. Hernández Cordero AI, Li X, Milne S, Yang CX, Bosse Y, Joubert P, *et al.* Multi-omics highlights ABO plasma protein as a causal risk factor for COVID-19. Hum Genet 2021; 140(6):969-79.
34. Nguyen A, David JK, Maden SK, Wood MA, Weeder BR, Nellore A, *et al.* Human Leukocyte Antigen Susceptibility Map for Severe Acute Respiratory Syndrome Coronavirus 2. J Virol 2020; 94(13):e00510-20.
35. Lin M, Tseng H-K, Trejaut JA, Lee H-L, Loo J-H, Chu C-C, *et al.* Association of HLA class I with severe acute respiratory syndrome coronavirus infection. BMC Med Genet 2003; 4:9.
36. Li W, Moore MJ, Vasilieva N, Sui J, Wong SK, Berne MA, *et al.* Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. Nature 2003; 426(6965):450-4.
37. Hamming I, Timens W, Bulthuis M, Lely AT, Navis GJ, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. J Pathol 2004; 203(2):631-7.
38. Kuba K, Imai Y, Rao S, Gao H, Guo F, Guan B, *et al.* A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. Nat Med 2005; 11(8):875-9.

39. Yan R, Zhang Y, Li Y, Xia L, Guo Y, Zhou Q. Structural basis for the recognition of SARS-CoV-2 by full-length human ACE2. Science 2020; 366(6485):1444-8.
40. Wan Y, Shang J, Graham R, Baric RS, Li F. Receptor recognition by the novel coronavirus from Wuhan: an analysis based on decade-long structural studies of SARS coronavirus. J Virol 2020; 94(7):e00127-20.
41. Du M, Cai G, Chen F, Christiani DC, Zhang Z, Wang M. Multiomics evaluation of gastrointestinal and other clinical characteristics of COVID-19. Gastroenterology 2020; 158(8):2298-2300.e7.
42. Li M-Y, Li L, Zhang Y, Wang X-S. Expression of the SARS-CoV-2 cell receptor gene ACE2 in a wide variety of human tissues. Infect Dis Poverty 2020; 9(1):45.
43. Zhou L, Niu Z, Jiang X, Zhang Z, Zheng Y, Wang Z, *et al*. SARS-CoV-2 targets by the pscRNA profiling of ACE2, TMPRSS2 and furin proteases. iScience 2020; 23(11):101744.
44. Qi J, Zhou Y, Hua J, Zhang L, Bian J, Liu B, *et al*. The scRNA-seq expression profiling of the receptor ACE2 and the cellular protease TMPRSS2 reveals human organs susceptible to SARS-CoV-2 infection. Int J Environ Res Public Health 2021; 18(1):284.
45. Chai X, Hu L, Zhang Y, Han W, Lu Z, Ke A, *et al*. Specific ACE2 expression in cholangiocytes may cause liver damage after 2019-nCoV infection. bioRxiv. Published online 2020. doi:10.1101/2020.02.03.931766
46. Xu L, Liu J, Lu M, Yang D, Zheng X. Liver injury during highly pathogenic human coronavirus infections. Liver Int 2020; 40(5):998-1004.
47. Sonzogni A, Previtali G, Seghezzi M, Alessio MG, Gianatti A, Licini L, *et al*. Liver histopathology in severe COVID 19 respiratory failure is suggestive of vascular alterations. Liver Int 2020; 40(9):2110-6.
48. Chau TN, Lee KC, Yao H, Tsang TY, Chow TC, Yeung YC, *et al*. SARS-associated viral hepatitis caused by a novel coronavirus: report of three cases. Hepatology 2004; 39(2):302-10.
49. Lagana SM, Kudose S, Iuga AC, Lee MJ, Fazlollahi L, Remotti HE, *et al*. Hepatic pathology in patients dying of COVID-19: a series of 40 cases including clinical, histologic, and virologic data. Mod Pathol 2020; 33(11):2147-55.
50. Klimstra WB, Ryman KD, Bernard KA, Nguyen KB, Biron CA, Johnston RE. Infection of neonatal mice with Sindbis virus results in a systemic inflammatory response syndrome. J Virol 1999; 73(12):10387-98.
51. Tartey S, Takeuchi O. Pathogen recognition and Toll-like receptor targeted therapeutics in innate immune cells. Int Rev Immunol 2017; 36(2):57-73.
52. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet 2020; 395(10229):1033-4.
53. Chen G, Wu D, Guo W, Cao Y, Huang D, Wang H, *et al*. Clinical and immunological features of severe and moderate coronavirus disease 2019. J Clin Invest 2020; 130(5):2620-9.
54. Wang Y, Liu S, Liu H, Li W, Lin F, Jiang L, *et al*. SARS-CoV-2 infection of the liver directly contributes to hepatic impairment in patients with COVID-19. J Hepatol 2020; 73(4):807-16.
55. Li Y, Xiao SY. Hepatic involvement in COVID-19 patients: Pathology, pathogenesis, and clinical implications. J Med Virol 2020; 92(9):1491-4.
56. Kavoliuniene A, Vaitiekiene A, Cesnaite G. Congestive hepatopathy and hypoxic hepatitis in heart failure: A cardiologist's point of view. Int J Cardiol 2013; 166(3):554-8.
57. Kotzampassi K, Paramythiotis D, Eleftheriadis E. Deterioration of visceral perfusion caused by intra-abdominal hypertension in pigs ventilated with positive end-expiratory pressure. Surg Today 2000; 30(11):987-92.
58. Olry A, Meunier L, Délire B, Larrey D, Horsmans Y, Le Louët H. Drug-induced liver injury and COVID-19 infection: the rules remain the same. Drug Saf 2020; 43(7):615-7.
59. Darunavir - LiverTox - NCBI Bookshelf. Accessed November 28, 2021. https://www.ncbi.nlm.nih.gov/books/NBK547994/
60. Pérez JV, Rodriguez Chinesta JM. Risk of hepatitis B reactivation associated with treatment against SARS-CoV-2 (COVID-19) with corticosteroids. Rev Clin Esp 2020; 220(8):534-6.
61. Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C, *et al*. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med 2020; 8(4):420-2.
62. Zhang B, Zhou X, Qiu Y, Song Y, Feng F, Feng J, *et al*. Clinical characteristics of 82 cases of death from COVID-19. PLoS One 2020; 15(7):e0235458.
63. Zhang Y, Zheng L, Liu L, Zhao M, Xiao J, Zhao Q. Liver impairment in COVID-19 patients: A retrospective analysis of 115 cases from a single centre in Wuhan city, China. Liver Int 2020; 40(9):2095-103.
64. Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, *et al*. Risk factors associated with Acute Respiratory Distress Syndrome and death in patients with Coronavirus Disease 2019 pneumonia in Wuhan, China. JAMA Intern Med 2020; 180(7):934-43.
65. Zhao M, Wang M, Zhang J, Gu J, Zhang P, Xu Y, *et al*. Comparison of clinical characteristics and outcomes of patients with coronavirus disease 2019 at different ages. Aging (Albany NY) 2020; 12(11):10070-86.
66. Hajifathalian K, Krisko T, Mehta A, Kumar S, Schwartz R, Fortune B, *et al*. Gastrointestinal and hepatic manifestations of 2019 novel coronavirus disease in a large cohort of infected patients from New York: clinical implications. Gastroenterology 2020; 159(3):1137-40.e2.
67. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, *et al*. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020; 395(10223):497-506.
68. World Health Organization (WHO). Infection Prevention and Control for the safe management of a dead body in the context of COVID-19. Interim guidance 24 March 2020 Background. Published 2020. Accessed December 12, 2021. https://apps.who.int/iris/handle/10665/331438

69. Miller JM, Astles R, Baszler T, Chapin K, Carey R, Garcia L, *et al.* Guidelines for Safe Work Practices in Human and Animal Medical Diagnostic Laboratories. Recommendations of a CDC-Convened, Biosafety Blue Ribbon Panel. MMWR Suppl 2012; 61(1):1-101.
70. Jonigk D, Märkl B, Helms J. COVID-19: what the clinician should know about post-mortem findings. Intensive Care Med 2021; 47(1):86-89.
71. Bradley BT, Maioli H, Johnston R, Chaudhry I, Fink SL, Xu H, *et al.* Histopathology and ultrastructural findings of fatal COVID-19 infections in Washington State: a case series. Lancet 2020; 396(10247):320-32.
72. Remmelink M, De Mendonça R, D'Haene N, de Clercq S, Verocq C, Lebrun L, *et al.* Unspecific post-mortem findings despite multiorgan viral spread in COVID-19 patients. Crit Care 2020; 24(1):1-10.
73. Guler E, Unal NG, Cinkooglu A, Savas R, Kose T, Pullukcu H, *et al.* Correlation of liver-to-spleen ratio, lung CT scores, clinical, and laboratory findings of COVID-19 patients with two consecutive CT scans. Abdom Radiol (NY) 2021; 46(4):1543-51.
74. Uchida Y, Uemura H, Yamaba S, Hamada D, Tarumoto N, Maesaki S, *et al.* Significance of liver dysfunction associated with decreased hepatic CT attenuation values in Japanese patients with severe COVID-19. J Gastroenterol 2020; 55(11):1098-106.
75. Medeiros AK, Barbisan CC, Cruz IR, de Araujo EM, Libanio BB, Albuquerque KS, *et al.* Higher frequency of hepatic steatosis at CT among COVID-19-positive patients. Abdom Radiol (NY) 2020; 45(9):2748-54.
76. Spogis J, Hagen F, Thaiss WM, Hoffmann T, Malek N, Nikolaou K, *et al.* Sonographic findings in coronavirus disease-19 associated liver damage. PLoS One 2021; 16(2):e0244781.
77. Kanchan T, Shrestha R, Krishan K. Post-mortem ultrasonography: a safer alternative to autopsies in COVID-19 deaths. J Ultrasound 2021; 24(4):577-8.
78. Centers for disease control and prevention. People with Certain Medical Conditions. Accessed December 12, 2021. https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html
79. Singh S, Khan A. Clinical characteristics and outcomes of coronavirus disease 2019 among patients with preexisting liver disease in the United States: A multicenter research network study. Gastroenterology 2020; 159(2):768-71.e3.
80. Albillos A, Lario M, Álvarez-Mon M. Cirrhosis-associated immune dysfunction: Distinctive features and clinical relevance. J Hepatol 2014; 61(6):1385-96.
81. Lippi G, de Oliveira MHS, Henry BM. Chronic liver disease is not associated with severity or mortality in Coronavirus disease 2019 (COVID-19): a pooled analysis. Eur J Gastroenterol Hepatol 2021; 33(1):114-5.
82. Kushner T, Cafardi J. Chronic liver disease and COVID-19: Alcohol use disorder/alcohol-associated liver disease, nonalcoholic fatty liver disease/nonalcoholic steatohepatitis, autoimmune liver disease, and compensated cirrhosis. Clin Liver Dis 2020; 15(5):195-9.
83. Strnad P, Tacke F, Koch A, Trautwein C. Liver-guardian, modifier and target of sepsis. Nat Rev Gastroenterol Hepatol 2017; 14(1):55-66.
84. Moon AM, Webb GJ, Aloman C, Armstrong MJ, Cargill T, Dhanasekaran R, *et al.* High mortality rates for SARS-CoV-2 infection in patients with pre-existing chronic liver disease and cirrhosis: Preliminary results from an international registry. J Hepatol 2020; 73(3):705-8.
85. Iavarone M, D'Ambrosio R, Soria A, Triolo M, Pugliese N, del Poggio P, *et al.* High rates of 30-day mortality in patients with cirrhosis and COVID-19. J Hepatol 2020; 73(5):1063-71.
86. Fix OK, Hameed B, Fontana RJ, Kwok RM, McGuire BM, Mulligan DC, *et al.* Clinical best practice advice for hepatology and liver transplant providers during the COVID-19 pandemic: AASLD expert panel consensus statement. Hepatology 2020; 72(1):287-304.
87. Webb GJ, Marjot T, Cook JA, Aloman C, Armstrong MJ, Brenner EJ, *et al.* Outcomes following SARS-CoV-2 infection in liver transplant recipients: an international registry study. Lancet Gastroenterol Hepatol 2020; 5(11):1008-16.
88. Qin J, Wang H, Qin X, Zhang P, Zhu L, Cai J, *et al.* Perioperative presentation of COVID-19 disease in a liver transplant recipient. Hepatology 2020; 72(4):1491-3.
89. Kim MY, Brennan DC, Shah P. General approach to the clinical care of solid organ transplant recipients with COVID-19 infection: management for transplant recipients. Curr Transplant Rep 2020; 7(4):366-78.
90. Sun J-K, Liu Y, Zou L, Zhang W-H, Li J-J, Wang Y, *et al.* Acute gastrointestinal injury in critically ill patients with COVID-19 in Wuhan, China. World J Gastroenterol 2020; 26(39):6087-97.
91. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, *et al.* Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020; 395(10223):507-13.
92. Wang Z, Yang B, Li Q, Wen L, Zhang R. Clinical features of 69 cases with coronavirus disease 2019 in Wuhan, China. Clin Infect Dis 2020; 71(15):769-77.
93. Cai Q, Huang D, Ou P, Yu H, Zhu Z, Xia Z, *et al.* COVID-19 in a designated infectious diseases hospital outside Hubei Province, China. Allergy 2020; 75(7):1742-52.
94. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, *et al.* clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA 2020; 322(11):1061-9.
95. Li L, Li S, Xu M, Yu P, Zheng S, Duan Z, *et al.* Risk factors related to hepatic injury in patients with corona virus disease 2019. medRxiv. Published online March 10, 2020:2020.02.28.20028514.
96. Fan Z, Chen L, Li J, Cheng X, Yang J, Tian C, *et al.* Clinical features of COVID-19-related liver functional abnormality. Clin Gastroenterol Hepatol 2020; 18(7):1561-6.
97. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, *et al.* Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020; 395(10229):1054-62.

98. Hu L, Chen S, Fu Y, Gao Z, Long H, Ren H-W, *et al.* Risk factors associated with clinical outcomes in 322 coronavirus disease 2019 (COVID-19) hospitalized patients in Wuhan, China. Clin Infect Dis 2020; 71(16):2089-98.
99. Fu L, Fei J, Xu S, Xiang H-X, Xiang Y, Hu B, *et al.* Liver dysfunction and its association with the risk of death in COVID-19 patients: A prospective cohort study. J Clin Transl Hepatol 2020; 8(3):246-54.
100. Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, *et al.* A trial of Lopinavir–Ritonavir in adults hospitalized with severe COVID-19. N Engl J Med 2020; 382(19):1787-99.
101. Shi H, Han X, Jiang N, Cao Y, Alwalid O, Gu J, *et al.* Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study. Lancet Infect Dis 2020; 20(4):425-34.
102. Liu C, Jiang ZC, Shao CX, Zhang HG, Yue HM, Chen ZH, *et al.* [Preliminary study of the relationship between novel coronavirus pneumonia and liver function damage: a multicenter study]. Zhonghua Gan Zang Bing Za Zhi 2020; 28(2):107-11. Article in Chinese.
103. Xie H, Zhao J, Lian N, Lin S, Xie Q, Zhuo H. Clinical characteristics of non-ICU hospitalized patients with coronavirus disease 2019 and liver injury: A retrospective study. Liver Int 2020; 40(6):1321-6.
104. Zhang JJ, Dong X, Cao YY, Yuan YD, Yang YB, Yan YQ, *et al*. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. Allergy 2020; 75(7):1730-41.
105. Arentz M, Yim E, Klaff L, Lokhandwala S, Riedo FX, Chong M, *et al.* Characteristics and outcomes of 21 critically ill patients with COVID-19 in Washington State. JAMA 2020; 322(16):1612-14.
106. Chen T, Wu D, Chen H, Yan W, Yang D, Chen G, *et al.* Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. BMJ 2020; 368:m1091.
107. Xu S, Fu L, Fei J, Xiang H-X, Xiang Y, Tan Z-X, *et al.* Acute kidney injury at early stage as a negative prognostic indicator of patients with COVID-19: a hospital-based retrospective analysis. medRxiv preprint. March 26, 2020. doi: https://doi.org/10.1101/2020.03.24.20042408
108. Cholankeril G, Podboy A, Aivaliotis VI, Tarlow B, Pham EA, Spencer SP, *et al.* High prevalence of concurrent gastrointestinal manifestations in patients with Severe Acute Respiratory Syndrome Coronavirus 2: Early experience from California. Gastroenterology 2020; 159(2):775-7.
109. Tabata S, Imai K, Kawano S, Ikeda M, Kodama T, Miyoshi K, *et al.* Clinical characteristics of COVID-19 in 104 people with SARS-CoV-2 infection on the Diamond Princess cruise ship: a retrospective analysis. Lancet Infect Dis 2020; 20(9):1043-50.
110. Luan YY, Liu Y, Liu X-Y, Yu B-J, Chen R-L, Peng M, *et al.* Coronavirus disease 2019 (COVID-19) associated coagulopathy and its impact on outcomes in Shenzhen, China: A retrospective cohort study. Thromb Res 2020; 195:62-8.
111. Guo T, Fan Y, Chen M, Wu X, Zhang L, He T, *et al.* Cardiovascular implications of fatal outcomes of patients with Coronavirus Disease 2019 (COVID-19). JAMA Cardiol 2020; 5(7):811-8.
112. Zhang H, Shang W, Liu Q, Zhang X, Zheng M, Yue M. Clinical characteristics of 194 cases of COVID-19 in Huanggang and Taian, China. Infection 2020; 48(5):687-94.
113. Yang L, Liu J, Zhang R, Li M, Li Z, Zhou X, *et al.* Epidemiological and clinical features of 200 hospitalized patients with coronavirus disease 2019 outside Wuhan, China: A descriptive study. J Clin Virol 2020; 129:104475.
114. Pan L, Mu M, Yang P, Sun Y, Wang R, Yan J, *et al.* Clinical characteristics of COVID-19 patients with digestive symptoms in Hubei, China: A descriptive, cross-sectional, multicenter study. Am J Gastroenterol 2020; 115(5):766-73.
115. Zhang G, Hu C, Luo L, Fang F, Chen Y, Li J, *et al.* Clinical features and short-term outcomes of 221 patients with COVID-19 in Wuhan, China. J Clin Virol 2020; 127:104364.
116. Webb BJ, Peltan ID, Jensen P, Hoda D, Hunter B, Silver A, *et al.* Clinical criteria for COVID-19-associated hyperinflammatory syndrome: a cohort study. Lancet Rheumatol 2020; 2(12):e754-e763.
117. Cai Q, Huang D, Yu H, Zhu Z, Xia Z, Su Y, *et al.* COVID-19: Abnormal liver function tests. J Hepatol 2020; 73(3):566-74.
118. Shi S, Qin M, Shen B, Cai Y, Liu T, Yang F, *et al.* Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. JAMA Cardiol 2020; 5(7):802-10.
119. Qin C, Zhou L, Hu Z, Zhang S, Yang S, Tao Y, *et al.* Dysregulation of immune response in patients with coronavirus 2019 (COVID-19) in Wuhan, China. Clin Infect Dis 2020; 71(15):762-8.
120. Mushtaq K, Khan MU, Iqbal F, Alsoub DH, Chaudhry HS, Ata F, *et al*. NAFLD is a predictor of liver injury in COVID-19 hospitalized patients but not of mortality, disease severity on the presentation or progression – The debate continues. J Hepatol 2021; 74(2):482-4.
121. Guisado-Vasco P, Valderas-Ortega S, Carralón-González MM, Roda-Santacruz AR, Gonzalez-Cortijo L, Sotres-Fernandez G, *et al.* Clinical characteristics and outcomes among hospitalized adults with severe COVID-19 admitted to a tertiary medical center and receiving antiviral, antimalarials, glucocorticoids, or immunomodulation with tocilizumab or cyclosporine: A retrospective observational study (COQUIMA cohort). EClinicalMedicine 2020; 28. doi:10.1016/j.eclinm.2020.10059
122. Jin X, Lian JS, Hu JH, Gao J, Zheng L, Zhang YM, *et al*. Epidemiological, clinical and virological characteristics of 74 cases of coronavirus-infected disease 2019 (COVID-19) with gastrointestinal symptoms. Gut 2020; 69(6):1002-9.
123. Zhang J, Wang X, Jia X, Li J, Hu K, Chen G, *et al.* Risk factors for disease severity, unimprovement, and mortality in COVID-19 patients in Wuhan, China. Clin Microbiol Infect 2020; 26(6):767-72.

124. Chen F, Chen W, Chen J, Xu D, Xie W, Wang X, *et al.* Clinical features and risk factors of COVID-19-associated liver injury and function: A retrospective analysis of 830 cases. Ann Hepatol 2021; 21:100267.
125. Guan W, Ni Z, Hu Y, Liang W, Ou C, He J, *et al.* Clinical characteristics of Coronavirus Disease 2019 in China. N Engl J Med 2020; 382(18):1708-20.
126. Luo S, Zhang X, Xu H. Don't overlook digestive symptoms in patients with 2019 Novel Coronavirus Disease (COVID-19). Clin Gastroenterol Hepatol 2020; 18(7):1636-7.
127. Liu J, Zhang L, Chen Y, Wu Z, Dong X, Teboul JL, *et al.* Association of sex with clinical outcomes in COVID-19 patients: A retrospective analysis of 1190 cases. Respir Med 2020; 173:106159.
128. Grasselli G, Zangrillo A, Zanella A, Antonelli M, Cabrini L, Castelli A, *et al.* Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy Region, Italy. JAMA 2020; 322(16):1574-81.
129. Elmunzer BJ, Spitzer RL, Foster LD, Merchant AA, Howard EF, Patel VA, *et al*. Digestive manifestations in patients hospitalized with Coronavirus Disease 2019. Clin Gastroenterol Hepatol 2021; 19(7):1354-65.e4.
130. Pun BT, Badenes R, Heras La Calle G, Orun OM, Chen W, Raman R, *et al.* Prevalence and risk factors for delirium in critically ill patients with COVID-19 (COVID-D): a multicentre cohort study. Lancet Respir Med 2021; 9(3):239-50.
131. Phipps MM, Barraza LH, LaSota ED, Sobieszczyk ME, Pereira MR, Zheng EX, *et al.* Acute liver injury in COVID-19: prevalence and association with clinical outcomes in a large U.S. cohort. Hepatology 2020; 72(3):807-17.
132. Price-Haywood EG, Burton J, Fort D, Seoane L. Hospitalization and mortality among black patients and white patients with COVID-19. N Engl J Med 2020; 382(26):2534-43.
133. Mikami T, Miyashita H, Yamada T, Harrington M, Steinberg D, Dunn A, *et al.* Risk factors for mortality in patients with COVID-19 in New York City. J Gen Intern Med 2021; 36(1):17-26.
134. Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, *et al.* Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. JAMA 2020; 322(20):2052-59.
135. Lei F, Liu YM, Zhou F, Qin JJ, Zhang P, Zhu L, *et al.* Longitudinal association between markers of liver injury and mortality in COVID-19 in China. Hepatology 2020; 72(2):389-98.
136. Marcello RK, Dolle J, Grami S, Adule R, Li Z, Tatem K, *et al.* Characteristics and outcomes of COVID-19 patients in New York City's public hospital system. PLoS One 2020; 15(12):e0243027.
137. Zhao CL, Rapkiewicz A, Maghsoodi-Deerwester M, Gupta M, Cao W, Palaia T, *et al.* Pathological findings in the postmortem liver of patients with coronavirus disease 2019 (COVID-19). Hum Pathol 2021; 109:59-68.
138. Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C, *et al*. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med 2020; 8(4):420-22.
139. Rapkiewicz AV, Mai X, Carsons SE, Pittaluga S, Kleiner DE, Berger JS, *et al*. Megakaryocytes and platelet-fibrin thrombi characterize multiorgan thrombosis at autopsy in COVID-19: A case series. EClinicalMedicine 2020; 24:100434.
140. Bösmüller H, Traxler S, Bitzer M, Haberle H, Raiser W, Nann D, *et al.* The evolution of pulmonary pathology in fatal COVID-19 disease: an autopsy study with clinical correlation. Virchows Arch 2020; 477(3):349-57.
141. Bryce C, Grimes Z, Pujadas E, Ahuja S, Beasley MB, Albrecht R, *et al.* Pathophysiology of SARS-CoV-2: The Mount Sinai COVID-19 autopsy experience. Mod Pathol 2021; 34(8): 1456-67.
142. Schaller T, Hirschbühl K, Burkhardt K, Braun G, Trepel M, Markl B, *et al.* Postmortem examination of patients with COVID-19. JAMA 2020; 322(24):2518-20.
143. Duarte-Neto AN, Monteiro RAA, da Silva LFF, Malheiros DM, de Oliveira EP, Theodoro-Filho J, *et al*. Pulmonary and systemic involvement in COVID-19 patients assessed with ultrasound-guided minimally invasive autopsy. Histopathology 2020; 77(2):186-97.
144. Lacy JM, Brooks EG, Akers J, Armstrong D, Decker L, Gonzalez A, *et al.* COVID-19: Postmortem diagnostic and biosafety considerations. Am J Forensic Med Pathol 2020; 41(3):143-51.
145. Edler C, Schröder AS, Aepfelbacher M, Fitzek A, Heinemann A, Heinrich F, *et al.* Dying with SARS-CoV-2 infection—an autopsy study of the first consecutive 80 cases in Hamburg, Germany. Int J Legal Med 2020; 134(4):1275-84.
146. Menter T, Haslbauer JD, Nienhold R, Savic S, Hopfer H, Deigendesch N, *et al.* Postmortem examination of COVID-19 patients reveals diffuse alveolar damage with severe capillary congestion and variegated findings in lungs and other organs suggesting vascular dysfunction. Histopathology 2020; 77(2):198-209.
147. Aguiar D, Lobrinus JA, Schibler M, Fracasso T, Lardi C. Inside the lungs of COVID-19 disease. Int J Legal Med 2020; 134(4):1271-74.
148. Zerehpoosh FB, Sabeti S, Bahrami-Motlagh H, Mokhtari M, Irvani SS, Torabinavid P, *et al.* Post-mortem histopathologic findings of vital organs in critically ill patients with COVID-19. Arch Iran Med 2021; 24(2):144-51.
149. Takahashi K, Kajiura K, Nasu M, Nakamura K, Sugata K, Matsuzaki A. Post-mortem biopsy of a patient with late exacerbation of COVID-19 pneumonia. Respirol Case Rep 2021; 9(4):e00724.
150. Buja LM, Wolf DA, Zhao B, Akkanti B, McDonald M, Lelenwa L, *et al.* The emerging spectrum of cardiopulmonary pathology of the coronavirus disease 2019 (COVID-19): Report of 3 autopsies from Houston, Texas, and review of autopsy findings from other United States cities. Cardiovasc Pathol 2020; 48:107233.
151. Fiel MI, El Jamal SM, Paniz-Mondolfi A, Gordon RE, Reidy J, Bandovic J, *et al*. Findings of Hepatic Severe Acute Respiratory Syndrome Coronavirus-2 Infection. Cell Mol Gastroenterol Hepatol 2021; 11(3):763-70.

Original Article

# The radiological and histopathological comparison of giant cell lipomas and atypical lipomatous tumors (ALT)/well differentiated liposarcomas (WDL)

Ayse Nur Toksoz Yildirim[1], Begumhan Baysal[2], Asmaa Alkandari[3], Erhan Okay[4], Tulay Zenginkinet[1], Aykut Celik[4]
[1]Department of Pathology, Istanbul Goztepe Prof. Dr. Suleyman Yalcin City Hospital, Istanbul, Turkey
[2]Department of Radiology, Istanbul Goztepe Prof. Dr. Suleyman Yalcin City Hospital, Istanbul, Turkey
[3]Faculty of Medicine, Kuwait University, Jabriya, Kuwait
[4]Department of Orthopaedics, Istanbul Goatee Prof. Dr. Suleyman Yalcin City Hospital, Istanbul, Turkey

Kuwait Medical Journal 2023; 55 (4): 292 -299

## ABSTRACT

**Objective:** The aim of this study is to make histological comparison between atypical lipomatous tumors (ALT)/well differentiated liposarcomas (WDL) and giant cell lipomas.
**Design**: Retrospective study
**Setting**: Istanbul Goztepe Prof. Dr. Suleyman Yalcin City Hospital Orthopaedics and Pathology Clinic
**Subjects**: Forty-five patients diagnosed with "giant cell lipomas or "atypical lipomatous tumors (ALT)/well differentiated liposarcomas (WDL)"
**Intervention**: The patients were assessed in terms of their histological and radiological features.
**Main outcome measure:** Radiological findings were able to discriminate the ALT/WDL from giant cell lipomas results.
**Results**: On T2 weighted MRI, septal structures were found in 15 out of 16 cases (93.8%) of ALT/WDL, whereas 12 out of 29 cases (41.4%) of lipoma displayed septa >2 mm ($P$<0.01). Septal contrast enhancement in ALT/WDL was statistically significant compared to lipoma group ($P$<0.01). For ALT/WDS, 13 of the 16 (81.3%) tumors were localized in the lower extremity ($P$<0.05). For less than 75% fat component in magnetic resonance imaging (MRI), ALT/WDL group displayed statistically significant difference in comparison with lipoma group.
**Conclusion**: Based on the results of our study, the imaging findings can be used to provide differential diagnoses and a plan for proper management. This is the first study to differentiate the ALT/WDL from giant cell lipomas based upon the MRI findings to assist conventional histopathological examination and it can be used as a base for further future researches.

**KEY WORDS**: atypical lipomatous tumors/well differentiated liposarcomas, cyclin dependent kinase 4, giant cell lipomas, murine double minute 2

## INTRODUCTION

Lipomas are the most common soft tissue tumors accounting for 50% of all soft tissue lesions with a prevalence of 2.1 per 1000 people[1]. Giant cell lipomas are greater than 10 cm in size with very rare incidence and may predispose to many radiological and pathological diagnostic challenges[2,3]. Histologically, atypical lipomatous tumor (ALT) and well differentiated liposarcoma (WDL) are in fact similar lesions. However, clinically, ALT is located in the extremities whereas WDL is located in the retroperitoneum and mediastinum[4]. ALT/WDL comprise 50% of all liposarcomas followed by myxoid/round cell, dedifferentiated and pleomorphic liposarcoma[5].

ALT/WDL has a risk of dedifferentiation and may progress, causing metastases and even death, therefore reaching a correct diagnosis is important to have proper management. Wide resection is advocated whenever feasible for ALT treatment due to its relatively high risk of recurrence and dedifferentiation[6]. The role of MRI findings in differentiating giant lipomas from ALT/WDL is unclear[7]. Previous studies demonstrated how to make radiological and histological differentiation of all lipomas from ALT/WDL[8-10]. There is no

*Address correspondence to:*
*Asmaa Alkandari, Alzahra, Block 1, Street 126, House 18, Postal code: 47760, Kuwait. Mob: +965 66086119; E-mail: asmaa98k@gmail.com*

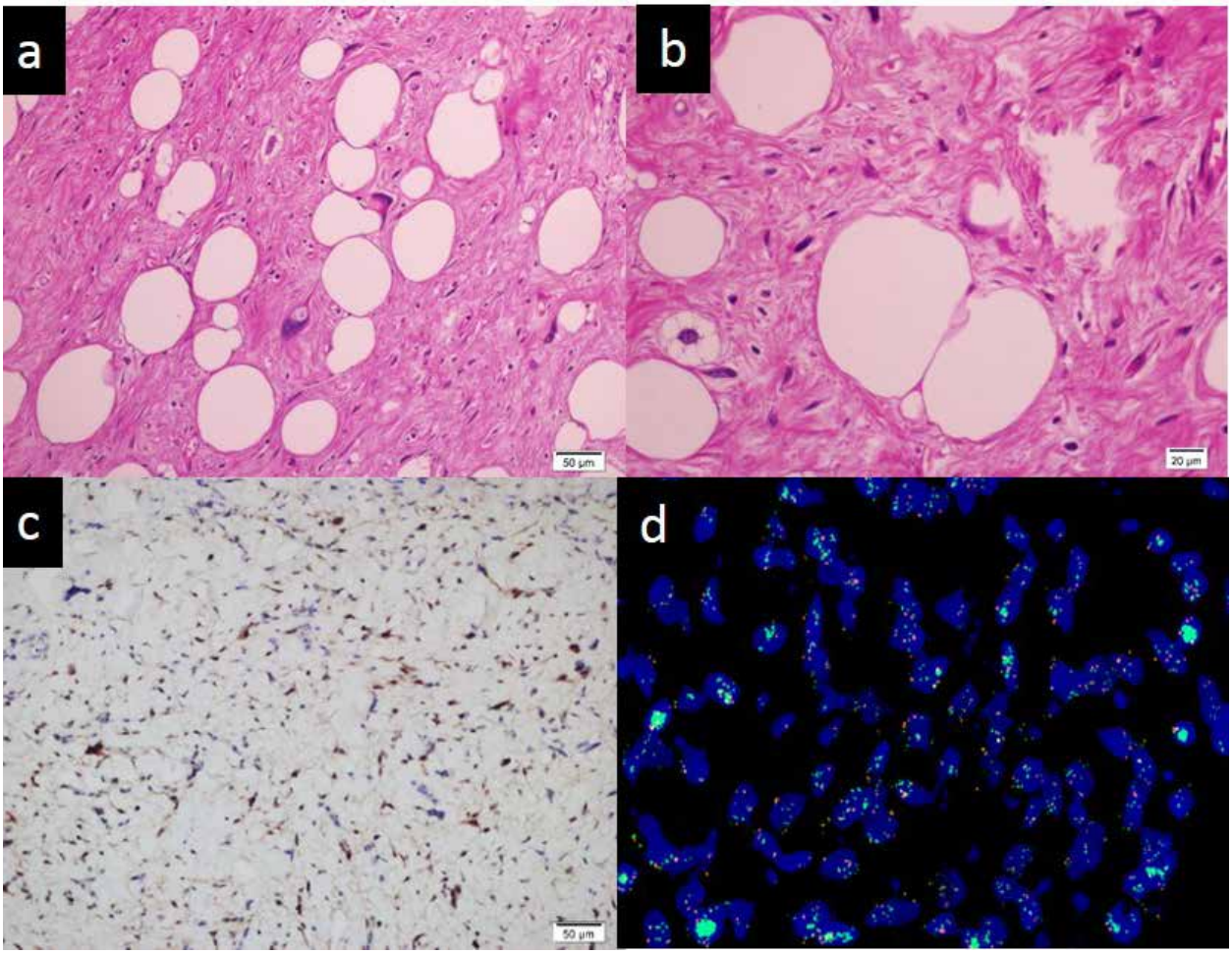


**Figure 1: a, b**. Histology of the well-differentiated liposarcoma. Spindle cells and a few multivacuolated lipoblasts giant cells are embedded in a sclerotic background (HE, ×200, HE, ×400). **c.** Immunohistochemical examination MDM2 and CDK4 were positive. **d.** Fluorescence in situ hybridization for MDM2 amplification status. Green MDM2 signals are located on the long arm of the chromosome 12.

focus to discern giant lipomas from ALT/WDL. The aim of this study is to present our results of whether magnetic resonance imaging (MRI) with selective features can be used to distinguish atypical lipomas from giant lipomas or to select patients who preferably undergo biopsy for the confirmation of diagnosis. Furthermore, this study aims to know if it could be a valuable tool for supporting the diagnoses in addition to classical histopathological examination in resource-limited pathological labs without adequate immunohistochemical or genetic analysis facilities.

## SUBJECTS AND METHODS

A retrospective study was performed in cooperation with Istanbul Medeniyet University Institutional Review Board. Patients who were diagnosed histopathologically with giant lipomas and ALT/WDL and treated at our orthopaedic institution from 2015 to 2020 were involved in this study (Table 1). Factors reviewed include age, gender, lesion location, lesion size based on preoperative MRI (greatest dimension on X, Y, Z axis respectively) and final histological diagnosis. Giant lipomas are defined as lesions more than 10 cm in maximal diameter. The follow up period was determined from the time of surgery to last clinic examination. The musculoskeletal pathologists performed a blinded, independent, randomized review of all histological slides.

Macroscopically, at least 1 slice per centimeter was sampled according to the tumor diameter in lipomas larger than 10 cm and in all cases with a preliminary diagnosis of liposarcoma. Fluorescence in situ hybridization (FISH) examination was not considered necessary in cases that had overt lipoblasts/atypical cells and was positive for murine double-minute type 2 (MDM2) and cyclin-dependent kinase 4 (CDK4) immunohistochemically. FISH examination was performed in all cases which were deeply located, large in diameter, or showed diffuse necrotic reactive changes and was not accompanied

**Table 1:** Patient details

| Patient | Superficial (0) Deep (1) | Septa thickness >2mm No (0) Yes (2) | Contrast (MRI) No (0) Yes (2) | Localisation upp. ext (1) low ext (2) retroperiton, pelvic (3) | Fat component <75% | Contrasting >1cm No (0) Yes (1) | Histological diagnosis |
|---|---|---|---|---|---|---|---|
| 1 | 1 | 2 | 2 | 2 | 1 | 1 | ALT/WDL |
| 2 | 1 | 2 | 2 | 2 | 0 | 1 | ALT/WDL |
| 3 | 1 | 2 | 2 | 2 | 0 | 1 | ALT/WDL |
| 4 | 1 | 2 | 2 | 2 | 0 | 1 | ALT/WDL |
| 5 | 1 | 2 | 2 | 2 | 0 | 1 | ALT/WDL |
| 6 | 1 | 2 | 2 | 3 | 0 | 1 | ALT/WDL |
| 7 | 1 | 2 | 2 | 2 | 0 | 1 | ALT/WDL |
| 8 | 0 | 2 | 0 | 2 | 0 | 0 | ALT/WDL |
| 9 | 0 | 2 | 2 | 2 | 0 | 1 | ALT/WDL |
| 10 | 1 | 2 | 0 | 2 | 1 | 1 | ALT/WDL |
| 11 | 1 | 0 | 2 | 3 | 0 | 1 | ALT/WDL |
| 12 | 1 | 2 | 0 | 1 | 0 | 0 | ALT/WDL |
| 13 | 0 | 2 | 0 | 2 | 0 | 0 | ALT/WDL |
| 14 | 1 | 2 | 2 | 2 | 0 | 1 | ALT/WDL |
| 15 | 1 | 2 | 2 | 2 | 0 | 0 | ALT/WDL |
| 16 | 1 | 2 | 2 | 2 | 1 | 1 | ALT/WDL |
| 17 | 0 | 0 | 2 | 2 | 0 | 0 | Lipoma |
| 18 | 1 | 2 | 0 | 2 | 0 | 0 | Lipoma |
| 19 | 1 | 2 | 0 | 3 | 0 | 0 | Lipoma |
| 20 | 1 | 0 | 0 | 1 | 0 | 0 | Lipoma |
| 21 | 1 | 0 | 0 | 3 | 0 | 0 | Lipoma |
| 22 | 0 | 2 | 0 | 3 | 0 | 0 | Lipoma |
| 23 | 0 | 0 | 0 | 1 | 0 | 0 | Lipoma |
| 24 | 1 | 2 | 0 | 1 | 0 | 0 | Lipoma |
| 25 | 1 | 2 | 0 | 1 | 0 | 0 | Lipoma |
| 26 | 1 | 0 | 0 | 2 | 0 | 0 | Lipoma |
| 27 | 1 | 0 | 0 | 2 | 0 | 0 | Lipoma |
| 28 | 1 | 0 | 0 | 1 | 0 | 0 | Lipoma |
| 29 | 1 | 2 | 0 | 2 | 0 | 0 | Lipoma |
| 30 | 0 | 0 | 0 | 1 | 0 | 0 | Lipoma |
| 31 | 1 | 0 | 0 | 1 | 0 | 0 | Lipoma |
| 32 | 0 | 0 | 0 | 2 | 0 | 0 | Lipoma |
| 33 | 0 | 0 | 0 | 3 | 0 | 0 | Lipoma |
| 34 | 1 | 0 | 0 | 2 | 0 | 0 | Lipoma |
| 35 | 0 | 0 | 0 | 1 | 0 | 0 | Lipoma |
| 36 | 0 | 0 | 0 | 1 | 0 | 0 | Lipoma |
| 37 | 0 | 0 | 0 | 1 | 0 | 0 | Lipoma |
| 38 | 0 | 0 | 0 | 1 | 0 | 0 | Lipoma |
| 39 | 0 | 2 | 0 | 2 | 0 | 0 | Lipoma |
| 40 | 0 | 2 | 0 | 1 | 0 | 0 | Lipoma |
| 41 | 1 | 2 | 0 | 1 | 0 | 0 | Lipoma |
| 42 | 1 | 2 | 0 | 2 | 0 | 0 | Lipoma |
| 43 | 1 | 2 | 2 | 2 | 0 | 0 | Lipoma |
| 44 | 0 | 0 | 0 | 2 | 0 | 0 | Lipoma |
| 45 | 1 | 2 | 0 | 2 | 0 | 0 | Lipoma |

by overt lipoblasts and was not stained with MDM2 and/or CDK4 (Figure 1, 2).

In MRI analysis, the presence of septal diameter >2 mm thickness was assessed. On fat suppressed T1 weighted images with contrast administration, enhancement of more than 1 cm of intratumoral lesions and enhancement of septal structures separately were evaluated. Less than 75% fat component on MRI was also assessed (Figure 3).

Number Cruncher Statistical System 2007 (Kaysville, Utah, USA) program was used for statistical analysis. While evaluating the study data, descriptive statistical methods (mean, standard deviation, median, frequency, ratio, minimum, maximum) as well as the distribution of data were evaluated with the Shapiro-Wilk test. The Mann-Whitney U test was used to compare the quantitative data between two groups that did not show normal distribution. Chi-square analysis was used to determine the relationship between qualitative data. Significance was evaluated at $P<0.01$ and $P<0.05$ levels.

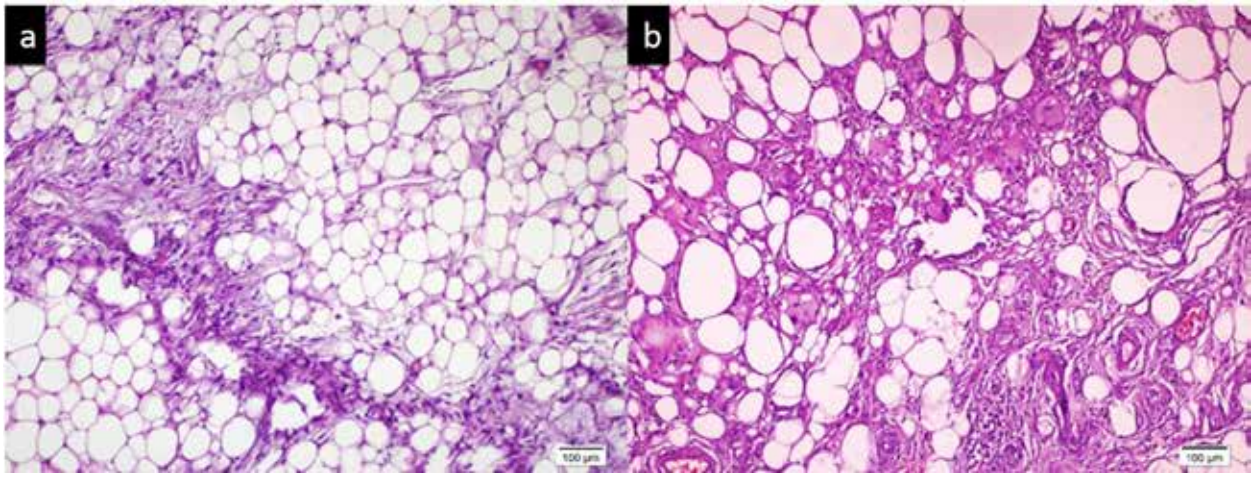


**Figure 2: a.** Lipoma consisting of mature fat cells with only a slight variation in cellular size and shape. **b**. Giant lipomas had prominent variation in cellular size and shape and histiocytic changes.

## RESULTS

Pathologic diagnoses included giant lipomas (n=29) and ALT/WDL (n=16). The mean ages of patients with lipoma and ALT/WDL were 55 years (range: 25-78) and 62.5 years (range: 28-89) respectively and the difference was not statistically significant. Preoperative core needle biopsy was performed for all cases included in this study first to rule out possible malignancy while taking into consideration the size of the lesions. There was no discrepancy in the diagnoses. Of the 16 cases with final diagnosis of ALT/WDL, preoperative biopsy was deemed as giant lipoma in only two cases. FISH analyses was performed for accurate diagnosis of ALT/WDL in these two cases due to suspected MRI findings. Of the 29 cases with the final diagnosis of giant lipoma, 12 cases due to having septa more than 2 mm with no overt lipoblasts/atypical cells histopathologically and was negative for MDM2 and/or CDK4 immunohistochemically underwent FISH analyses.

No statistically significant relationship was found between the groups regarding gender ($P$>0.05).

**Table 2:** Patient characteristics

| Demographic data | Groups | | *P*-value |
|---|---|---|---|
| | Atypical lipoma | Lipoma | |
| Gender | | | 0.579 |
| Women | 8 (50%) | 15 (51.7%) | |
| Men | 8 (50%) | 14 (48.3%) | |
| Localization | | | 0.075 |
| Superficial | 3 (18.8%) | 13 (44.8%) | |
| Deep | 13 (81.3%) | 16 (55.2%) | |
| Anatomic localization | | | 0.019 |
| Upper ext | 1 (6.3%) | 13 (44.8%) | |
| Lower ext | 13 (81.3%) | 12 (41.4%) | |
| Other | 2 (12.5%) | 4 (13.8%) | |

**Table 3:** Radiological features

| Demographic data | Groups | | *P*-value |
|---|---|---|---|
| | Atypical lipoma | Lipoma | |
| Septal thickness >2mm | | | 0.001 |
| No | 1(6.3%) | 17(58.6%) | |
| Yes | 15 (93.8%) | 12(41.4%) | |
| Septal contrast enhancement (MRI) | | | 0.001 |
| Yes | 4(25%) | 27 (93.1%) | |
| No | 12 (75%) | 2 (6.9%) | |
| <75% fat component | | | 0.039 |
| No | 13 (81.3%) | 29 (100%) | |
| Yes | 3 (18.2%) | 0 (0%) | |
| Contrasting greater than 1 cm | | | 0.001 |
| No | 4 (25%) | 29 (100%) | |
| Yes | 12 (75%) | 0 (0%) | |

No statistically significant relationship was found between the groups regarding superficial-deep localization ($P$>0.05). A statistically significant relationship was found between the groups regarding localization ($P$=0.019; $P$<0.05) (Table 2). There was no statistical significance for gender difference between the groups (Table 2). A statistically significant relationship was found between the groups regarding septal thickness >2 mm ($P$=0.001; $P$<0.01). A statistically significant relationship was found between the groups regarding septal contrast enhancement (MRI) ($P$=0.001; $P$<0.01). A statistically significant relationship was found between the groups regarding <75% fat component ($P$=0.039; $P$<0.05). A statistically significant relationship was found between the groups regarding contrasting area greater than 1 cm ($P$=0.001; $P$<0.01) (Table 3).

The tumor size was significantly larger in cases of ALT/WDL in the X, Y and Z axis than in cases of lipoma. The average tumor size of ALT/WDL in X axis was 171.5 mm (range: 60-244) compared to 115

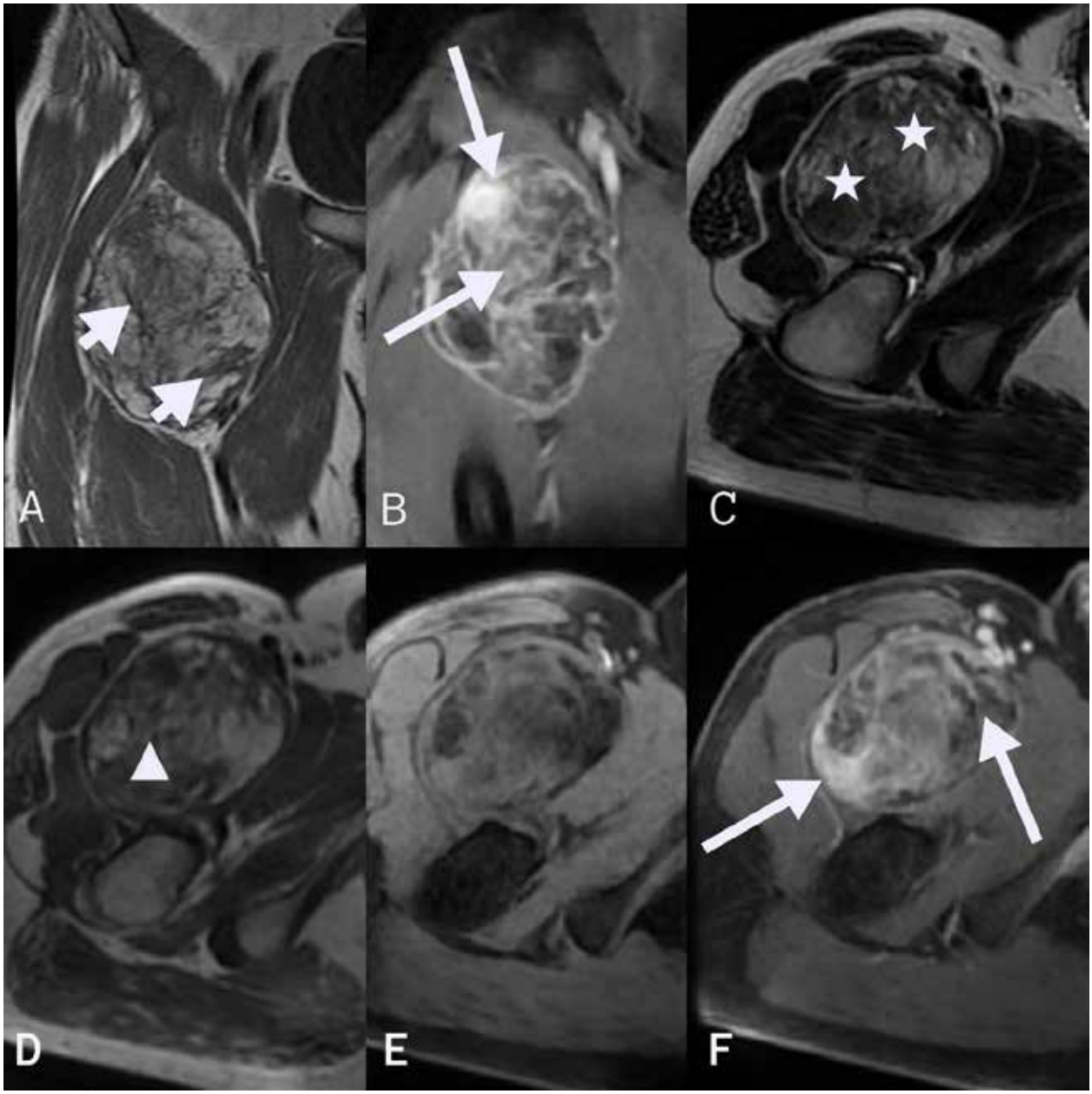


**Figure 3:** 43-year-old male patient with an atypical lipomatous tumor at the right anterior thigh region. (A) Coronal T1-weighted MR (C) axial T2-weighted MR (D) axial T1-weighted MR images with thick septa (>2mm)(short arrows) and less than 75% fat containing component (arrow head and asteriks) (B) Coronal and (F) axial fat-suppressed postcontrast T1-weighted MR images show heterogeneous and nodular enhancement (long arrows). (E) Axial fat-suppressed pre-contrast T1-weighted image shows partial fat suprression and with heterogeneous signal higher than subcutaneous fat.

mm (range: 50-190) in giant cell lipomas. The average tumor size of ALT/WDL in Y axis was 97.5 mm (range: 35-240) compared to 65 mm (range: 32-140) in giant lipomas. In addition, the average size of ALT/WDL in Z axis was 80 mm (range: 38-250) comparing to 55 mm (range: 20-105) in giant lipomas. Depth of the tumor (superficial or deep) was not significantly different between the groups (Table 2). On T2 weighted MRI, septal structures were found in 15 out of 16 cases (93.8%) of ALT/WDL, whereas 12 of 29 cases (41.4%) of giant lipoma displayed septa >2 mm ($P$<0.01; Table 3). Septal contrast enhancement in ALT/WDL was statistically significant compared to giant lipoma group ($P$<0.01; Table 3). For ALT/WDL, 13 of the 16 (81.3%) tumors were localized in the lower extremity ($P$<0.05). For less than 75% fat component in MRI, ALT/WDL group displayed statistically significant difference in comparison with giant lipoma group. Although 3 out of the 16 ALT/WDL patients (18.2%) had less than 75% fat component, no patients with

giant lipoma had less than 75% fat component (Table 3). Enhancement of more than 1 cm of intratumoral lesion in ALT/WDL was statistically significant compared to giant lipoma group ($P$<0.01). There was no contrasting greater than 1 cm in lipoma group (Table 3).

## DISCUSSION

Atypical lipomatous tumor and well differentiated liposarcomas are in fact synonyms that are morphologically and genetically identical. ALT is a locally aggressive tumor of extremities while WDL is located in the retroperitoneum and mediastinum. ALT/WDL accounts for approximately 40-45% of all liposarcomas. If ALT/WDL does not undergo dedifferentiation, they have no potential for metastases. ALT/WDL are reported to have MDM2 and CDK4 amplification as a characteristic genetic alteration[7,8]. MRI is important for differentiating lipoma and ALT/WDL. Thickened or nodular septa more than 2 mm, non-adipose tissue within tumor mass, foci of T2 weighed signal lesions, contrast enhancement and size greater than 5 cm are in favor for ALT/WDL[9,10].

Core needle biopsy prior to final resection is important for diagnosis in selected cases. Beside the classical morphological histopathological examination, immunohistochemical study with CDK4 and MDM2 is important for differential diagnosis[8]. Histologically, atypical hyperchromatic nuclei containing variable sized adipocytes are found scattered throughout the lesion. However, these tumors have fibrous septa complicating the diagnosis and these under-represented cells throughout the lesion usually requires extensive sectioning of the specimens and further investigation of histopathological sections.

The hallmark of ALT/WDL is the presence of lipoblasts with cytoplasmic vacuoles and scalloped nuclei in the histopathological specimens; however these cells are not always presented[4,11].

Lipomas are composed of mature adipocytes that do not have cellular atypia and they are mostly solitary, slow growing and painless masses occurring at the subcutaneous tissue and rarely deep to the fascia. These lipomas usually present as a small mass of less than 2-3 cm and for a lipoma to be referred as a giant one, it should be at least 10 cm in the axial or coronal dimension or weigh a minimum of 1000 g. These types of lipomas can cause compression to the adjacent anatomic structures[12,13].

Giant cell lipomas are rarely mentioned in the English literature with usually only case reports or series, and this can predispose to diagnostic challenges both radiologically and pathologically. Differentiating giant cell lipomas from ALT/WDL is of utmost importance to have an appropriate treatment strategy[2]. Dedifferentiation risk of well differentiated liposarcoma is reported to be between 1-4% and dedifferentiation is associated with a dismal prognosis. Therefore, it is crucial to select patients who could benefit from the preoperative biopsy based on the MRI imaging properties as it is not cost effective to perform biopsy for each case, especially with deep seated lipomatous tumors[14].

After taking the biopsy, it is not always possible to give accurate diagnoses with histopathological examination based on the morphological properties as stated above. Therefore, immunohistochemical staining for CDK4 and/or MDM2 or even one step further for polymerase chain reaction or FISH analyses of CDK4 and/or MDM2 gene amplification may be needed as immunohistochemical staining does not always give positive results in atypical lipomas. The value of MDM2 and CDK4 is to amplify levels using real-time polymerase chain reaction for the differential diagnosis of liposarcomas and their histologic mimickers[15]. Although staining for MDM2 or CDK4 gives low sensitivity of 45% and 41% respectively, it has a specificity of 98% and 92% respectively[16]. However, these resources could not be presented in every pathological unit, especially in the developing countries, and this condition may predispose to a diagnostic challenge.

Nagano *et al* created a scoring system to discriminate lipoma from ALT/WDL by assessing 4 criteria which are the diameter of the lesion, location (deep or superficial,) presence of septa and their thickness, and the lesion contrast enhancement. Based on this scoring system, they reported 100% sensitivity and 77% specificity[10]. Cheng *et al* proposed a complex clinical scoring system based on the clinical parameters including the age, sex, size, location, presence of thick septa, and contrast enhancement of more than 1 cm and fat component detected on MRI of less than 75%[17] Kransdorf *et al* reported that older age, presence of thick septa more than 2 mm, larger tumor size of more than 10 cm, decreased fat composition, and nonfatty nodular/lobular areas within the lesion favors the diagnoses of well differentiated liposarcoma[18]. Ohguri T *et al* also found more prominent septal enhancement of ALT lesion compared to lipomas[19]. The diameter of the lesions is important to differentiate lipomas from ALT/WDL, however giant cell lipomas can cause further diagnostic challenge as they are larger than 10 cm and could also have necrosis histopathologically[20].

There was no tendency toward a certain sex distribution, neither in the patients' group with lipomas nor the patients' group with ALTs/WDL as

stated by the other previous studies[17]. According to Knebel *et al*, the presence of nodules, thick septa, maximum tumor diameter, and contrast enhancement yields a high sensitivity and substantial specificity for differentiating lipomas from ALTs. In our study, we had evaluated both the contrast enhancement of the septa and more than 1 cm nodular or lobular contrast area within the lesion[21]. Small cohort size was the limitation of our study; however it is comparable to other studies in the literature[10,19]. Our cohort comprised of ALT mostly located in thigh as stated by Bird *et al*[22]. However, lipomas were evenly distributed between upper and lower extremities. Taking the age into consideration, in contrast to Bird *et al*[22], the age difference is not statistically significant between the giant cell lipoma and ALT/WDL group in this study.

In contrast with the other studies, there was no statistically significant difference for deep or superficial localization of giant cell lipomas and ALT/WDL[10,23]. In this study, the diameter was not taken into consideration as all tumors were more than 10 cm and different from other studies; therefore, we compared the atypical lipomas with the giant cell lipomas. Although most of the lipomas are located in the subcutaneous tissue, the majority of giant cell lipomas (55.2%) in this cohort study were located deep to fascia resembling most of the atypical lipomas.

This was the first study concerning the differentiation of atypical lipomas from giant lipomas based on MRI characteristics. Although septal contrast enhancement, nonspecific septal diameter, nodular tumoral enhancement of more than 1 cm, and less than 75% fat component of the tumoral lesion can be used as an adjunct to guide for differential diagnoses and management of ALT/WDL, more studies with larger series are needed.

## CONCLUSION

In areas with limited immunohistochemical and genetic analyses resources, MRI could be a valuable adjunct along with the classical histopathological examination for differentiation of ALT/WDLs from giant lipomas.

## ACKNOWLEDGMENT

The authors stated that they have no conflict of interest.

**Author contribution:** Ayse Nur Toksoz Yildirim: substantial contributions to the conception and design of the work; agreement to be accountable for all the aspects of work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved; final approval of the version to be published. Begumhan Baysal: substantial contributions to the conception or design of the work; the acquisition, analysis and interpretation of data for the work. Asmaa Alkandari and Erhan Okay: drafting the work and revising it critically for important intellectual content; final approval of the version to be published; Tulay Zenginkinet and Aykut Celik: acquisition, analysis, and interpretation of data.

## REFERENCES

1. Rydholm A, Berg NO. Size, site and clinical incidence of lipoma. Factors in the differential diagnosis of lipoma and sarcoma. Acta Orthop Scand 1983; 54(6):929-34.
2. Terzioglu A, Tuncali D, Yuksel A, Bingul F, Aslan G. Giant lipomas: a series of 12 consecutive cases and a giant liposarcoma of the thigh. Dermatol Surg 2004; 30(3):463-7.
3. Gungor M, Sir E, Aksoy A, Agirbas S. Giant lipoma extending into two thigh canals: A case report. Acta Orthop Traumatol Turc 2017; 51(3):270-2.
4. Kooby DA, Antonescu CR, Brennan MF, Singer S. Atypical lipomatous tumor/well-differentiated liposarcoma of the extremity and trunk wall: importance of histological subtype with treatment recommendations. Ann Surg Oncol 2004; 11(1):78-84.
5. Yang L, Chen S, Luo P, Yan W, Wang C. Liposarcoma: advances in cellular and molecular genetics alterations and corresponding clinical treatment. J Cancer 2020; 11(1):100-7.
6. Yamamoto N, Hayashi K, Tanzawa Y, Kimura H, Takeuchi A, Igarashi K, *et al*. Treatment strategies for well-differentiated liposarcomas and therapeutic outcomes. Anticancer Res 2012; 32(5):1821-5.
7. Gupta P, Potti TA, Wuertzer SD, Lenchik L, Pacholke DA. Spectrum of fat-containing soft-tissue masses at MR Imaging: the common, the uncommon, the characteristic, and the sometimes confusing. Radiographics 2016; 36(3):753-66.
8. Kammerer-Jacquet SF, Thierry S, Cabillic F, Lannes M, Burtin F, Henno S, *et al.* Differential diagnosis of atypical lipomatous tumor/well-differentiated liposarcoma and dedifferentiated liposarcoma: utility of p16 in combination with MDM2 and CDK4 immunohistochemistry. Hum Pathol 2017; 59:34-40.
9. Brisson M, Kashima T, Delaney D, Tirabosco R, Clarke A, Cro S, *et al*. MRI characteristics of lipoma and atypical lipomatous tumor/well-differentiated liposarcoma: retrospective comparison with histology and MDM2 gene amplification. Skeletal Radiol 2013; 42(5):635-47.
10. Nagano S, Yokouchi M, Setoguchi T, Ishidou Y, Sasaki H, Shimada H, *et al*. Differentiation of lipoma and atypical lipomatous tumor by a scoring system: implication of increased vascularity on pathogenesis of liposarcoma. BMC Musculoskelet Disord 2015; 16:36.
11. Chrisinger JSA. Update on lipomatous tumors with emphasis on emerging entities, unusual anatomic sites, and variant histologic patterns. Surg Pathol Clin 2019; 12(1):21-33.

12. Gaskin CM, Helms CA. Lipomas, lipoma variants, and well-differentiated liposarcomas (atypical lipomas): results of MRI evaluations of 126 consecutive fatty masses. AJR Am J Roentgenol 2004; 182(3):733-9.
13. Allen B, Rader C, Babigian A. Giant lipomas of the upper extremity. Can J Plast Surg 2007; 15(3):141-4.
14. Papanastassiou ID, Piskopakis A, Gerochristou MA, Chloros GD, Savvidou OD, Issaiades D, *et al*. Dedifferentiation of an atypical lipomatous tumor of the thigh - a 6 year follow-up study. J Musculoskelet Neuronal Interact 2019; 19(1):123-6.
15. Shimada S, Ishizawa T, Ishizawa K, Matsumura T, Hasegawa T, Hirose T. The value of MDM2 and CDK4 amplification levels using real-time polymerase chain reaction for the differential diagnosis of liposarcomas and their histologic mimickers. Hum Pathol 2006; 37(9):1123-9.
16. Clay MR, Martinez AP, Weiss SW, Edgar MA. MDM2 and CDK4 immunohistochemistry: Should it be used in problematic differentiated lipomatous tumors?: A new perspective. Am J Surg Pathol 2016; 40(12):1647-52.
17. Cheng Y, Ko AT, Huang JH, Lee BC, Yang RS, Liang CW, *et al*. Developing a clinical scoring system to differentiate deep-seated atypical lipomatous tumor from lipoma of soft tissue. Asian J Surg 2019; 42(8):832-8.
18. Kransdorf MJ, Bancroft LW, Peterson JJ, Murphey MD, Foster WC, Temple HT. Imaging of fatty tumors: distinction of lipoma and well-differentiated liposarcoma. Radiology 2002; 224(1):99-104.
19. Ohguri T, Aoki T, Hisaoka M, Watanabe H, Nakamura K, Hashimoto H, *et al.* Differential diagnosis of benign peripheral lipoma from well-differentiated liposarcoma on MR imaging: is comparison of margins and internal characteristics useful? AJR Am J Roentgenol 2003; 180(6):1689-94.
20. Nakamura Y, Fujisawa Y, Obara S, Saito A, Nakamura Y, Kawachi Y, *et al.* Giant lipoma with fat necrosis of the back mimicking atypical lipomatous tumor in MRI findings. J Clin Exp Dermatol Res 2013; S6:013.
21. Knebel C, Neumann J, Schwaiger BJ, Karampinos DC, Pfeiffer D, Specht K, *et al*. Differentiating atypical lipomatous tumors from lipomas with magnetic resonance imaging: a comparison with MDM2 gene amplification status. BMC Cancer 2019; 19(1):309.
22. Bird JE, Morse LJ, Feng L, Wang WL, Lin PP, Moon BS, *et al.* Non-radiographic risk factors differentiating atypical lipomatous tumors from lipomas. Front Oncol 2016; 6:197.
23. Johnson CN, Ha AS, Chen E, Davidson D. Lipomatous soft-tissue tumors. J Am Acad Orthop Surg 2018; 26(22):779-88.

Original Article

# Factors affecting complications in percutaneous nephrolithotomy

Yahya Doganay[1], Ibrahim Untan[2], Abdullah Demirtas[3]
[1]Department of Urology, Tokat State Hospital, Tokat, Turkey
[2]Department of Urology, Training and Research Hospital, Ahi Evran University, Kirsehir, Turkey
[3]Department of Urology, Faculty of Medicine Hospitals, Erciyes University, Kayseri, Turkey

Kuwait Medical Journal 2023; 55 (4): 300 - 306

## ABSTRACT

**Objective:** To evaluate the factors affecting percutaneous nephrolithotomy complication rates in overall and specific contexts
**Design:** Retrospective study
**Setting:** Urology clinics at Erciyes University Faculty of Medicine Hospitals from 2006 to 2013
**Subjects:** Data from 700 adults treated with percutaneous nephrolithotomy. Records of pre-, peri- and post-operative statements.
**Interventions:** All patients underwent percutaneous nephrolithotomy. Complications, residues and influencing factors were noted. The effects of these variables on procedure-related complications were investigated.
**Main outcome measures:** Patients were grouped according to their body mass index (BMI) and complication grades and then compared in terms of variables. Univariate and multivariate analyses were used to determine predictive factors affecting complication rates.
**Results:** Patients were divided into groups according to complication grades. It was observed that the grade of complications increased significantly as the stone burden, duration of operation, duration of fluoroscopy, and access count increased, ($P$=0.002, 0.001, 0.001, 0.001, respectively). In the entire cohort and small stone subgroup, no association was found; however, in the large stone subgroup, as BMI increased, grade II complications increased and stone clearance decreased ($P$=0.039 and 0.041, respectively). In multivariate analysis, the independent factors in the complicated outcome were stone burden (odds ratio [OR] 1.59) and access count (OR: 1.71).
**Conclusion:** Many of the percutaneous nephrolithotomy complications were included in the lower Clavien grades, and major complications were uncommon. To further reduce complication rates, it would be beneficial to consider the parameters, such as the duration of both surgery and fluoroscopy, access count, BMI (especially those with high stone burden), and stone burden.

**KEY WORDS:** access count, body mass index, complication, percutaneous nephrolithotomy, stone burden

## INTRODUCTION

Urinary stone disease is an important part of urological practice. The main treatment modalities for the urinary stone disease are extracorporeal shock wave lithotripsy, rigid ureterorenoscopy, flexible ureterorenoscopy, percutaneous nephrolithotomy (PCNL), open surgery and laparoscopic surgery. Among these treatment options, PCNL has gained more popularity due to technological improvements in the last decades[1].

The standard treatment for patients with renal calculi before the mid-1950s was open stone surgery[2]. The existence of a relatively avascular plane 5 mm posterior to the midline of the kidney was established through the work of Joseph Hyrtl in 1882 and Max Brödel in 1902[3]. It was not until 1941 that Rupel and Brown would perform the first nephroscopy by placing a rigid cystoscope through a nephrostomy tract so that stones could be removed during open surgery[4]. Willard Goodwin, in 1955, is credited with

*Address correspondence to:*
*Ibrahim Untan, M.D., Kervansaray Mah. 2019. Sok. No:1 40100 Kırşehir, Turkey. Tel: +90 5362708283; +90 3862134515 (ext: 1140); Fax: +90 3862134519; E-mail: ibrahimuntan@erciyes.edu.tr. ORCID ID: 0000-0002-6958-3625.*

performing the first nephrostomy tube placement[5]. By 1976, Fernström and Johansson were the first to describe a technique for extracting renal calculi through a percutaneous nephrostomy under radiologic control[6]. In a later paper, they would illustrate the use of polythene dilators for tract dilation[7]. In 1978, Arthur Smith would describe the first antegrade stent placement and would coin the term "endourology" to describe closed, controlled manipulation of the genitourinary tract[8]. His collaboration with Kurt Amplatz, an interventional radiologist and medical inventor, would lead to numerous innovations which would further advance PCNL[9]. Advances in radiology, from improvements in fluoroscopy to the use of preoperative computed tomography, would further aid in renal access. The development of various lithotripsy devices and the introduction of the holmium laser improved the efficacy of stone fragmentation and clearance. Numerous factors contributed to the development of the modern day-PCNL and this technique will continue to evolve in the future.

Currently, the indications for PCNL include large size renal calculi (>1.5-2 cm), staghorn calculi, upper tract calculi not responding to other modalities of treatment, lower pole stones, cystine nephrolithiasis and stones in anatomically abnormal kidneys[10].

A wide variety of complications can result from this procedure, including bleeding, injury to surrounding structures, infection, positioning-related injuries, thromboembolic disease and even death[11]. Currently, a specialized grading system for the assessment of PCNL-related complications is lacking, and the modified Clavien-Dindo classification of surgical complications is the most widely accepted reporting system. Clavien *et al* proposed a simple and effective system for grading surgical complications in 1992[12]. In 2004, Dindo *et al* modified the original proposal into a more robust and standardized grading system[13]. Since its inception, the Clavien-Dindo classification system has been used to accurately grade surgical complications in numerous urological procedures[14]. Based on the latter classification, the vast majority of PCNL complications are of low grade, while major complications are very rare[15].

The purpose of PCNL is to remove kidney stones with the least renal damage and complications. An uncomplicated PCNL brings with it a rapid recovery period, a short hospitalization and a low analgesic requirement[16]. Predicting complications reduces morbidity and mortality considerably. Identifying the factors that increase these complications can be useful to prevent, diagnose and treat these problems if they occur.

Some factors that are thought to affect the complications and stone clearance in PCNL are stone burden, BMI, access count, duration of fluoroscopy and operation. The current study aimed to evaluate the effect of these factors on the intraoperative and postoperative outcomes of the PCNL procedure in patients with renal stone. Thus, using these factors, it tried to indicate whether the complications could be predicted and recognized early or not.

## SUBJECTS AND METHODS

This study was conducted under the approval of the Ethical Council of Erciyes University, Faculty of Medicine (03.01.2012/2012-73). All individual participants included in the study gave informed written consent prior to starting the study. All procedures performed in human participants abided by the ethical standards of the institutional and/or national research committee and by the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

### Study participants

Data from PCNL surgeries performed on 700 patients in our clinic between January 2006 and May 2013 were retrospectively analyzed. Patients under 18 years of age, without sufficient records, with chronic, unregulated disease, and those who were bedridden were excluded from the study. Those with a history of open stone surgery and who underwent bilateral PCNL were also excluded from the study. Patients with chronic diseases consulted with the relevant specialist before surgery. All patients underwent surgery after being stabilized for their chronic diseases.

### Pre-operative workup

Blood tests including complete blood count, biochemical parameters, bleeding and coagulation times and enzyme-linked immunosorbent assay were performed on all patients before surgery. Urine cultures of all patients were studied, and patients with positive urine cultures underwent surgery under antibiotic pressure after appropriate antibiotic treatment was given, and the urine was sterilized. Medications of patients using antiaggregant or anticoagulant drugs were discontinued 7-10 days before the operation. All patients underwent pre-operative evaluations with direct urinary system radiography and total abdominal ultrasonography. Patients with normal glomerular filtration rates (GFRs) were evaluated with intravenous urography. Patients with low GFRs and with non-opaque stones were evaluated with whole abdominal computerized tomography. The size of the stones was calculated in square millimeters ($mm^2$) by multiplying the largest diameter and the diameter perpendicular to each other. In multiple stones, the surface of each stone was calculated separately and added together. Pre-operatively, patients' age, genders, serum creatinine and GFR values, body mass index

(BMI), stone sizes, and locations in the kidney were recorded. GFR calculations were performed according to the Cockcroft-Gault formula[17].

**PCNL technique**

After administration of general anesthesia while the patient was in the lithotomy position, a 6F ureteral catheter was inserted into the renal pelvis. Then the patient was turned into the prone position, and contrast media was given through the ureteral catheter, after which time, pelvicalyceal system was visualized. Using a 20 cm-long percutaneous access needle (18G Percutaneous Access Needle, Boston Scientific Corporation, Natick MA, USA), access into the suitable calyx was obtained. For dilatation, the Amplatz dilator set (Amplatz Renal Dilator Set, Cook Medical, IN, USA) was used. For all patients, the same type of percutaneous access needle and dilator set were used. An entrance into the pelvicalyceal system was made with a 26F rigid nephroscope, and the stones were fragmented with the aid of an ultrasonic lithotriptor (Swiss Lithoclast, EMS, Nyon, Switzerland). Stone fragments were removed using stone forceps or basket (Perc-N Circle, Cook Medikal, IN, USA). A 16F nephrostomy tube for drainage (Malecot Nephrostomy Catheter, Cook Medical) was placed in the renal pelvis or suitable calyx.

**Postoperative evaluation and data classification**

On the first post-operative day, the residue was evaluated by performing direct urinary system radiography and ultrasonography for opaque and non-opaque stones, respectively. Those who were stone-free or had clinically insignificant residual fragments were considered to have undergone a successful surgery. A stone size ≤4 mm was accepted as clinically insignificant residual fragments[18].

Blood loss requiring transfusion or detection of a hematoma on radiological imaging was considered a hemorrhagic complication. Treatments consisted of conservative follow-up based on lack of mobilization, transfusion or selective embolization. A fever of 38 °C or above was accepted as a complication. In cases that did not respond to antibiotics, a 4.7-F double-J-stent was inserted to eliminate the obstruction. Extravasation complications were diagnosed with antegrade pyelography performed at the end of the operation. Urine leakage persisting 48 hours after removal of the nephrostomy tube was considered prolonged urine leakage. Unless extravasation could be treated by keeping the nephrostomy in place for a few days under antibiotic treatment, a 4.7-F double-J-stent was placed into the area. Unless urine leakage could be treated by high-pressure dressing under antibiotic treatment, a 4.7-F double-J-stent was placed into the area of the nephrostomy. In case of a pneumothorax, a chest drain was inserted. The patient was transferred to the ward with supplemental oxygen administered through a nasal cannula or face mask, depending on

**Table 1:** Patients' descriptives

| Variables | Descriptives | |
|---|---|---|
| | Mean | Median |
| Age (year) | 46.6±13.5 | 48 (18-83) |
| BMI (kg/m$^2$) | 27.4±4.6 | 27.6 (17.1-52.6) |
| Preoperative creatinin (mg/dl) | 1.04±0.4 | 1.0 (0.3-4.9) |
| Preoperative GFR (ml/dk/1.73m$^2$) | 94±30.1 | 94 (26-193) |
| Postoperative creatinin (mg/dl) | 1.05 (± 0.4) | 1.0 (0.3-4.8) |
| Postoperative GFR (ml/dk/1.73m$^2$) | 92 (± 28.7) | 91 (25 – 190) |
| Stone burden (mm$^2$) | 312 (± 205.7) | 251 (120 – 901) |
| Operative time (minutes) | 87.3 (± 46.9) | 85 (30 – 251) |
| Nephrostomized time (days) | 2.7 (± 1.78) | 2 (1 – 15) |
| Fluoroscopy time (minutes) | 14.5(± 9.1) | 2 (2–39) |
| Access count | 1.5 (± 0.8) | 1 (1 – 6) |
| Uni / multi access | 446 (64%) / 254 (36%) | |
| Male / female | 433 (62%) / 267 (38%) | |
| Right / left | 326 (47%) / 374 (53%) | |
| Stone clear | 557 (80%) | |
| Overall complications | 208 (21%) | |
| Hemorrhage | 118 (17%) | |
| Fever | 45 (6%) | |
| Extravasation | 19 (3%) | |
| Prolonged urine leakage | 17(2%) | |
| Pneumothorax | 7 (1%) | |
| Arteriovenous fistula | 2 (<1%) | |

BMI: body mass index; GFR: glomerular filtration rates

**Table 2:** Conversion of complications from specific content to Clavien-Dindo grade

| Overall complications | Descriptives | Clavien-Dindo classification grade | | | | |
|---|---|---|---|---|---|---|
| | | I | II | III | IV | V |
| Hemorrhage | 118 (57%) | 12 (10%) | 97 (82%) | 8 (7%) | 1 (1%) | - |
| Fever | 45 (22%) | 24 (54%) | 15 (33%) | 6 (13%) | - | - |
| Extravasation | 19 (9%) | - | 12 (63%) | 7 (37%) | - | - |
| Prolonged urine leakage | 17 (8%) | - | 10 (59%) | 7 (41%) | - | - |
| Pneumothorax | 7 (3%) | - | - | 6 (86%) | 1 (14%) | - |
| Arteriovenous fistula | 2 (1%) | - | - | 2 (100%) | - | - |
| Total | 208 | 36 (17%) | 134 (64%) | 36 (17 %) | 2 (1%) | - |

**Table 3:** Comparison of variables according to BMI

| Variables | U&N-BMI (n=223) | PO-BMI (n=284) | O-BMI (n=193) | *P* |
|---|---|---|---|---|
| Age (year) | 39.21±14.9 | 46.41±12.6 | 48.90±12.9 | 0.001 |
| Stone burden ($mm^2$) | 303±199.8 | 311±203.3 | 334±210.1 | 0.124 |
| Operative time (mins) | 86.3±45.3 | 88.9±50.3 | 89.0±44.8 | 0.638 |
| Fluoroscopy time (minutes) | 9.5±6.1 | 12.3±7.1 | 14.1±9.1 | 0.416 |
| Access count | 1.3±1.0 | 1.5±0.9 | 1.6±1.1 | 0.300 |
| Overall complications | 47 (21%) | 79 (28%) | 82 (42%) | 0.093 |

BMI: body mass index; U&N-BMI: underweight and normal weight BMI; PO-BMI: pre-obese BMI; O-BMI: obese BMI

the oxygen saturation at the time of discharge from the post-anesthesia care unit. Arteriovenous fistulas were diagnosed by arteriography and treated by selective embolization. These complications were categorized according to the severity based on the Clavien-Dindo Classification, and the treatment was given accordingly.

BMI was categorized according to the World Health Organization BMI classification[19]. The groups consisted of underweight and normal weight, pre-obese and obese patients.

**Statistics**

IBM SPSS version 22.0 (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0 Armonk, NY: IBM Corp.) was used for statistical analysis of the datasets. Categorical measurements were summarized as numbers and percentages, while numerical measurements were summarized as mean and standard deviation. A chi-square test and analysis of variance were used to compare categorical measurements between groups. The variables were integrated into univariate and multivariate regression analysis models to predict PCNL-related complications. The statistical significance level was taken as 0.05 in all tests.

## RESULTS

Different PCNL surgical parameters from 700 patients were evaluated (Table 1). Complications that occurred in 208 patients were converted into grades according to the Clavien-Dindo classification in terms of their severity and choice of management techniques. Most of the complications were grade II (64%) and fortunately, no grade V (death) complications occurred (Table 2).

Patients were separated and analyzed according to their BMI. It was seen that BMI increased with increasing age (*P*=0.001). No significant differences were seen with respect to other parameters (Table 3).

Patients were divided into complication grade groups and compared according to variables. As the stone burden increased, the grade of complications increased significantly (*P*=0.002). A significant correlation was observed between the uptrend of both the duration of operation and fluoroscopy and the grade of complications (*P*=0.001 and 0.001, respectively). It was also observed that as the access count increased, the grade of complication increased significantly (*P*=0.001) as shown in Table 4.

The patients were first divided into two groups according to the mean stone burden, and these groups were divided into three subgroups according to BMI. No significant difference in any parameter according to BMI in the group with less stone burden (<312 $mm^2$, n=305) was found. In the group with high stone burden (≥312 $mm^2$, n=395), grade II complications and stone clearance were significantly high (*P*=0.039 and 0.041, respectively).

Variables were subject to univariate and multivariate analyses in terms of the effects on the complication. In the univariate analysis, the influence variables were BMI (OR: 1.20), fluoroscopy time (OR:

**Table 4:** Comparison of the grades according to the complications in terms of variables

| Variables | Grade 0 | Grade I | Grade II | Grade III | Grade IV | *P* |
|---|---|---|---|---|---|---|
| U&N-BMI | 176 (79%) | 19 (9%) | 26 (12%) | 1 (<1%) | 1 (<1%) | 0.247 |
| PO-BMI | 205 (72%) | 12 (4%) | 54 (19%) | 13 (5%) | - | 0.131 |
| O-BMI | 111 (58%) | 5 (3%) | 54 (28%) | 22 (11%) | 1 (<1%) | 0.061 |
| Stone burden ($mm^2$) | 289±221.3 | 311±201.3 | 398±291.1 | 403±211 | 399±28.8 | 0.002 |
| Operative time (minutes) | 77.3±51.9 | 87.3±61.8 | 124.9±54.5 | 133±55 | 243±10 | 0.001 |
| Fluoroscopy time (minutes) | 9.8±6.6 | 10.4±6.9 | 11.6±7.3 | 15.6±9.7 | 25.1±15 | 0.001 |
| Access count | 1.3±1 | 1.5±1.2 | 1.7±1.4 | 1.9±1.6 | 2.5±0.7 | 0.001 |

BMI: body mass index; U&N-BMI: underweight and normal weight BMI; PO-BMI: pre-obese BMI; O-BMI: obese BMI

1.65), stone burden (OR: 2.28), operative time (OR: 2.49) and multi-access (OR: 3.71). In the multivariate analysis, the independent factors in the complicated outcome were stone burden (OR: 1.59) and multi-access (OR 1.71) as shown in Table 5.

**Table 5:** Univariate and multivariate analysis of variables on complications.

| Variables | *P* | OR | 95% CI |
|---|---|---|---|
| Univariate | | | |
| Stone burden | 0.001 | 2.28 | 1.239 - 3.935 |
| Operative time | 0.012 | 2.49 | 1.155 - 4.532 |
| BMI | 0.038 | 1.20 | 1.003 - 6.912 |
| Fluoroscopy time | 0.021 | 1.65 | 1.004 - 2.844 |
| Multi-access | 0.001 | 3.71 | 1.461 - 9.425 |
| Multivariate | | | |
| Stone burden | 0.003 | 1.59 | 1.130 - 1.480 |
| Multi-access | 0.001 | 1.71 | 1.170 - 1.921 |

BMI: body mass index

## DISCUSSION

Nephrolithiasis is a disease that tends to display and recur in Turkey[20]. Regardless of having a stone-related risk factor, if a person has had urolithiasis once, they tend to have stone disease again and then throughout their life[21]. Therefore, repetitive interventions may be required. With the technological developments in recent years, many studies have been carried out and new methods have been shown to increase patient comfort and establish techniques that will facilitate repetitive interventions that are less invasive.

Today, in the European Association of Urology guidelines, extracorporeal shock wave lithotripsy is recommended as the first choice of treatment for stones with a diameter of ≤20 mm, while PCNL is recommended as the first choice for stones >20 mm[22]. Besides, PCNL is the treatment method that should be considered in the first place in infected stones, in the presence of obstructive uropathy, and in patients with kidney anomalies[23]. As with any surgical procedure, sometimes it is possible to encounter unwanted situations and complications during or after surgery in PCNL. The obesity status of patients who underwent PCNL, the use of multiple access and the long duration of surgery and fluoroscopy can also affect surgical success and complication rates.

In our study, no significant differences in terms of complications between different BMI groups were observed. Similar results have been obtained in other studies on this subject[24]. In our study, contrary to the literature, a comparison of BMI and complication grades was performed in large and small stone subgroups in addition to the overall cohort. In the group with high stone burden, unlike the general group and small stone subgroup, grade II complications were high and stone clearance was low. Only a limited number of studies in the literature address stone burden, but do not address stone burden and BMI as common denominators[25]. These studies generally indicate that BMI and stone burden do not affect PCNL results[26,27]. It is the originality of our study to show that BMI-related effects on the complications occur with increasing stone burden.

In our study, complicated patients were grouped, and stone burden, operation and fluoroscopy times, and access count were found to be correlated with complication grades. The association between the operative time and complications, especially hemorrhaging, has been previously discussed in the literature and similar results with the results of our study have been reported[28]. The correct proportion between fluoroscopy and surgery times is expected, but not enough studies directly addressing the fluoroscopy time and PCNL results have been reported. In our study, a significant relationship between the duration of fluoroscopy and complications was found. In our study, the stone burden was found to be a prognostic factor in terms of complications. Our results are compatible with very few publications in the literature, and our patient number is higher than reported in these publications. Our discovery that access count increases the risk of complications is also supported by the literature[29].

All impact factors discussed in our study were then subject to univariate and multivariate analyses. In this analysis, success, multiple access and stone burden were found to be factors that independently caused an increase in complications. Although the comparisons when individually considered are comparable with those reported in the literature, no publications that examine all these parameters at the same time could be found.

The major limitation of our study is that only stone size and not the number of stones was considered. One good aspect of our study is the exclusion of uncontrolled comorbidities. Thus, this step prevented these conditions from adding outside issues to the procedure-related complications.

## CONCLUSION

In conclusion, it may be appropriate to consider necessary precautions and change the technique while planning PCNL in patients with the high stone burden. During the operation, it would be appropriate to remember that the complications will increase when the fluoroscopy and operation times are prolonged. Knowing that the complication rate will increase in cases of multiple access can help the surgeon to be prepared for any potential complications. The effect

of these factors on stone clearance is also important in terms of sharing pre-operative information with patients. Most importantly, it would be appropriate to keep in mind that the PCNL technique, which was previously known to be reliable in every BMI class, may have higher complications in patients with both high stone burden and high BMI.

**ACKNOWLEDGMENTS**

We thank all patients who participated in the study and those who carried out the extensive clinical and laboratory work. We also would like to express our gratitude to ICO (Partner, Wildcard LCC, New York, NY, USA) for his valuable comments as a native English speaker on our article.

**Authors' contributions:** Ibrahim Untan and Yahya Doganay conceived and designed the study; Yahya Doganay collected data; Ibrahim Untan analyzed the data and wrote the manuscript; Abdullah Demirtas provided supervision.

**Availability of data and materials:** The data that support the findings of this study are available from the corresponding author upon reasonable request.

**Competing interests:** The authors declare no conflict of interest.

**Funding:** The authors received no funding from an external source.

**REFERENCES**

1. Guler A, Erbin A, Ucpinar B, Savun M, Sarilar O, Akbulut MF. Comparison of miniaturized percutaneous nephrolithotomy and standard percutaneous nephrolithotomy for the treatment of large kidney stones: a randomized prospective study. Urolithiasis 2019; 47(3):289-95.
2. Patel SR, Nakada SY. The history and development of percutaneous nephrolithotomy. In: Patel SR, Moran ME, Nakada SY, editors. The history of technologic advancements in urology. Cham: Springer International Publishing; 2018. p. 123-32.
3. Schultheiss D, Engel RM, Crosby RW, Lees GP, Truss MC, Jonas U. Max Brodel (1870-1941) and medical illustration in urology. J Urol 2000; 164(4):1137-42.
4. Rupel E, Brown R. Nephroscopy with removal of stone following nephrostomy for obstructive calculous anuria. J Urol 1941; 46(2):177-82.
5. Palapattu GS, Bloom DA, Smith RB, Boxer RJ. Willard E. Goodwin: educator, innovator and pioneer. J Urol 2004; 172(1):40-4.
6. Fernström I, Johansson B. Percutaneous pyelolithotomy: a new extraction technique. Scand J Urol Nephrol 1976; 10(3):257-9.
7. Shah J, Whitfield H. Urolithiasis through the ages. BJU Int 2002; 89(8):801-10.
8. Smith AD, Lange PH, Miller RP, Reinke DB. Introduction of the Gibbons ureteral stent facilitated by antecedent percutaneous nephrostomy. J Urol 1978; 120(5):543-4.
9. Smith AD. A personal perspective on the origins of endourology and the endourological society. J Endourol 2002; 16(10):705-8.
10. Sabler IM, Katafigiotis I, Gofrit ON, Duvdevani M. Present indications and techniques of percutaneous nephrolithotomy: What the future holds? Asian J Urol 2018; 5(4):287-94.
11. Wollin DA, Preminger GM. Percutaneous nephrolithotomy: complications and how to deal with them. Urolithiasis 2018; 46(1):87-97.
12. Clavien PA, Sanabria JR, Strasberg SM. Proposed classification of complications of surgery with examples of utility in cholecystectomy. Surgery 1992; 111(5):518-26.
13. Dindo D, Demartines N, Clavien P-A. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004; 240(2):205-13.
14. Donat SM. Standards for surgical complication reporting in urologic oncology: time for a change. Urology 2007; 69(2):221-5.
15. Kyriazis I, Panagopoulos V, Kallidonis P, Özsoy M, Vasilas M, Liatsikos E. Complications in percutaneous nephrolithotomy. World J Urol 2015; 33(8):1069-77.
16. Taylor E, Miller J, Chi T, Stoller ML. Complications associated with percutaneous nephrolithotomy. Transl Androl Urol 2012; 1(4):223-8.
17. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976; 16(1):31-41.
18. Altunrende F, Tefekli A, Stein RJ, Autorino R, Yuruk E, Laydner H, *et al*. Clinically insignificant residual fragments after percutaneous nephrolithotomy: medium-term follow-up. J Endourol 2011; 25(6):941-5.
19. Nuttall FQ. Body mass ındex: obesity, BMI, and health: a critical review. Nutr Today 2015; 50(3):117-28.
20. Koyuncu HH, Yencilek F, Eryildirim B, Sarica K. Family history in stone disease: how important is it for the onset of the disease and the incidence of recurrence? Urol Res 2010; 38(2):105-9.
21. Alelign T, Petros B. Kidney stone disease: an update on current concepts. Adv Urol 2018; 2018:3068364.
22. Turk C, Petrik A, Sarica K, Seitz C, Skolarikos A, Straub M, *et al*. EAU guidelines on interventional treatment for urolithiasis. Eur Urol 2016; 69(3):475-82.
23. Assimos D, Krambeck A, Miller NL, Monga M, Murad MH, Nelson CP, *et al*. Surgical management of stones: American Urological Association/ Endourological Society guideline, PART I. J Urol 2016; 196(4):1153-60.
24. Isoglu CS, Suelozgen T, Boyacioglu H, Koc G. Effects of body mass index on the outcomes of percutaneous nephrolithotomy. Int Braz J Urol 2017; 43(4):698-703.

25. Maghsoudi R, Etemadian M, Shadpour P, Radfar MH, Ghasemi H, Shati M. Number of tracts or stone size: which influences outcome of percutaneous nephrolithotomy for staghorn renal stones? Urol Int 2012; 89(1):103-6.
26. Simsek A, Ozgor F, Akbulut MF, Kucuktopcu O, Berberoglu AY, Sarilar O, *et al*. Does body mass index effect the success of percutaneous nephrolithotomy? Turk J Urol 2014; 40(2):104-9.
27. Noureldin YA, Andonian S. Do percutaneous nephrolithotomy outcomes depend on the way stone burden ıs measured? J Endourol 2015; 29(9):975-7.
28. Sugihara T, Yasunaga H, Horiguchi H, Fujimura T, Nishimatsu H, Kume H, *et al*. Longer operative time is associated with higher risk of severe complications after percutaneous nephrolithotomy: analysis of 1511 cases from a Japanese nationwide database. Int J Urol 2013; 20(12):1193-8.
29. Muslumanoglu AY, Tefekli A, Karadag MA, Tok A, Sari E, Berberoglu Y. Impact of percutaneous access point number and location on complication and success rates in percutaneous nephrolithotomy. Urol Int 2006; 77(4):340-6.

Original Article

# Current status of nitrous oxide use in operating rooms of Turkey

Hilmi Demirkiran[1], Arzu Esen Tekeli[1], Cevdet Yardimci[2], Zeki Korkutata[1], Siddik Keskin[4], Nurcin Gulhas[3]
[1]Department of Anesthesiology and Reanimation, University of Van Yuzuncu Yil Medical Faculty, Van, Turkey
[2]Department of Anesthesiology and Reanimation, University of Yozgat Bozok Medical Faculty, Yozgat, Turkey
[3]Department of Anesthesiology and Reanimation, University of Inonu Medical Faculty, Malatya, Turkey
[4]Department of Biostatistics, Van Yuzuncu Yil University Medical Faculty, Van, Turkey

Kuwait Medical Journal 2023; 55 (4): 307 - 313

## ABSTRACT

**Objective:** Investigating the justifications of nitrous oxide ($N_2O$) use in Turkey's hospitals and usage trends during the last five years.
**Design:** A cross-sectional study
**Setting:** A total of 170 university hospitals, training and research hospitals, state hospitals and private hospitals in Turkey.
**Subjects:** Clinical chiefs of 170 anesthesia departments
**Interventions:** A survey was conducted. The Kruskal-Wallis, Mann-Whitney U, Kolmogorov-Smirnov, Chi-square and Fisher tests were performed. This trial was registered at Clinical Trials.gov (NCT04124562).
**Main outcome measure(s):** Hospital type, frequency of $N_2O$ use, how many times general anesthesia was used in a month, number of cases $N_2O$ was used on the day of the study, the status of $N_2O$ use by anesthetists in the last five years, and the reasons for its use were questioned.
**Results:** $N_2O$ use combined with inhaled anesthetics was reported by 119 (72.1%) clinical chiefs of anesthesia departments. The mean number of general anesthesia cases in one month in 165 (84.1%) clinics included in this study was reported to be 95,044. The number of cases using $N_2O$ combined with inhalational anesthetics was 1401 (39.6%) in one day. Regarding $N_2O$ usage in the last five years, 68 (41.2%) anesthetists responded that their usage rate had decreased, 48 (29.1%) stated that they had stopped using, and 47 (28.5%) anesthetists responded that their usage rate was unchanged. Stopping or reducing $N_2O$ use due to environmental or global climate and pollution concerns were observed more frequently in the operating rooms of the university hospitals ($P<0.05$).
**Conclusion:** Despite a reduced usage rate of $N_2O$ in Turkey, it is still higher than that of European countries.

**KEY WORDS:** environmental concerns, nitrous oxide, side effects, Turkey

## INTRODUCTION

Nitrous oxide ($N_2O$), discovered approximately 250 years ago, is the oldest anesthetic in medical practice. $N_2O$ is a relatively reliable anesthetic, and the primary indication for its widespread use is sedation in several interventional procedures[1]. $N_2O$ is used in general anesthesia with other anesthetics in the balanced anesthesia technique because it is ideal as the secondary gas and its intraoperative awareness-preventing effects[2,3]. In addition, this anesthetic agent is promising regarding the treatment of chronic postsurgical pain[4] and treatment-resistant depression[5].

$N_2O$ has the most extended atmospheric life, a period of 114 years, and 298-fold increased global warming potential ($GWP_{100}$) compared to carbon dioxide ($CO_2$)[6]. However, $N_2O$ is not the only anesthetic agent that contributes to global warming[7]. Furthermore, there are concerns about the $N_2O$ use regarding not only its environmental effects, but also its effects on healthcare workers and patients[8,9].

*Address correspondence to:*
*Associate Prof. Dr. Hilmi Demirkiran, Department of Anesthesiology and Reanimation, University of Van Yuzuncu Yil Medical Faculty, Van, Turkey. Tel: +90 5336676188; E-mail: h.dkiran@hotmail.com.*

Nevertheless, the use of $N_2O$ as an anesthetic has been decreasing in several countries for various reasons. The use of $N_2O$ as an anesthetic had decreased to 21% in 2011 in the USA[10]. In a survey conducted in New Zealand and Australia in 2017, the $N_2O$ usage rate based on two out of three respondents was reported as 0%-20%[11]. On the other hand, the data regarding $N_2O$ usage in Turkey is insufficient. Therefore, this study aimed to investigate the rate of $N_2O$ use in Turkey and its potential avoidance reasons.

## SUBJECTS AND METHODS

Overall, 170 different hospitals located in Turkey's various geographical regions participated in this cross-sectional survey study. The hospitals participating in the study were divided into the following four groups: 1) university hospitals; 2) training and research hospitals; 3) state hospitals; and 4) private hospitals. For the sample size, a preliminary study was conducted for the usage rate of $N_2O$, and it was found as 80%. The sample size was determined as 196 with a 5% margin of error at the 95% confidence level[12].

The approval of the local ethics committee (#2019-NCREC-13-02) and necessary formal approvals were obtained for the research. Participation in the study was voluntary. Telephone conversations were conducted with the clinical chiefs of the anesthesia departments for the study. An electronic survey link (see the appendix), created using the SurveyMonkey software, was sent to the participants. A reminder e-mail was sent two weeks later. The access to the online questionnaire was stopped after one month. The data were collected through SurveyMonkey Audience between September 15th, 2019 and October 15th, 2019, following the Helsinki Declaration guidelines. The survey questionnaire was related to the hospital characteristics, $N_2O$ use in the hospital, the number of general anesthesia cases in the hospital over the preceding month, the number of general anesthesia cases on the day of the study, the number of cases of

## Appendix

The survey was constructed using the SurveyMonkey Audience (SurveyMonkey Inc. California, USA).

1. Hospital Name
2. Type of hospital (University hospital / Training and Research Hospital / State Hospital / Private Hospital)
3. Do you use $N_2O$ combined with inhalational anesthetics? (Y/N)
4. What are your reasons to prefer if you use $N_2O$? (You can choose more than one item)
   - Low cost
   - Minimal effect on hemodynamics
   - Analgesic effect
   - Potential to reduce the incidence of chronic pain
   - Fast onset and termination of its effect
   - To be suitable for anesthesia induction
   - No irritation to the respiratory tract
   - The second gas effect when used with other inhalational anesthetics
   - Anxiolytic effect
   - No significant biotransformation
   - Other (please specify)
5. How has your $N_2O$ use changed in your clinic in the last five years? (Stopped, Decreased, Not changed, Increased)
6. In which year did the use of $N_2O$ decrease or stop in your clinic? Not changed / in 2015 and before / 2016 / 2017 / 2018 / 2019
7. Reasons to stop or reduce using $N_2O$ (You can choose more than one option. If your $N_2O$ use has not stopped or decreased, skip this question)
   - Postoperative nausea and vomiting
   - Low efficiency
   - Your concerns about the environmental or global climate
   - Concerns about pollution in operating theaters
   - Other inhalational agents were more advantageous
   - Concern for diffusion hypoxia
   - Effect of increasing pneumothorax / pneumocranium / intestinal gas /air embolism by being transferred to flexible cavities
   - Other (please specify)
8. How many times was general anesthesia applied in your hospital on the day of the study?
9. How many times was inhalation anesthesia applied in your hospital on the day of the study?
10. In how many cases was $N_2O$ administered together with inhalation anesthetics in your hospital on the day of the study?
11. How many times was general anesthesia applied in your hospital in one month?.

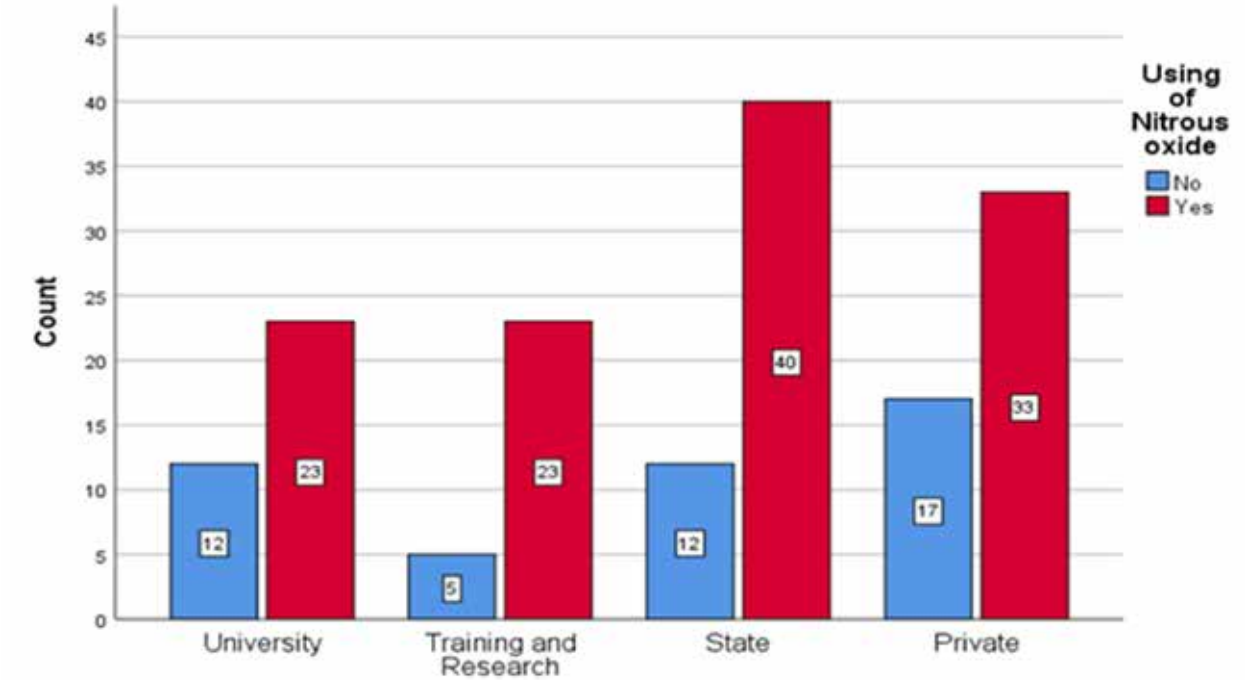


**Figure 1:** The anesthesiologists' $N_2O$ usage status according to hospital types

$N_2O$ use, the trend of $N_2O$ use in the last five years, and the reasons for using or avoiding $N_2O$ in clinical practice. This trial's abstract was registered at Clinical Trials.gov (#NCT04124562).

### Statistical analysis

The mean, standard deviation, median, lowest and highest values, frequency and ratio were used in descriptive statistics of the data. The variables' distributions were evaluated using the Kolmogorov-Smirnov test. The Kruskal-Wallis and Mann-Whitney U tests were performed for independent quantitative data. The Chi-square test was performed to analyze independent qualitative data, and the Fischer test was performed when the conditions of the Chi-square test were not met. A *P*-value of <0.05 was considered statistically significant. Statistical analysis was performed using SPSS 22.0.

## RESULTS

Among the 196 randomly selected hospitals, 170 (85%) anesthesia clinics responded to the questionnaire. The responses of five clinics were excluded due to missing data. Hence, responses from 165 clinics were included in the study.

Among the university, training and research, state and private hospitals, 119 (72%) anesthesiologists reported using $N_2O$ combined with inhalation anesthetics, and 46 (38%) reported not using $N_2O$. No significant difference was determined between the hospital types regarding the rate of using $N_2O$ in combination with inhalational anesthetics (Figure 1).

The hospital types in which the participating anesthetists worked were as follows: 35 (21%) university hospitals, 28 (17%) training and research hospitals, 52 (32%) state hospitals and 50 (30%) private hospitals. In the 165 anesthesia clinics, the average number of reported general anesthesia cases was 95,044 for the month and 7098 for the day of the study. In 3536 (49.8%) of these cases, inhalational anesthesia was used in 1401 (39.2%), of whom $N_2O$ was used in combination (Table 1). The mean number of general anesthesia cases in one month, the number of cases in whom general anesthesia was administered on

**Table 1:** Numbers of general anesthesia (GA) cases according to hospital types

| Number of GA | University | Training and Research | State | Private | Total |
|---|---|---|---|---|---|
| No. of GA 1 day n (%) | 1614(22.7%) | 1399 (19.7%) | 3493 (49.4%) | 582 (8.2%) | 7098 |
| No. of inh. an. 1 day n (%) | 1128 (32.0%) | 1103 (31.1%) | 863(24.4%) | 442 (12.5%) | 3536 |
| No. of inh. an. + $N_2O$ 1 day n (%) | 203(14.5%) | 576 (41.1%) | 495 (35.3%) | 127 (9.1%) | 1401 |
| No. of GA 1 monthn (%) | 32,581 (24.3%) | 30,320 (31.9%) | 20,463 (21.5%) | 11,680 (12.3%) | 95,044 |

Inh. an.: Inhalation anesthesia. Descriptive statistics were presented as numbers and percentages

**Table 2:** Reasons of anesthesiologists for preferring $N_2O$ according to hospital types

| Variable | University | | Training and Research | | State | | Private | | *P*-value |
|---|---|---|---|---|---|---|---|---|---|
| | n | % | n | % | n | % | | % | |
| $N_2O$ usage in general anesthesia | | | | | | | | | 0.303 |
| No | 12 | 34.3 | 5 | 17.9 | 12 | 23.1 | 17 | 34.0 | |
| Yes | 23 | 65.7 | 23 | 82.1 | 40 | 76.9 | 33 | 66.0 | |
| If you are using $N_2O$, what are your reasons for preferring it? | | | | | | | | | |
| Low cost | 10 | 43.5 | 3 | 13.0 | 16 | 40.0 | 16 | 48.5 | 0.188 |
| Minimal effect on hemodynamics | 7 | 30.4 | 5 | 21.7 | 10 | 25.0 | 11 | 33.3 | 0.974 |
| Analgesic effect | 18 | 78.3 | 19 | 82.6 | 37 | 92.5 | 29 | 87.9 | 0.234 |
| Potential to reduce the incidence of chronic pain | 2 | 8.7 | 1 | 4.3 | 3 | 7.5 | 1 | 3.0 | >0.05 |
| Fast onset and termination of its effect | 5 | 21.7 | 10 | 43.5 | 14 | 35.0 | 17 | 51.5 | 0.170 |
| No irritation to the respiratory tract | 1 | 4.3 | 0 | 0.0 | 3 | 7.5 | 5 | 15.2 | >0.05 |
| To be suitable for anesthesia induction | 6 | 26.1 | 1 | 4.3 | 2 | 5.0 | 8 | 24.2 | 0.064 |
| Second gas effect | 14 | 60.9 | 16 | 69.6 | 30 | 75.0 | 24 | 72.7 | 0.358 |
| Anxiolytic effect | 0 | 0.0 | 1 | 4.3 | 1 | 2.5 | 2 | 6.1 | >0.05 |
| No significant biotransformation | 1 | 4.3 | 2 | 8.7 | 0 | 0.0 | 1 | 3.0 | >0.05 |
| Other | | | | | | | | | |
| Otolaryngology cases | 0 | 0.0 | 0 | 0.0 | 1 | 2.5 | 0 | 0.0 | >0.05 |
| Infrastructure problem | 1 | 4.3 | 0 | 0.0 | 1 | 2.5 | 2 | 6.1 | >0.05 |

Descriptive statistics were presented as numbers and percentages; #Chi-square, statistically significant result ($P<0.05$)

the day of the study, and the number of cases with inhalational anesthetic use in general anesthesia cases were significantly higher in the university hospitals and training and research hospitals compared to the state and private hospitals ($P<0.05$).

No significant difference was observed between the university and the training and research hospitals concerning the number of general anesthesia cases performed in one month, the number of general anesthesia cases on the day of the study, and the number of cases in whom inhalational anesthetics were used for general anesthesia. Moreover, no significant differences were determined between the state and private hospital groups regarding the mean number of general anesthesia cases in one month, the number of general anesthesia cases on the day of the study, and the number of cases in whom inhalational anesthetics were used (Table 1). The number of cases in whom $N_2O$ was used as the second gas was significantly higher in the training and research hospital group compared to the university, state and private hospital groups ($P<0.05$). $N_2O$ usage rate during general anesthesia did not differ significantly among the four hospital types (Table 1). Furthermore, the reasons for the $N_2O$ preference of the anesthetists did not differ significantly among the four hospital groups. The reasons for anesthesiologists' $N_2O$ preference were presented in Table 2.

When the last five years were considered, 47 (28.5%) anesthesia clinics reported that $N_2O$ usage had not changed, whereas 68 (41.2%) reported that it had decreased, 48 (29.1%) reported that it had stopped, and 2 (1.2%) reported that it had increased (Table 3). Notably, the decrease or cessation rate of $N_2O$ use was significantly higher in university hospitals in the last five years compared to the other hospital types.

On the other hand, the reduction or cessation rate of $N_2O$ use in private hospitals in the last five years was significantly higher than that of state hospitals ($P<0.05$; Table 3). Reducing or stopping $N_2O$ use for causes related to environmental or global climate or pollution concerns in operating theatres was significantly higher in the university hospitals than the training and research, state and private hospitals ($P<0.05$). No significant difference was determined among the hospital groups regarding the causes for stopping or decreasing $N_2O$ use (Table 3).

## DISCUSSION

This study revealed that even though $N_2O$ use has decreased in Turkey in recent years, 72% of anesthetists in all hospital groups have preferred using $N_2O$ combined with inhalational anesthetics. In a survey conducted in 2009, Chinkungwa *et al* reported that 64.3% of participants did not use $N_2O$, whereas 33.3% used $N_2O$ in general anesthesia practice[13]. A more recent study conducted in Australia and New Zealand to determine general anesthetic selection reported that 66% of respondents rarely used $N_2O$[11]. In a survey conducted in 2012 among the Scandinavian countries' public hospitals, the rate of $N_2O$ use combined with inhaled anesthetics was reported to decrease to 12%; this rate was lowest in Denmark (0.6%) and highest in Iceland (38.6%)[14]. Furthermore, approximately eight years ago, the usage rate of $N_2O$ as an anesthetic in the USA had decreased to 21%[10]. The $N_2O$ usage rate in the USA (39.6%) was higher than in most European

**Table 3:** The status of anesthesiologists' $N_2O$ use in the last five years according to hospital types

| Variable | University | | Training and Research | | State | | Private | | *P*-value |
|---|---|---|---|---|---|---|---|---|---|
| | n | % | n | % | n | % | n | % | |
| In which direction has the frequency of nitrous oxide usage changed in your hospital in the last five years? | | | | | | | | | 0.002 |
| Decreased | 21 | 60.0 | 12 | 42.9 | 16 | 30.8 | 19 | 38.0 | |
| Stopped | 11 | 31.4 | 7 | 25.0 | 12 | 23.1 | 18 | 36.0 | |
| Not changed | 3 | 8.6 | 8 | 28.6 | 23 | 44.2 | 13 | 26.0 | |
| Increased | 0 | 0.0 | 1 | 3.6 | 1 | 1.9 | 0 | 0.0 | |
| Since which year has nitrous oxide use decreased/ stopped in your hospital? | | | | | | | | | 0.003 |
| Not decreased | 2 | 5.7 | 8 | 28.6 | 22 | 42.3 | 15 | 30.0 | |
| 2015 and before | 21 | 60.0 | 10 | 35.7 | 12 | 23.1 | 16 | 32.0 | |
| 2016 | 4 | 11.4 | 4 | 14.3 | 6 | 11.5 | 7 | 14.0 | |
| 2017 | 5 | 14.3 | 2 | 7.1 | 5 | 9.6 | 6 | 12.0 | |
| 2018 | 2 | 5.7 | 4 | 14.3 | 4 | 7.7 | 4 | 8.0 | |
| 2019 | 1 | 2.9 | 0 | 0.0 | 3 | 5.8 | 2 | 4.0 | |
| What is your reason to reduce and/or stop using nitrous oxide? | | | | | | | | | |
| Vomiting | 13 | 37.1 | 7 | 25.0 | 7 | 13.5 | 11 | 22.0 | 0.082 |
| Low efficiency | 4 | 11.4 | 0 | 0.0 | 3 | 5.8 | 7 | 14.0 | 0.142 |
| Environmental/global climate concerns | 19 | 54.3 | 9 | 32.1 | 14 | 26.9 | 14 | 28.0 | 0.038 |
| Concerns about pollution in operating theaters | 23 | 65.7 | 8 | 28.6 | 21 | 40.4 | 20 | 40.0 | 0.018 |
| Other inhalational agents being more advantageous | 5 | 14.3 | 2 | 7.1 | 7 | 13.5 | 6 | 12.0 | 0.827 |
| Concern about diffusion hypoxia | 14 | 40.0 | 8 | 28.6 | 19 | 36.5 | 22 | 44.0 | 0.589 |
| Expansion in flexible cavities | 21 | 60.0 | 12 | 42.9 | 25 | 48.1 | 26 | 52.0 | 0.557 |
| Other | | | | | | | | | |
| I prefer short-acting opioids | 2 | 5.7 | 2 | 7.1 | 0 | 0.0 | 2 | 4.0 | >0.05 |
| Infrastructure problem | 0 | 0.0 | 1 | 3.6 | 0 | 0.0 | 0 | 0.0 | >0.05 |
| Type of operation | 0 | 0.0 | 2 | 7.1 | 0 | 0.0 | 3 | 6.0 | >0.05 |
| Causes cognitive impairment | 0 | 0.0 | 1 | 3.6 | 0 | 0.0 | 0 | 0.0 | >0.05 |

Descriptive statistics were presented as numbers and percentages. #Chi-square, statistically significant result ($P<0.05$)

countries and similar to the Icelandic rate. Unlike previous studies, the rate of $N_2O$ use in the present study did not differ among the university, training and research, state and private hospital types.

The most common reasons for choosing $N_2O$ were associated with previous experience, low cost, the anesthetic effect's rapid onset and termination, anxiolytic effect, to reduce the minimum alveolar concentration of inhaled anesthetics, as well as the $N_2O$'s features, such as not depressing respiration and not getting metabolized[14]. In this study, the most common reason for $N_2O$ use was its analgesic feature.

In 2007, Sheraton *et al* reported that 57% of anesthetists in the UK had reduced the use of $N_2O$ in the preceding five years[15]. A 2011 survey on the use of $N_2O$ in Scandinavian countries reported that 34% of clinics had stopped $N_2O$ use, 62% had reduced its use, and 4% had not changed their usage rate[14]. In the present study, 41.2% of the participants responded that $N_2O$ use had decreased, and 29.1% responded that they had stopped using $N_2O$. Of the anesthetists who responded to the question "In which year did $N_2O$ use decrease/stop?", 28.5% responded that usage was "unchanged," 35.8% stated that usage had decreased or stopped "before 2015," 12.7% stated that usage had decreased or stopped in 2016, 10.9% responded that usage had decreased or stopped in 2017, and few responded that usage had decreased or stopped in 2018 and 2019.

In a 2019 survey conducted in Canada, anesthetists' anesthetic gas selection rate based on the environmental effects was determined as 40.8%[16]. In a survey among the members of the American Society of Anesthesiologists in 2013, 13% of respondents stated that they considered the global warming potential when choosing an inhalational anesthetic agent[17]. In the present study, 33.9% of anesthesiologists stated that they reduced $N_2O$ use due to environmental or global climate concerns.

The harmful effects of waste anesthetic gases (WAG) on human health are related to their concentrations and the exposure times in the working environment. No health risks occur when the exposure to WAG is under the limits set by the law (25-100 ppm)[1,8]. However, some studies justify anesthetists' concerns regarding the pollution associated with $N_2O$ that can occur in operating theatres[9,18]. In a study conducted between 2013 and 2017, Zaffina *et al* reported that the environmental concentration of $N_2O$ could be reduced, and the chronic exposure of

healthcare personnel could be prevented by a suitable gas cleaning system[19].

Notably, all inhalation anesthetics influence global warming and ozone layer depletion, and minimum alveolar concentration and fresh gas flow rate affect the occurrence of anesthetic gases' environmental effects[20]. The effects of anesthetic gases (per kilogram) on global warming are compared to the $GWP_{100}$ effect of $CO_2$. For example, the effect of desflurane is 2540 times greater than that of $CO_2$, that of isoflurane is 510 times greater, that of $N_2O$ is 298 times greater, and that of sevoflurane is 130 times greater. The greenhouse gas effect of $N_2O$ was determined to be similar to desflurane when used in high concentrations. In the UK, inhalation anesthetics account for 2.5% of greenhouse gas emissions originating from the national health sector[6]. However, two-thirds of the global $CO_2$ emission associated with $N_2O$ consists of agricultural activities, and only 1% is associated with anesthetics. In Turkey, $N_2O$ emissions from medical sources are not measured, probably because of their negligible amounts[20,21].

When combined with other inhalation anesthetics, propofol and opioids, $N_2O$ reduces the requirement for anesthetics[13]. Even though $N_2O$ inhibits the activity of methionine synthase and vitamin B12, the relationship between $N_2O$ and increased DNA damage has not been demonstrated clearly in humans[9]. However, guidelines should be followed to minimize occupational exposure[22]. $N_2O$ was determined to be associated with patient morbidity; on the other hand, it did not increase mortality[4]. The risk of postoperative nausea and vomiting increases with $N_2O$ anesthesia, but prophylactic antiemetic therapy has been shown to reduce this effect[4]. However, when the primary risk for postoperative nausea and vomiting is low, $N_2O$ has little effect on nausea and vomiting[23]. Its proven side effects are enlargement of air-filled spaces, absorption atelectasis, neurotoxicity, environmental pollution and substance addiction[4]. Moreover, no evidence exists regarding the toxic effects of WAGs in pregnant women when exposed under legal limits[1].

Despite improvements in anesthesia devices and waste systems, cleaning the anesthetic gases from the operating room environment cannot be guaranteed. Moreover, new ideal anesthetic gases have not yet been discovered. Therefore, $N_2O$ use should not be stopped or abandoned for exposure prevention and environmental pollution concerns. Nevertheless, to improve the working environment, appropriate systems for waste and ventilation should be installed, low flow with closed-circuit anesthesia, and a double mask system for inhalation and induction should be used[8,24].

Our study had some limitations. The major limitation of this study was that it did not question the duration of $N_2O$ use and the amount of fresh gas flow. Another limitation was not to question the use of other halogenated anesthetic gases with greenhouse gas effects and the avoidance status of unnecessary fresh gas flow rate. Moreover, whether guidelines for $N_2O$ use were present in the clinics was not questioned.

## CONCLUSION

Even though the usage rate of $N_2O$ has decreased in Turkey, it is still higher than the rate in European countries. In Turkey, anesthesiologists' preference for $N_2O$ is based on potential risks, environmental pollution concerns and effects as an analgesic and a secondary gas. Nevertheless, this study's data may provide an opportunity to review the anesthesiologists' reasons to prefer $N_2O$ in Turkey.

## ACKNOWLEDGMENT

We thank all clinicians who participated in our study.

**Authors' contributions:** Hilmi Demirkiran designed the study, drafted the work and wrote the manuscript. Arzu Esen Tekeli, Cevdet Yardimci and Zeki Korkutata collected data, reviewed the literature, interpreted the data and contributed to editing the manuscript. Siddik Keskin and Nurcin Gulhas contributed to data collection, revised the scientific background of the study, made statistical analysis and interpreted the data. All authors read and approved the final manuscript.

**Disclosure statement:** The authors declare that they have no competing interests.

**Funding:** None

## REFERENCES

1. Buhre W, Disma N, Hendrickx J, DeHert S, Hollmann MW, Huhn R, *et al*. European Society of Anaesthesiology Task Force on Nitrous Oxide: a narrative review of its role in clinical practice. Br J Anaesth 2019; 122(5):587-604.
2. Nanda P, Prakash P, Choudhury KJ, Singh VP, Prakash S. A prospective, randomised, controlled clinical trial to evaluate the effect of nitrous oxide on propofol requirement in elective craniotomy in which entropy was used to measure depth of anaesthesia. South Afr J Anaesth Analg 2016; 22(1):25-9.
3. Zafirova Z, Sheehan C, Hosseinian L. Update on nitrous oxide and its use in anesthesia practice. Best Pract Res Clin Anaesthesiol 2018; 32(2):113-23.
4. Chan MT, Peyton PJ, Myles PS, Leslie K, Buckley N, Kasza J, *et al*. Chronic postsurgical pain in the Evaluation of Nitrous Oxide in the Gas Mixture for Anaesthesia (ENIGMA)-II trial. Br J Anaesth 2016; 117(6):801-11.

5. Nagele P, Duma A, Kopec M, Gebara MA, Parsoei A, Walker M, *et al*. Nitrous oxide for treatment-resistant major depression: a proof-of-concept trial. Biol Psychiatry 2015; 78(1):10-8.
6. Sherman J, McGain F. Environmental sustainability in anesthesia: pollution prevention and patient safety. Adv Anesth 2016; 34(1):47-61.
7. Alexander R, Poznikoff A, Malherbe S. Greenhouse gases: the choice of volatile anesthetic does matter. Can J Anesth 2018; 65(2):221-2.
8. Deng HB, Li FX, Cai YH, Xu SY. Waste anesthetic gas exposure and strategies for solution. J Anesth 2018; 32(2):269-82.
9. Eftimova B, Sholjakova M, Mirakovski D, Hadzi-Nikolova M. Health effects associated with exposure to anesthetic gas nitrous oxide-N2O in clinical hospital–Shtip Personel. Open Access Maced J Med Sci. 2017; 5(6):800-4.
10. McKay RE. Nitrous oxide and cardiovascular outcome: perspective from the POISE trial. Anesth Analg 2013; 116(5):962-5.
11. McGain F, Bishop JR, Elliot-Jones LM, Story DA, Imberger GL. A survey of the choice of general anaesthetic agents in Australia and New Zealand. Anaesth Intensive Care 2019; 47(3):235-41.
12. Daniel WW, Cross CL. Biostatistics: a foundation for analysis in the health sciences. 10th ed. United States of America: Wiley; 2018.
13. Chikungwa M. Current nitrous oxide use in general anaesthesia: an electronic survey. Eur J Anaesthesiol 2009; 26(12):1088-90.
14. Husum B, Stenqvist O, Alahuhta S, Sigurdsson GH, Dale O. Current use of nitrous oxide in public hospitals in Scandinavian countries. Acta Anaesthesiol Scand 2013; 57(9):1131-7.
15. Sheraton T, Gildersleve C, Hall JE. The use of nitrous oxide in paediatric anaesthetic practice in the United Kingdom: a questionnaire survey. Anaesthesia 2007; 62(1):62-6.
16. Petre MA, Bahrey L, Levine M, van Rensburg A, Crawford M, Matava C. A national survey on attitudes and barriers on recycling and environmental sustainability efforts among Canadian anesthesiologists: an opportunity for knowledge translation. Can J Anesth 2019; 66(3):272-86.
17. Ard Jr JL, Tobin K, Huncke T, Kline R, Ryan SM, Bell C. A survey of the American Society of Anesthesiologists regarding environmental attitudes, knowledge, and organization. A A Case Rep 2016; 6(7):208-16.
18. Maroufi SS, Gharavi M, Behnam M, Samadikuchaksaraei A. Nitrous oxide levels in operating and recovery rooms of Iranian hospitals. Iran J Public Health 2011; 40(2):75-9.
19. Zaffina S, Lembo M, Gilardi F, Bussu A, Pattavina F, Tucci MG, *et al*. Nitrous oxide occupational exposure in conscious sedation procedures in dental ambulatories: a pilot retrospective observational study in an Italian pediatric hospital. BMC Anesthesiol 2019; 19(1):42.
20. Weinberg L, Tay S, Aykanat V, Segal R, Tan CO, Peyton P, *et al*. Changing patterns in volatile anaesthetic agent consumption over seven years in Victorian public hospitals. Anaesth Intensive Care 2014; 42(5):579-83.
21. Seventh National Communication Of Turkey Under The UNFCCC [Internet]. Ankara, Turkey: Minister of Environment and Urbanization; c2018 [cited 2020 March 03rd]. Available from: https://unfccc.int/sites/default/files/resource/496715_Turkey-NC7-1-7th%20National%20Communication%20of%20Turkey.pdf.
22. Controlling Exposures to Nitrous Oxide During Anesthetic Administration [Internet]. National Institute for Occupational Safety Health; 2014 [cited 2020 March 03]. Available from: https://www.cdc.gov/niosh/docs/94-100/.
23. Gan TJ, Diemunsch P, Habib AS, Kovac A, Kranke P, Meyer TA, *et al*. Consensus guidelines for the management of postoperative nausea and vomiting. Anesth Analg 2014; 118(1):85-113.
24. Greening the operating room and perioperative arena: environmental sustainability for anesthesia practice [Internet]. Illinois: American Society of Anaesthesiologists; c2015 [cited 2020 March 03rd]. Available from: https://www.asahq.org/about-asa/governance-and-committees/asa-committees/committee-on-equipment-and-facilities/environmental-sustainability/greening-the-operating-room.

Original Article

# Comparison of clinical outcome between β-lactam/β-lactamase inhibitor (BLBLI) and carbapenem for treatment of extended-spectrum β-lactamase (ESBL) urinary tract infection

Nur Hafiza Muharam[1,2], Nurahan Maning[2], Zakuan Zainy Deris[1,3]
[1]Department of Medical Microbiology and Parasitology, School of Medical Sciences, Universiti Sains Malaysia Health Campus, 16150 Kubang Kerian, Kelantan, Malaysia
[2]Department of Pathology, Hospital Raja Perempuan Zainab II, 15586 Kota Bharu, Kelantan, Malaysia
[3]Infection Control and Hospital Epidemiology Unit, Hospital Universiti Sains Malaysia, Universiti Sains Malaysia Health Campus, 16150 Kubang Kerian, Kelantan, Malaysia

Kuwait Medical Journal 2023; 55 (4): 314 - 321

## ABSTRACT

**Objective**: The aim of this study was to compare the outcomes between β-lactam/β-lactamase inhibitor combinations (BLBLI) and carbapenem for the treatment of extended-spectrum β-lactamase (ESBL)-producing Enterobactaeriacae urinary tract infections (UTI).
**Design**: Retrospective study
**Setting**: Hospital Raja Perempuan Zainab II, Kota Bharu, Kelantan, Malaysia
**Subjects**: A total of 79 patients with ESBL-producing Enterobactaeriacae urinary tract infection between January 2015 and December 2017 that fulfill inclusion and exclusion criteria were eligible in this study.
**Intervention**: Medical records of all the patients were reviewed and the data were collected retrospectively.
**Main outcome measures**: Clinical and microbiological outcomes were evaluated in a retrospective study of patients with ESBL-producing Enterobactaeriacae UTI from a tertiary center in Malaysia. Demographic data, clinical and microbiological characteristics, and outcomes in patients received definitive therapy with BLBLI and carbapenem were compared. Further analysis was done by controlling the confounders using multiple logistic regression.
**Results**: Clinical failure rate for those treated with BLBLI vs. carbapenem were 18.8% (6/32) vs. 23.4% (11/47) respectively. After adjusting for the confounders, the only significant risk factors for clinical failure were severe sepsis or septic shock at presentation (OR: 21.812; 95% CI: 3.735, 127.373; *P*=0.001), presence of external catheter (OR: 9.741; 95% CI: 1.720, 55.162; *P*=0.010), and presence of other concomitant infection (OR: 5.168; 95% CI: 1.272, 20.990; *P*=0.022). Empirical and definitive treatment with BLBLI were not associated with increased risk of clinical failure.
**Conclusion**: BLBLI was non-inferior to carbapenem for treatment of ESBL-producing Enterobactaeriacae UTI.

**KEY WORDS:** carbapenem, ESBL, urinary tract infection, β-lactam/β-lactamase inhibitor

## INTRODUCTION

Extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae are a major health concern worldwide[1,2]. The infections due to these organisms lead to limited choice of chemo-therapeutic agents and are associated with higher mortality rates compared to susceptible counterparts[3]. Although the plasmid-mediated ESBL-producing organism was first described in the early 1960s[4], the earliest reports from Malaysia were documented in 2000[5,6]. Ariffin *et al* found more than half of the *Klebsiella pneumoniae* isolated from febrile neutropenia patients were ESBL

*Address correspondence to:*
*Zakuan Zainy Deris, PhD, Department of Medical Microbiology and Parasitology, School of Medical Sciences, Universiti Sains Malaysia Health Campus, 16150 Kubang Kerian, Kelantan, Malaysia. Tel: 609-7676250; E-mail: zakuan@usm.my*

producers[5]. $bla_{SHV}$, $bla_{CTXM}$ and $bla_{TEM}$ were the most commonly encountered ESBL genes in Malaysia which contributed to 94.4%, 79.6% and 57.4% of *K. pneumoniae* respectively[7]. Almost eighty percent of the ESBL-producing *K. pneumoniae* harboured more than ESBL genes[7]. These ESBL genes were responsible for Enterobacteriaceae resistance in environment and veterinary sectors in Malaysia[8,9].

Earlier studies demonstrated carbapenems are antibiotics of choice in treating ESBL-producing Enterobactaeriacae infections[1,2]. Besides their stability to most β-lactamases hydrolytic activity, carbapenems have broad spectrum activity[10]. Overuse of this drug not only contributes to selective pressure of carbapenem-susceptible organisms, but it also associated with emergence of carbapenem-resistant organisms[2,10,11]. Thus, it is necessary to use carbapenem judiciously and more effort is needed to look for possible effective alternatives. In view of conflicting results on the use of β-lactam/β-lactamase inhibitor combinations (BLBLI) for bacteraemia and severe ESBL-producing Enterobactaeriacae infections, we conducted a study comparing the clinical efficacy between BLBLI and carbapenem for ESBL-producing Enterobactaeriacae urinary tract infections.

## SUBJECTS AND METHODS

### Study design and participants

This retrospective study was conducted in Hospital Raja Perempuan Zainab II, the largest hospital on the east coast of Peninsular Malaysia, from 1st of January 2015 to 31st of December 2017. It was approved by the Human Research Ethics Committee (JEPeM), Universiti Sains Malaysia (JEPeM code: USM/JEPeM/17020079) and Medical Research and Ethics Committee (MREC), Ministry of Health Malaysia (NMRR-17-120-34201).

All inpatients with urinary symptoms and positive urine culture of ESBL-producing organism after 48 hours of admission within the study period were included in this study. The ESBL isolated from urine specimens were susceptible to amoxicillin/clavulanate, piperacillin/tazobactam and carbapenems (ertapenem, imipenem and meropenem), and the participants in this study should also be treated with either BLBLI (amoxicillin/clavulanate or piperacillin/tazobactam) or carbapenem (ertapenem, imipenem or meropenem). Since there was no standard guideline for the treatment of ESBL-producing Enterobactaeriacae urinary tract infection (UTI) in Malaysia at that time[12], the choice of BLBLI or carbapenem solely depended on the managing team's judgement. If the patient has multiple UTI episodes in one admission, only the first episode of ESBL-producing Enterobactaeriacae UTI infection was analysed. Mixed growth of organisms from one episode of UTI were excluded from the study.

### Variables definition

In this study, symptomatic UTI was classified as cystitis, pyelonephritis and urosepsis based on clinical symptoms as described by Smelov *et al*[13]. Both clinical and microbiological outcomes were measured. Clinical cure was defined as return to pre-infection state with improvement of signs and symptoms that did not warrant further antibiotic therapy. Mortality was also evaluated in this study, where attributable mortality was regarded if the death was attributed directly to the ESBL-producing Enterobactaeriacae infection, such as death within 72 hours after a culture positive for ESBL-producing organism.

### Microbiology method

All isolated Enterobacteriaceae from urine sample with bacterial count of $>10^5$ CFU/mL, and resistance to any third-generation cephalosporin were subsequently screened for ESBL according to latest Clinical and Laboratory Institute guidelines[14]. Four Enterobacteriaceae with Clinical and Laboratory Institute breakpoints were tested: *Klebsiella pneumoniae, K. oxytoca, Escherichia coli* and *Proteus mirabilis*. The isolates with ceftazidime (30 μg) of ≤22 mm and/or cefotaxime (30 μg) of ≤27 mm inhibition diameter on Muller-Hinton agar of antimicrobial susceptibility test were proceeded for phenotypic ESBL testing. The confirmatory test was performed using ceftazidime and cefotaxime discs alone and in combination with clavulanic acid (30/10 μg). An increase of >5 mm in the zone of inhibition for the combination of ceftazidime or cefotaxime/clavulanic acid disc versus the zone for the disc containing the drug alone will be considered a confirmed ESBL producer[14].

### Statistical analysis

For clinical evaluation, all statistical analyses were performed using SPSS version 24 (IBM Corp, Armonk, NY). Categorical variables were compared using the Pearson Chi-square or Fisher's exact tests where applicable, while continuous variables were compared using the independent t-test. *P*-value of <0.05 were regarded as statistically significant.

To identify the risk factors of clinical failure, simple logistic regression was initially used to screen. Variables that showed difference in the clinical outcome ($P$<0.25) were included in the multiple logistic regression model. The Hosmer-Lemeshow goodness of fit test and area under receiver operating characteristics curve were used to assess the fitness of the model.

## RESULTS

### Demographic and clinical characteristics

Due to stringent inclusion/exclusion criteria, a total of 79 patients with ESBL-producing Enterobactaeriacae

urinary tract infection were eligible in this study. Thirty-two (40.5%) patients were included in BLBLI group, while the remaining were included in carbapenem group. There were no significant differences in age, gender, underlying comorbidity, underlying risk factor, concomitant infection and surgical intervention between these two groups (Table 1).

Patients treated with carbapenem were more likely to present with severe pyelonephritis and severe urosepsis than patients treated with BLBLI.

**Table 1:** Comparison of demographics, clinical characteristics, microbiological characteristics and treatment details between patients treated with β-lactam/β-lactamase inhibitor and carbapenem

| Variables | Definitive therapy | | *P*-value |
|---|---|---|---|
| | BLBLI (n = 32) | Carbapenem (n = 47) | |
| **Demographics** | | | |
| Age (mean) | 61.97±11.12 | 60.53±13.59 | 0.622 |
| Gender | | | |
| Male | 15 (46.9) | 20 (42.6) | 0.704 |
| Female | 17 (53.1) | 27 (57.4) | |
| **Clinical characteristics** | | | |
| Charlson comorbidity index (mean) | 4.25±2.45 | 3.81±2.40 | 0.429 |
| Comorbidity | | | |
| Diabetes mellitus | 18 (56.3) | 20 (42.6) | 0.232 |
| Hypertension | 17 (53.1) | 20 (42.6) | 0.354 |
| Renal impairment | 13 (40.6) | 15 (31.9) | 0.427 |
| Ischemic heart disease | 4 (12.5) | 3 (6.4) | 0.432 |
| Cerebrovascular accident | 4 (12.5) | 7 (14.9) | 1.000 |
| Malignancy | 4 (12.5) | 5 (10.6) | 1.000 |
| Connective tissue disease | 0 (0.0) | 1 (2.1) | 1.000 |
| No comorbid | 8 (25.0) | 13 (27.5) | 0.793 |
| Clinical presentation | | | |
| Cystitis | 9 (28.1) | 8 (17.0) | 0.238 |
| Mild to moderate pyelonephritis | 9 (28.1) | 5 (10.6) | 0.046 |
| Severe pyelonephritis | 0 (0.0) | 8 (17.0) | 0.019 |
| Simple urosepsis | 11 (34.4) | 12 (25.5) | 0.396 |
| Severe urosepsis | 1 (3.1) | 10 (21.3) | 0.024 |
| Urosepsis with shock | 2 (6.3) | 4 (8.5) | 1.000 |
| Underlying risk factor | | | |
| Renal abscess/ pyonephrosis | 2 (6.3) | 8 (17.0) | 0.189 |
| Urolithiasis | 8 (25.0) | 11 (23.4) | 0.871 |
| Prostate enlargement | 2 (6.3) | 7 (14.9) | 0.299 |
| Bladder tumour | 2 (6.3) | 4 (8.5) | 1.000 |
| Neurogenic bladder | 5 (15.6) | 3 (6.4) | 0.258 |
| External catheter | 10 (31.3) | 9 (19.1) | 0.217 |
| No risk factor | 8 (25.0) | 14 (29.8) | 0.641 |
| Presence ≥2 risk factor | 9 (28.1) | 10 (21.3) | 0.484 |
| Other concomitant infection | 10 (31.3) | 12 (25.5) | 0.578 |
| Surgical intervention | 8 (25.0) | 11 (23.4) | 0.871 |
| **Microbiological characteristics** | | | |
| Organism isolated | | | |
| Escherichia coli | 18 (56.3) | 33 (70.2) | 0.203 |
| Klebsiella pneumoniae | 12 (37.5) | 13 (27.7) | 0.356 |
| Proteus mirabilis | 2 (6.3) | 1 (2.1) | 0.563 |
| Other source with ESBL isolates (beside urine specimen) | | | |
| Blood | 3 (9.4) | 18 (38.3) | 0.004 |
| Tracheal aspirate | 1 (3.1) | 1.8 (4.3) | 1.000 |
| Pus/tissue | 3 (9.4) | 4 (8.5) | 1.000 |
| None | 25 (78.1) | 24 (51.1) | 0.015 |
| Previous ESBL-producing Enterobactaeriacae infection | 9 (28.1) | 6 (12.8) | 0.088 |
| **Treatment details** | | | |
| Empirical treatment | | | |
| Cephalosporin | 16 (50.0) | 26 (55.3) | 0.642 |
| BLBLI | 13 (40.6) | 15 (31.9) | 0.427 |
| Carbapenem | 1 (3.1) | 5 (10.6) | 0.392 |
| Others | 2 (6.3) | 1 (2.1) | 0.563 |
| Duration of definitive treatment (mean) | 8.31±7.16 | 7.89±4.6 | 0.752 |

BLBLI: β-lactam/β-lactamase inhibitor; ESBL: extended-spectrum β-lactamase

On the other hand, patients treated with BLBLI group were more likely to present with mild to moderate pyelonephritis (Table 1).

**Microbiological characteristics**

*Escherichia coli* was the most common organism isolated in both BLBLI and carbapenem group [18 (56.3%) vs. 33 (70.2%)], followed by *Klebsiella pneumoniae* [12 (37.5%) vs. 13 (27.7%)] and *Proteus mirabilis* [2 (6.3%) vs. 1 (2.1%)]. No ESBL-producing *K. oxytoca* was isolated from urinary sample in the study period. ESBL-producing Enterobactaeriacae bacteraemia were more in patients treated with carbapenem compared to BLBLI [18 (38.3%) vs. 3 (9.4%)]. Most of the patients in BLBLI group did not have other sources of ESBL-producing Enterobactaeriacae isolate [25 (78.1%) vs. 24 (51.1%)]. Nine (28.1%) patients in BLBLI and six (12.8%) patients in carbapenem groups were documented to have previous ESBL infections (Table 1).

**Treatment details**

Among the BLBLI group, 30 (93.8%) patients were treated with piperacillin/tazobactam and two (6.2%) patients were treated with amoxicillin/clavulanate. For carbapenem group, 10 (21.3%), 7 (14.9%) and 30 (63.8%) patients were treated with meropenem, imipenem and ertapenem respectively. Cephalosporin was the most common empirical treatment received before obtaining the culture result. Sixteen out of 42 (38.1%) patients who received empirical cephalosporin were changed to BLBLI, while the other 26 (61.9%) patients were changed to carbapenem.

Among 28 patients who received empirical BLBLI, 13 (46.4%) continued to receive BLBLI while the other 15 (53.6%) were escalated to carbapenem. Only one out of six (16.7%) patients with empirical carbapenem were deescalated to BLBLI after the culture result was obtained, while the remaining five (83.3%) patients continued with carbapenem. The duration of definitive treatment was also not statistically different between both groups with a mean of 8.31±7.16 days and 7.89±4.6 days for BLBLI and carbapenem groups respectively (Table 1).

**Outcome of infection**

Table 2 shows 26 (81.3%) patients who received definitive BLBLI and 36 (76.6%) patients who received carbapenem improved in clinical signs and symptoms following at least 72 hours of treatment. Out of 62 patients with clinical success from both groups, 38 (19 BLBLI; 19 carbapenem) patients also had microbiological success, one (carbapenem only) had persistence of culture (microbiological failure), five (one BLBLI; four carbapenem) had breakthrough infection, while remaining 18 (6 BLBLI; 12 carbapenem) patients did not have any repeat culture following treatment. For breakthrough infection, one patient who received definitive treatment with BLBLI (piperacillin/tazobactam) had isolated *Candida sp.* from the repeated culture. Of the other four patients who received carbapenem (all ertapenem), two patients also isolated *Candida sp*, one *P. aeruginosa* and one *Enterococcus sp*.

**Table 2:** Comparison of clinical and microbiological outcomes between patients treated with β-lactam/β-lactamase inhibitor and carbapenem

| Demographic / Clinical characteristic | Definitive therapy | | *P*-value |
|---|---|---|---|
| | BLBLI* (n=32) | Carbapenem (n=47) | |
| Clinical outcome | | | |
| Success | 26 (81.3) | 36 (76.6) | 0.621 |
| Failure | 6 (18.8) | 11 (23.4) | |
| Mortality | 5 (15.6) | 8 (17.0) | 0.869 |
| Microbiological outcome | | | |
| Success | 21 (65.6) | 23 (48.9) | 0.143 |
| Failure | 2 (6.3) | 4 (8.5) | 1.000 |
| Breakthrough infection | 2 (6.3) | 5 (10.6) | 0.695 |
| No repeat culture | 7 (21.9) | 15 (31.9) | 0.328 |

BLBLI: β-lactam/β-lactamase inhibitor

One out of six (16.7%) patients who showed no clinical improvement with BLBLI were subsequently escalated to carbapenem and survived at the end of treatment. The other five (83.3%) patients with clinical failure were associated with mortality. Among all mortality cases in BLBLI group, three patients had other concomitant infections (one non-typhoidal salmonellosis, two necrotizing fasciitis), one patient complicated with A. baumannii multidrug resistant sepsis, and one died due to aspiration pneumonia. However, none presented with either severe sepsis or septic shock. In carbapenem group, three (27.3%) patients who were treated with ertapenem did not show clinical improvement after at least five days of treatment, and subsequently requested to be discharged at their own risk. The remaining eight (72.7%) patients with clinical failure died at the end of treatment: three were complicated with *A. baumannii* multidrug resistant sepsis; two complicated with severe hospital acquired pneumonia; one complicated with persistent candidaemia; one had other concomitant infection (necrotizing fasciitis); and one died due to acute coronary syndrome. Out of 11 patients with clinical failure in the carbapenem group, one had septic shock at presentation, seven presented with severe sepsis and three presented with simple urosepsis. All patients presented with either cystitis or pyelonephritis were successfully treated with carbapenem (Table 2).

**Table 3:** Association between different variables and clinical failure by single logistic regression and multiple logistic regression

| Variable | Single logistic regression | | Multiple logistic regression | |
|---|---|---|---|---|
| | Crude OR (95% CI) | *P*-value | Adjusted OR (95% CI) | *P*-value |
| Age | 1.010 (0.966, 1.055) | 0.661 | | |
| Male gender | 0.621 (0.204, 1.889) | 0.401 | | |
| Charlson comorbidity index[a] | 1.176 (0.934, 1.480) | 0.169 | | |
| Comorbidity | | | | |
| Diabetes mellitus | 2.377 (0.780, 7.242) | 0.128 | | |
| Hypertension | 1.366 (0.466, 4.005) | 0.570 | | |
| Renal impairment | 0.992 (0.322, 3.047) | 0.988 | | |
| Ischemic heart disease | 1.520 (0.268, 8.622) | 0.636 | | |
| Cerebrovascular accident | 0.784 (0.153, 4.031) | 0.772 | | |
| Malignancy | 1.048 (0.197, 5.576) | 0.957 | | |
| Clinical presentation | | | 21.812 (3.735, 127.373) | 0.001 |
| Severe urosepsis/ urosepsis with shock | 7.594 (2.270, 25.405) | 0.001 | | |
| Underlying risk factor | | | | |
| Renal abscess/ pyonephrosis | 0.368 (0.043, 3.129) | 0.359 | | |
| Urolithiasis | 0.616 (0.156, 2.426) | 0.489 | | |
| Prostate enlargement | 0.422 (0.049, 3.630) | 0.422 | | |
| Bladder tumour | 0.713 (0.078, 6.544) | 0.764 | | |
| Neurogenic bladder | 1.244 (0.228, 6.803) | 0.801 | | |
| External catheter | 4.121 (1.300, 13.067) | 0.016 | 9.741 (1.720, 55.162) | 0.010 |
| Presence ≥2 risk factors | 0.353 (0.073, 1.709) | 0.196 | | |
| Other concomitant infection | 5.952 (1.879, 18.859) | 0.002 | 5.168 (1.272, 20.990) | 0.022 |
| Surgical intervention | 0.964 (0.273, 3.407) | 0.955 | | |
| Organism isolated[b] | | | | |
| *Escherichia coli* | 1 | | | |
| *Klebsiella pneumoniae* | 0.619 (0.177, 2.160) | 0.452 | | |
| *Proteus mirabilis* | 1.625 (0.135, 19.524) | 0.702 | | |
| ESBL-producing Enterobactaeriacae bacteraemia | 1.198 (0.364, 3.931) | 0.766 | | |
| Previous ESBL-producing Enterobactaeriacae infection | 0.214 (0.026, 1.761) | 0.152 | | |
| Empirical therapy[c] | 1 | | | |
| Carbapenem | 0.500 (0.028, 8.952) | | | |
| Others | 0.135 (0.021, 0.862) | 0.638 | | |
| Cephalosporin | 0.400 (0.066, 2.415) | 0.034 | | |
| BLBLI | | 0.318 | | |
| Definitive therapy[c] | | | | |
| Carbapenem | 1 | | | |
| BLBLI | 0.755 (0.248, 2.304) | 0.622 | | |
| Duration of definitive treatment | 1.019 (0.935, 1.111) | 0.670 | | |

* OR:odds ratio; CI: confidence interval; BLBLI: β-lactam/β-lactamase inhibitor; ESBL: extended-spectrum β-lactamase; [a] per unit; [b] Reference: *Escherichia coli;* [c] Reference: carbapenem

**Factors associated with clinical failure**

The model showed a *P*-value of 0.214 for Hosmer-Lemeshow goodness of fit test and area under receiver operating characteristics curve was 88.1%, which showed good predictive ability. After adjusting for the confounders, the only significant risk factors for clinical failure were severe sepsis or septic shock at presentation (OR: 21.812; 95% CI: 3.735, 127.373), presence of external catheter (OR: 9.741; 95% CI: 1.720, 55.162) and presence of other concomitant infection (OR: 5.168; 95% CI: 1.272, 20.990). Other variables including empirical and definitive treatment with BLBLI were not significantly associated with increased risk of clinical failure (Table 3).

## DISCUSSION

Our study showed BLBLIs have good clinical and microbiological response that is comparable to carbapenem group. Though the difference was not statistically significant, carbapenem group showed slightly higher failure rate compared to BLBLI group that could be explained by a higher proportion of patients in this group who presented with severe sepsis or septic shock and associated with bacteraemia. While most of the patients in both treatment groups have underlying comorbidities and risk factors, these did not significantly contribute to clinical failure. After adjusting for the confounders, the only significant risk factors for clinical failure

were severe sepsis or septic shock at presentation, presence of external catheter and presence of other concomitant infection with 22-, 10- and 5-times increased risk of clinical failure respectively. This finding is in line with previous reports on the use of piperacillin/tazobactam for the treatment of uncomplicated UTI[15].

We also found that the use of BLBLI either as empirical or definitive treatment in our study did not associate with clinical failure. However, we cannot conclude whether BLBLI is effective in cases with bloodstream infection because a very small number of the patients (3 out of 32) in this group were associated with bacteraemia. Although all of them showed clinical improvement at the end of treatment, one of the patients who received carbapenem initially as empirical treatment was deescalated to piperacillin/tazobactam, which could be contributed to good clinical outcome.

A few previous reports indicated clinical improvement with BLBLI therapy in UTI or bloodstream infection from the urinary source[16-18]. Rodríguez-Baño *et al* in a prospective cohort study comparing BLBLI and carbapenem for treatment of *E. coli* ESBL bloodstream infection, reported higher failure rate in carbapenem group for both empirical and definitive treatment. The 30-day mortality in the empiric cohort was 10% and 19% and in the definitive cohort was 9% and 17% for BLBLI and carbapenem respectively[16]. Similar to our study, this difference in the outcome suggested that the cohort of patients treated with carbapenem are more severely ill. Gavin *et al* showed similar clinical success after piperacillin/tazobactam treatment regardless of the isolate's minimal inhibitory concentration to that antibiotic[17]. A randomized controlled trial for the treatment of UTI caused by ESBL-producing *E. coli* by Seo *et al* indicated a similar result. The clinical success rate was 93.9% and 97% in BLBLI and carbapenem group, respectively, without statistical difference. The microbiological success was at 97% and 28-day mortality rate was 6.1% in both groups[18].

The use of BLBLI for the treatment of bloodstream infections caused by ESBL-producing Enterobacteriaceae have shown some beneficial effects. In a multinational, retrospective cohort study, Gutiérrez-Gutiérrez *et al* studied a larger sample size on the use of BLBLI for treatment of bloodstream infections due to ESBL-producing Enterobacteriaceae[19]. They found active BLBLIs are as effective as carbapenems for the treatment of bloodstream infections due to ESBL-producing Enterobacteriaceae in different clinical conditions. The clinical success rates with BLBLIs and carbapenems were 80% and 78.9% in the empirical treatment cohort and 90.2% and 85.5% in the definitive therapy cohort respectively, with no statistical difference. This is almost comparable with our study with the clinical improvement at 81.3% among patients who received BLBLI and 76.6% in carbapenems group. The 30-day mortality rates among BLBLI were at 9.8-17.6% and 13.9-20% in carbapenems group in their study, were comparable to our study at 15.6% and 17% in BLBLI and carbapenems group, respectively. Ng *et al* also found the use of empiric piperacillin-tazobactam was not associated with increased 30-day mortality. The mortality rate was almost similar between those who received empiric piperacillin/tazobactam (30.9%) and a carbapenem (29.8%). Those who received empiric piperacillin/tazobactam had additional effect of a lower 30-day acquisition of multi-drug resistant and fungal infections with 7.4% vs. 24.6% in carbapenem group[20].

However, there are a few studies that show a contradictory finding when comparing BLBLI and carbapenem for the treatment of infection by ESBL-producing Enterobacteriaceae. Tamma *et al* found the 14-day mortality rate in bloodstream infections were 16.5% in the BLBLI group and 8.1% in the carbapenem group, which calculated as a 1.92 times increased risk of death in BLBLI group compared to patients receiving carbapenem[21]. A publication by MERINO Trial group also showed piperacillin/tazobactam group was inferior to carbapenem group for ESBL-producing Enterobactaeriacae bloodstream infection. Though majority of the subjects had urinary source (54.8% in piperacillin/tazobactam group; 67% in carbapenem group), thirty-day mortality was found to be higher in those treated with piperacillin/tazobactam compared to carbapenem (6.9% vs. 3.1%; $P$=0.44)[22].

## CONCLUSION

In conclusion, our study found BLBLI was non-inferior to carbapenem for treatment of ESBL-producing Enterobactaeriacae urinary tract infection. Thus, piperacillin/tazobactam still can be an acceptable alternative for treatment of ESBL-producing Enterobactaeriacae infection but must be limited to mild cases of urinary tract infection. Due to limited cases of severe UTI treated with BLBLI, the use of piperacillin/tazobactam in UTI with bacteraemia patients was not supported in this study.

## ACKNOWLEDGMENTS

We would like to acknowledge the infection control team at Hospital Raja Perempuan Zainab II (particularly SN Laily Yusnida Yakub, SN Mazuin Ismail, SN Noranita Mohd Fathil, SN Norani Shafii,

SN Norasiah Mokhtar and SN Maznah Hassan) for their efforts in assisting with data collection and Dr. Azura Hussin and Dr Siti Nur Fairuz Salim, for their opinions and suggestions throughout the study and manuscript preparation.

**Author's contribution:** Nur Hafiza Muharam: the conception and design of the study, and acquisition of data, and analysis and interpretation of data drafting the article, final approval of the version to be submitted; Nurahan Maning: conception and design of the study and final approval of the version to be submitted; Zakuan Zainy Deris: supervised the whole study. The conception and design of the study, and analysis and interpretation of data drafting the article and revising it critically for important intellectual content, final approval of the version to be submitted.

**Conflict of interest:** None

**Ethical approval statement:** This study was approved by Human Research Ethics Committee (JEPeM), Universiti Sains Malaysia (JEPeM code: USM/JEPeM/17020079) and Medical Research and Ethics Committee (MREC), Ministry of Health Malaysia (NMRR-17-120-34201).

**Funding sources:** This work was supported by the USAINS Grant 2016 and USM Research University grant 1001/PPSP/812167.

## REFERENCES

1. Peirano G, Pitout JDD. Extended-spectrum β-lactamase-producing enterobacteriaceae: Update on molecular epidemiology and treatment options. Drugs 2019; 79(14):1529-41.
2. Rodríguez-Baño J, Gutiérrez-Gutiérrez B, Machuca I, Pascual A. Treatment of infections caused by extended-spectrum-beta-lactamase-, AmpC-, and carbapenemase-producing enterobacteriaceae. Clin Microbiol Rev 2018; 31(2):e00079-17.
3. Gutiérrez-Gutiérrez B, Rodríguez-Baño J. Current options for the treatment of infections due to extended-spectrum beta-lactamase-producing Enterobacteriaceae in different groups of patients. Clin Microbiol Infect 2019; 25(8):932-42.
4. Bradford PA. Extended-spectrum β-lactamases in the 21st century: characterization, epidemiology, and detection of this important resistance threat. Clin Microbiol Rev 2001; 14(4):933-51.
5. Ariffin H, Navaratnam P, Mohamed M, Arasu A, Abdullah WA, Lee CL, *et al*. Ceftazidime-resistant *Klebsiella pneumoniae* bloodstream infection in children with febrile neutropenia. Int J Infect Dis 2000; 4(1):21-5.
6. Parasakthi N, Vadivelu J, Ariffin H, Iyer L, Palasubramaniam S, Arasu A. Epidemiology and molecular characterization of nosocomially transmitted multidrug-resistant *Klebsiella pneumoniae*. Int J Infect Dis 2000; 4(3):123-8.
7. Ngoi ST, Chong CW, Ponnampalavanar SS, Tang SN, Idris N, Jabar KA, *et al*. Genetic mechanisms and correlated risk factors of antimicrobial-resistant ESKAPEE pathogens isolated in a tertiary hospital in Malaysia. Antimicrobial Resistance & Infection Control 2021; 10(1):70.
8. Kamaruzzaman EA, Abdul Aziz S, Bitrus AA, Zakaria Z, Hassan L. Occurrence and characteristics of extended-spectrum β-lactamase-producing Escherichia coli from dairy cattle, milk, and farm environments in peninsular Malaysia. Pathogens 2020; 9(12):1007.
9. Tissera S, Lee SM. Isolation of extended spectrum β-lactamase (ESBL) producing bacteria from urban surface waters in Malaysia. Malays J Med Sci 2013; 20(3):14-22.
10. Papp-Wallace KM, Endimiani A, Taracila MA, Bonomo RA. Carbapenems: past, present, and future. Antimicrob Agents Chemother 2011; 55(11):4943-60.
11. Gupta N, Limbago BM, Patel JB, Kallen AJ. Carbapenem-resistant Enterobacteriaceae: epidemiology and prevention. Clin Infect Dis 2011; 53(1):60-7.
12. Malaysian Ministry of Health. National Antibiotic Guidelines 2nd Ed., 2014. Available at https://www.pharmacy.gov.my/v2/sites/default/files/document-upload/national-antibiotic-guideline-2014-full-versionjun2015_1.pdf
13. Smelov V, Naber K, Johansen TEB. Improved classification of urinary tract infection: future considerations. Eur Urol Suppl 2016; 15(4):71-80.
14. Clinical & Laboratory Standards Institute (CLSI) M100. (2018). Tests for Extended-Spectrum β-Lactamases in Klebsiella pneumoniae, Klebsiella oxytoca, Escherichia coli, and Proteus mirabilis (28th ed.). Wayne, PA: Clinical and Laboratory Standards Institute.
15. Seo YB, Lee J, Kim YK, Lee SS, Lee J-A, Kim HY, *et al*. Randomized controlled trial of piperacillin-tazobactam, cefepime and ertapenem for the treatment of urinary tract infection caused by extended-spectrum beta-lactamase-producing *Escherichia coli*. BMC Infect Dis 2017; 17(1):404.
16. Rodríguez-Baño J, Navarro MD, Retamar P, Picón E, Pascual Á. Extended-Spectrum Beta-Lactamases–Red Española de Investigación en Patología Infecciosa/Grupo de Estudio de Infección Hospitalaria Group. β-lactam/β-lactam inhibitor combinations for the treatment of bacteremia due to extended-spectrum β-lactamase–producing *Escherichia coli*: a post hoc analysis of prospective cohorts. Clin Infect Dis 2012; 54(2):167-74.
17. Gavin PJ, Suseno MT, Thomson RB Jr, Gaydos JM, Pierson CL, Halstead DC, *et al*. Clinical correlation of the CLSI susceptibility breakpoint for piperacillin- tazobactam against extended-spectrum-beta-lactamase-producing *Escherichia coli* and *Klebsiella* species. Antimicrob Agents Chemother 2006; 50(6):2244-7.
18. Seo YB, Lee J, Kim YK, Lee SS, Lee J-A, Kim HY, *et al.* Randomized controlled trial of piperacillin-tazobactam, cefepime and ertapenem for the treatment of urinary tract infection caused by extended-spectrum beta-lactamase-producing *Escherichia coli*. BMC Infect Dis 2017; 17(1):404.

19. Gutiérrez-Gutiérrez B, Pérez-Galera S, Salamanca E, de Cueto M, Calbo E, Almirante B, *et al*. A multinational, preregistered cohort study of β-lactam/β-lactamase inhibitor combinations for treatment of bloodstream infections due to extended-spectrum-β-lactamase-producing Enterobacteriaceae. Antimicrob Agents Chemother 2016; 60(7):4159-69.
20. Ng TM, Khong WX, Harris PN, De PP, Chow A, Tambyah PA, *et al*. Empiric piperacillin-tazobactam versus carbapenems in the treatment of bacteraemia due to extended-spectrum beta-lactamase-producing enterobacteriaceae. PLoS One 2016; 11(4):e0153686.
21. Tamma PD, Han JH, Rock C, Harris AD, Lautenbach E, Hsu AJ, *et al.* Carbapenem therapy is associated with improved survival compared with piperacillin-tazobactam for patients with extended-spectrum β-lactamase bacteremia. Clin Infect Dis 2015; 60(9):1319-25.
22. Harris PNA, Tambyah PA, Lye DC, Mo Y, Lee TH, Yilmaz M, *et al*. MERINO Trial Investigators and the Australasian Society for Infectious Disease Clinical Research Network (ASID-CRN). Effect of piperacillin-tazobactam vs meropenem on 30-day mortality for patients with *E. coli* or *Klebsiella pneumoniae* bloodstream infection and ceftriaxone resistance: A randomized clinical trial. JAMA 2018; 320(10):984-94.

Original Article

# Positive N-Cadherin immunostaining in uterine endometrioid carcinoma is associated with better survival

Wafaey Gomaa[1,2], Ibtihal Zabermawi[3], Bassam Al-Maghrabi[4], Jaudah Al-Maghrabi[1,5]
[1]Department of Pathology, Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia
[2]Department of Pathology, Faculty of Medicine, Minia University, Al-Minia, Egypt
[3]Department of Pathology, East Jeddah Hospital, Jeddah, Saudi Arabia
[4]Faculty of Dentistry, King Abdulaziz University, Jeddah, Saudi Arabia
[5]Department of Pathology and Laboratory Medicine, King Faisal Specialist Hospital and Research Centre, Jeddah, Saudi Arabia

Kuwait Medical Journal 2023; 55 (4): 322 - 328

## ABSTRACT

**Objectives:** The objective of the current study is to define the immunostaining pattern of N-cadherin in uterine endometrioid carcinoma and its relation to clinicopathological features and its prognostic significance.
**Design:** A retrospective study of N-Cadherin immunostaining in uterine endometrioid carcinoma and non-neoplastic endometrial tissue
**Setting:** Paraffin embedded tissue block were retrieved from the archives of Department of Pathology, King Abdulaziz University Hospital, Jeddah, Saudi Arabia.
**Subjects:** Seventy-one uterine endometrioid carcinomas and 30 non-neoplastic endometria were included in the study.
**Interventions:** Tissue microarrays were constructed. Immunostaining for N-Cadherin was done.
**Main outcome measure:** Statistical analysis of the immunostaining results to address the prognostic significance of N-cadherin immunostaining.
**Results:** In non-neoplastic tissues, positive immunostaining was observed in 13.3%. In endometrioid carcinoma, positive immunostaining was seen in 40.8%. The positive immunostaining was higher in endometrioid carcinoma than in non-neoplastic tissues. In endometrioid carcinoma, positive immunostaining showed no relation with most clinicopathological feature. On the other hand, positive immunostaining was associated with better survival outcomes for overall survival ($P$=0.007) and disease-free survival ($P$=0.028).
**Conclusion:** In summary, we show positive N-cadherin immunostaining in uterine endometrioid carcinoma that is associated with better survival outcomes. This finding is novel and contradicting many other studies in other organs. Our finding is challenging and needs more highlight to the pattern of N-cadherin in uterine endometrioid carcinoma using more cohort of cases and molecular pathology studies to confirm its exact role.

**KEY WORDS**: endometrium, immunohistochemistry, N-cadherin, tissue microarray

## INTRODUCTION

Endometrial carcinoma (EC) is the most common malignancy of the female genital tract[1] with an approximate life risk of 3%[2]. EC has an increased incidence and has doubled its death rate[3]. EC comprises 4% of all cancers in women globally[4]. In Saudi Arabia, EC constitutes 2.9% of newly diagnosed malignancies in females[5]. The 5-year overall survival in patients without metastasis ranges between 74 to 91%, while it reaches as low as 20% in cases with metastasis[6]. Most of the deaths associated are caused by chemotherapy-resistant metastases. Therefore, investigation of the molecular mechanisms behind endometrial cancer metastasis would provide insight for the development of improved therapies[7].

*Address correspondence to:*
*Professor Jaudah Al-Maghrabi, Department of Pathology, Faculty of Medicine, King Abdulaziz University, P.O. BOX 80205, Jeddah 21589, Saudi Arabia.*
*Tel: +966 12 6401000 (ext: 17069); Mob: +966 504680456; Fax: +966 12 6408433; E-mail: jalmaghrabi@hotmail.com*

The epithelial to mesenchymal transition is a key molecular mechanism predicting cancer metastasis. Epithelial to mesenchymal transition is characterized by loss of the epithelial marker E-cadherin, an increase in the mesenchymal markers vimentin and N-cadherin[8]. N-cadherin is a member of cadherin superfamily that mediates cell-cell interaction in epithelial tissue[9]. For example, N-cadherin overexpression has been correlated with tumour aggressiveness and metastasis in prostate cancer, melanoma, breast cancer and colon cancer[10-14]. N-cadherin expression could help in deciding prognosis of cancer patients; patients with high N-cadherin expression have a significantly lower overall survival and event-free survival rate than those with low N-cadherin expression[15].

There is little known about N-cadherin expression in EC with limited conclusions. The objective of the current study is to define the immunostaining pattern of N-cadherin in EC and its relation to clinicopathological features and its prognostic significance.

## MATERIALS AND METHODS

### Patients

The study included paraffin wax tumour blocks from 71 patients diagnosed with uterine endometrioid carcinoma in the period from 2003-2012. Also, paraffin blocks from non-neoplastic endometria of 30 patients in the period from 1995-1998 were included (20 proliferative endometrium and 10 secretory endometrium). All blocks were retrieved from the archives of the Department of Pathology at King Abdulaziz University, Jeddah, Saudi Arabia. Some clinicopathological characteristics of patients are listed in Table 1. For statistical purpose, FIGO stages were classified into limited to uterine corpus (FIGO Stage I and II) and beyond the uterine corpus (FIGO III and IV). Also, grade was reclassified as low grade (grade I) and high grade (grades II and III). Data is shown in Table 1. The study was performed in accordance with the ethics committee of Faculty of Medicine, King Abdulaziz University, Saudi Arabia, and declaration of Helsinki.

**Table 1:** Clinicopathological features of endometrioid carcinoma (n=71)

| Parameter | Number (%) |
|---|---|
| Age | |
| < 60 years | 49 (69) |
| > 60 years | 22 (31) |
| FIGO tumour grade | |
| Grade 1 | 44 (62) |
| Grade 2 | 16 (22.5) |
| Grade 3 | 11 (15.5) |
| Tumour size | |
| < 2 cm | 35 (49.3) |
| > 2 cm | 36 (50.7) |
| Myometrial invasion | |
| < 50% | 57 (80.3) |
| > 50% | 14 (19.7) |
| Lymphovascular | |
| Absent | 68 (95.8) |
| Present | 3 (4.2) |
| Surgical resection margin | |
| Free | 67 (94.4) |
| Involved | 4 (5.6) |
| Lymph node metastasis | |
| Absent | 33 (46.5) |
| Present | 4 (5.6) |
| Not sampled | 34 (47.9) |
| FIGO staging | |
| I | 51 (71.8) |
| II | 7 (9.85) |
| III | 7 (9.85) |
| IV | 6 (8.5) |
| Local recurrence | |
| Absent | 60 (84.5) |
| Present | 11 (15.5) |

FIGO: International Federation of Gynaecology and Obstetrics Stage I: Tumour confined to corpus uteri; IA: Tumour limited to endometrium or invades less than one-half of the myometrium; IB: Tumour invades one-half or more of the myometrium; Stage II: Tumour invades stromal connective tissue of the cervix but does not extend beyond uterus; Stage III: There is regional tumour spread; IIIA: Tumour involves serosa and/or adnexa (direct extension or metastasis); IIIB: Vaginal involvement (direct extension or metastasis) or parametrial involvement; IIIC: The tumour involves regional lymph nodes; IIIC1: Regional lymph node metastasis to pelvic lymph nodes; IIIC2: Regional lymph node metastasis to para-aortic lymph nodes, with or without positive pelvic lymph nodes; Stage IV: The tumour invades contiguous organs or has metastasized to remote organ sites; IVA: Tumour invades bladder mucosa and/or bowel mucosa (bullous oedema is not sufficient to classify a tumour as T4); IVB: Distant metastasis

### Tissue microarray

Archival paraffin-embedded tumour samples and neoplastic tissues were selected, and representative areas were marked on haematoxylin and eosin-stained slides. Two tissue cylinders (cores) with a diameter of 1.5 mm was punched from morphologically representative tissue areas of each 'donor' tissue block and brought into new recipient paraffin blocks by using a tissue microarrayer instrument (TMA Master 1.14 SP3 (3D Histech Ltd. Budapest, Hungary). Placenta tissue was used for orientation[16].

### Immunohistochemistry

TMA blocks of tumours were cut at 4 μm and mounted on positive-charged slides (Leica Microsystems Plus Slides). Sections were deparaffinised in xylene and rehydrated in an automated immunostainer (BenchMark XT, Ventana® Medical Systems Inc., Tucson, AZ, USA). Pre-treatment was done using prediluted cell conditioning solution (CC1) for 60 minutes. Monoclonal mouse anti-human N-cadherin antibody (Clone 6G11 from Dako) was used at dilution

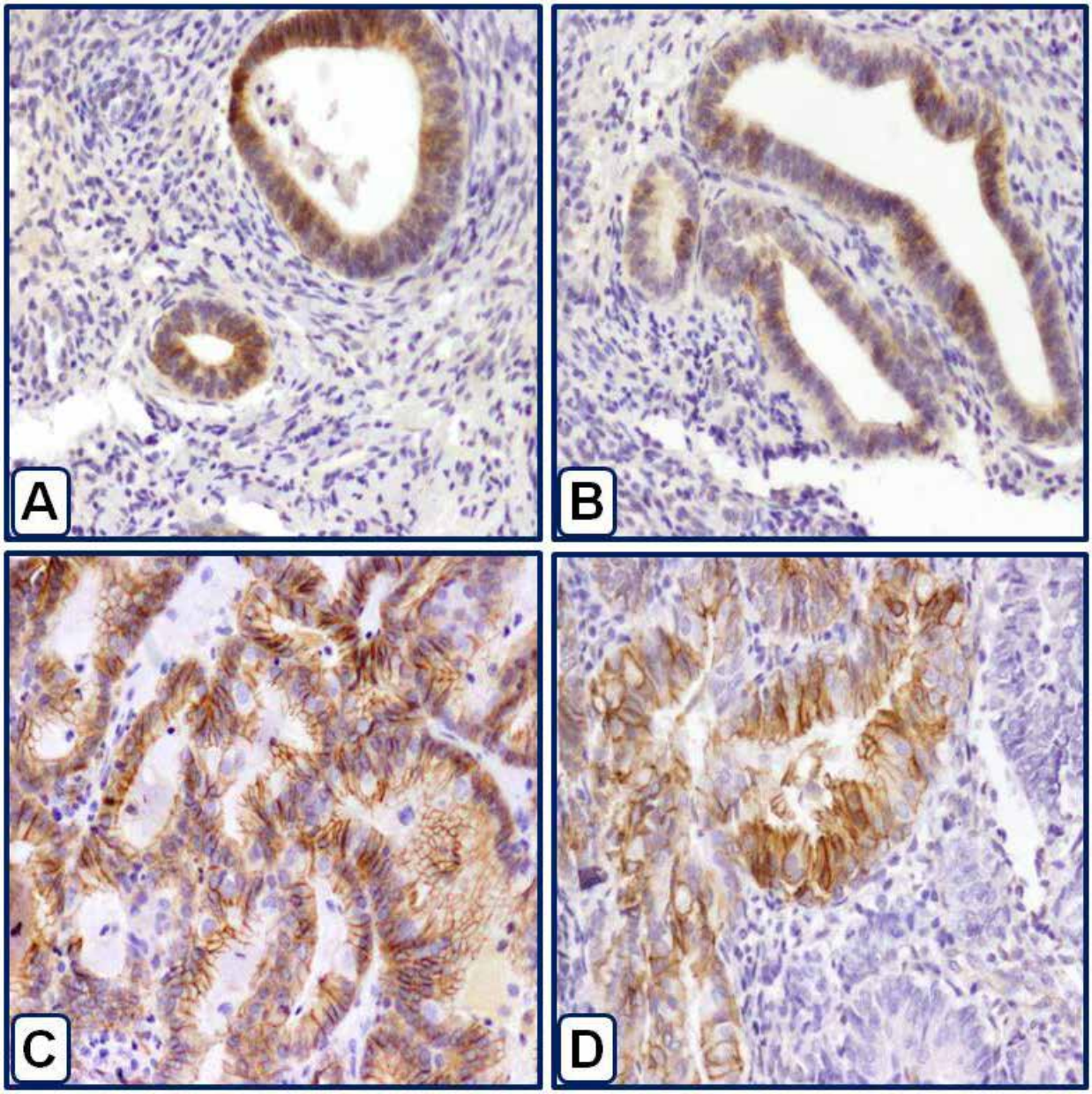


**Figure 1:** Immunostaining of N-cadherin in non-neoplastic endometrium and endometrioid carcinoma. Membranous immunostaining is detected proliferative endometrium (A-100X), secretory endometrium (B-100X), well-differentiated endometrioid carcinoma (C-100X), and in moderately differentiated endometrioid carcinoma (D-200X). Immunohistochemical labelling was done using the anti N-Cadherin antibody and diaminobenzidine used as the chromogen and haematoxylin as counterstain.

1:50 with incubation time 30 minutes. Ventana® I-view DAB detection kit was used according to kit manufacturer instructions. Subsequently, slides were washed, counterstained with Mayer's haematoxylin and mounted. Negative control and positive control slides were included.

**Interpretation of N-cadherin immunostaining**

N-cadherin membranous immunostaining was reported as the percentage of positive cells. The percentage of positive cells ≥5% indicates N-cadherin-positive expression and <5% N-cadherin-negative expression[17].

**Statistical analysis**

Differences between groups of patients were tested by using Mann Whitney test (in case of two groups) and Kruskal Wallis test (in case of three or more groups). Wilcoxon rank sum test was used to test difference between two related groups of paired variables. Non-parametric chi-square was used to test variance along one variable. The Kaplan-Meier procedure was used

**Table 2:** Categories of immunostaining in primary tumours and non-neoplastic endometrium

| Immunostaining Pattern | Primary tumour (n=71) | Non-neoplastic endometrium (n=30) | *P*-value |
|---|---|---|---|
| Low immunostaining | 42 (59.2%) | 26 (86.7%) | |
| High immunostaining | 29 (40.8%) | 4 (13.3%) | 0.034# |
| *P*-value | <0.001* | <0.001* | |

*One sample non-parametric chi-square test
# Mann-Whitney test

to calculate the survival probabilities and the Log Rank test was used to compare the difference between survivals. Statistical procedures were performed using SPSS® Release 16.0. Statistical significance was determined at P-value of ≤0.05 and was two-sided.

## RESULTS

Immunostaining of N-cadherin was indicated by membranous brown colour in non-neoplastic and neoplastic endometrial (Figure 1). In non-neoplastic endometrial tissues, positive immunostaining was observed in 13.3%. The occurrence of negative immunostaining was statistically more than positive immunostaining (*P*≤0.001). In proliferative endometrium, positive N-cadherin immunostaining was shown in 15% (3/20), while in secretory endometrium only one showed positive immunostaining (10%). In endometrioid carcinoma, positive N-cadherin immunostaining was seen in 40.8%. The occurrence of negative immunostaining was statistically more than positive immunostaining (*P*≤0.001). The positive N-cadherin immunostaining was higher in endometrioid carcinoma than in non-neoplastic tissues. Data is shown in Table 2.

**Table 3:** Relation between clinicopathological features and N-cadherin immunostaining in tumours (n=71)

| Parameter | *P*-value |
|---|---|
| Age | 0.122 |
| < 60 years | |
| > 60 years | |
| FIGO tumour grade | 0.989 |
| Low (FIGO grade I) | |
| High (FIGO grade II and III) | |
| Tumour size | 0.887 |
| < 2 cm | |
| > 2 cm | |
| Myometrial invasion | 0.665 |
| < 50% | |
| > 50% | |
| Lymphovascular | 0.356 |
| Absent | |
| Present | |
| Surgical resection margin | 0.703 |
| Free | |
| Involved | |
| Lymph node metastasis | 0.400 |
| Absent | |
| Present | |
| Not sampled | |
| FIGO staging | 0.245 |
| Early (FIGO stage I and II) | |
| Late (FIGO stage III and IV) | |
| Local recurrence | 0.318 |
| Absent | |
| Present | |

FIGO: International Federation of Gynaecology and Obstetrics

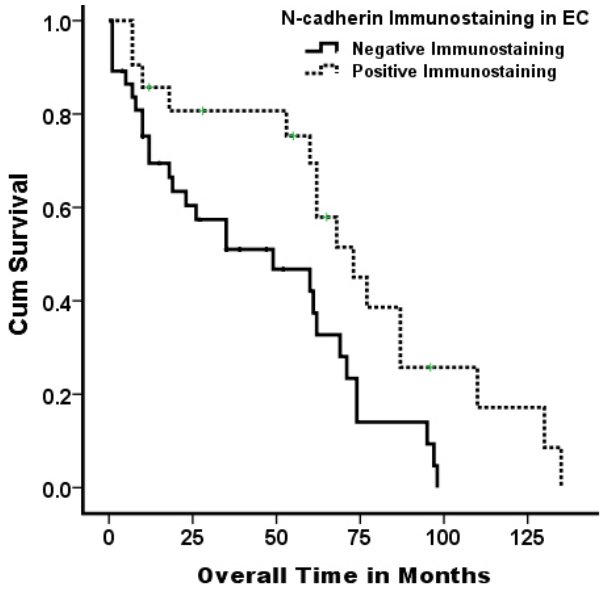


**Figure 2:** Overall survival curve (Kaplan Meier) according to N-cadherin immunostaining. Positive N-cadherin immunostaining is associated with better overall survival {Log Rank (Mantel-Cox)=7.35, *P*=0.007)}.

In endometrioid carcinoma, positive N-cadherin immunostaining showed no relation with most clinicopathological features (Table 3). On the other hand, positive N-cadherin immunostaining was associated with better survival outcomes for overall survival (Log Rank (Mantel-Cox)=7.35, *P*=0.007; Figure 2) and better disease free survival (Log Rank (Mantel-Cox)=4.824, *P*=0.028; Figure 3).

## DISCUSSION

During tumour progression, cancer cells undergo major changes in the expression of the adhesion molecules resulting in detachment from original tissue and acquisition of a highly motile and invasive phenotype[18]. The adhesion of the cells is influenced by cadherin which are calcium-dependent cell molecules involved in maintaining the epithelial structure and normal tissue architecture[19]. Previous studies claimed that the abnormal level of E-cadherin is associated with tumour progression and metastasis[20], while N-cadherin is associated with a heightened invasive potential in cancer[21,22].

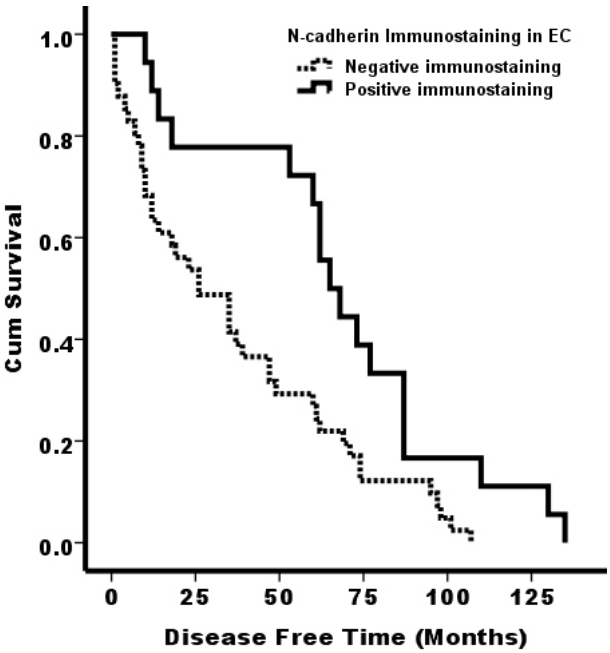


**Figure 3:** Disease survival curve (Kaplan Meier) according to N-cadherin immunostaining. Positive N-cadherin immunostaining is associated with better disease-free survival {Log Rank (Mantel-Cox)=4.824, *P*=0.028)}.

In the present study, N-cadherin was highly expressed in endometrioid carcinoma (40.8%), which comes in congruence with what had been reported by Xie *et al*[23]. This finding could raise the importance of N-cadherin expression as a possible indicator for the clinical evaluation and prognosis of endometrial cancer. The N-cadherin is abnormally expressed in some epithelial tumours, and its ability to enhance the invasion and metastasis of tumour cells is more evident than that of the E-cadherin[22], as it has an essential role in the maturation and stabilisation of normal vessels and tumour-associated angiogenic vessels[18]. Moreover, it had been suggested that E-cadherin may be, in some of the biological phases of the tumour, converted to N-cadherin[22].

Regarding N-cadherin expression in endometrial epithelium, Tsuchiya *et al* addressed that there is a total difference between proliferative and secretory phases; while N-cadherin is strongly presented in the epithelium of the endometrial gland in the proliferative phase, no N-cadherin is observed in the early and late secretory phases[24]. That might partially explain our findings where positive N-cadherin immunostaining was shown in 15% (3/20) in proliferative endometrium, while in secretory endometrium only one showed positive immunostaining (10%). In a study conducted by Prudkin *et al*, they examined cadherin expression in cases with lung cancer, found that squamous cell carcinoma had reduced E-cadherin expression and increased N-cadherin cytoplasmic expression, and this phenotype was associated with relatively few clinicopathological features[25], which supports our findings, where positive N-cadherin immunostaining showed no association with most clinicopathological features in endometrioid carcinoma. On the other side, in another study carried out by Luo *et al*, the authors concluded that high expression of cytoplasmic and nuclear N-cadherin was associated with a majority of the clinicopathological variables, including lymph node metastasis, distant metastasis and clinical stage[26]. Our study showed that positive N-cadherin immunostaining was associated with better survival outcomes expressed as overall survival and disease-free survival. In this respect, the review of published literature showed that the nature of the link between N-cadherin expression and prognosis of the cancer patients varies between different researches. For example, Tothill *et al* reported that patients with overexpressed N-cadherin had obvious lower overall survival rate than those with moderate and low expression, and patients with low expression had a better survival rate than those with moderate and high expression, they concluded that high N-cadherin expression may lead to tumour aggressiveness and metastatic potential in colorectal cancer, and may prove to be a possible prognostic factor[27]. Quattrocchi *et al* revealed significant inverse correlation between N-cadherin expression and 36-month overall survival and significant negative association between high expression of N-cadherin and progression-free survival[28]. On the same line, Nakashima showed that N-cadherin overexpression was associated with poor outcome in patients[29], which came in agreement with previous studies[21,30,31], it has been demonstrated that there is a significant positive association between high N-cadherin expression and poor overall survival. On the other side, Abufaraj argued that N-cadherin expression is associated with higher probabilities of disease recurrence but not progression or survival outcomes[32], in contrast to Lascombe who addressed that N-cadherin expression is an independent prognostic marker for tumour progression[33]. Despite these discrepancies in the findings, N-cadherin is viewed as an important therapeutic target among experts[18].

The discrepancy between our findings and other N-cadherin studies especially in the endometrium may be due to the immunohistochemistry technique which depends on multiple variables, such as the fixation method, preservation technique, specimen handling, choice of antibodies and variation in the scoring methods. The limitations of our study were the relatively low number of specimens (neoplastic and non-neoplastic).

## CONCLUSION

In summary, our study confirms the overexpression of N-cadherin in uterine endometrioid carcinoma. However, it is not associated with any clinicopathological parameter. On the other hand, positive N-cadherin is associated with high survival probabilities. This finding is novel and contradicting many other studies in other organs. Our finding is challenging and needs more highlight to the pattern of N-cadherin in uterine endometrioid carcinoma using more cohort of cases and molecular pathology studies to confirm its exact role.

## ACKNOWLEDGMENT

**Author contribution:** WG contributed to tissue microarray design, scoring of immunostaining, statistical analysis and drafted the manuscript. IZ shared in scoring of immunostaining and drafting of the manuscript. BM shared in data collection and immunostaining. JM contributed to histological examination and selection of paraffin blocks included in study, contributed to the design of the study and revised the manuscript. The manuscript has been read and approved by all authors, the requirements for authorship have been met, and each author believes that the manuscript represents honest work.

## REFERENCES

1. SGO Clinical Practice Endometrial Cancer Working Group; Burke WM, Orr J, Leitao M, Salom E, Gehrig P, Olawaiye AB, *et al*. Endometrial cancer: a review and current management strategies: part I. Gynecol Oncol 2014; 134(2):385-92.
2. Leslie KK, Thiel KW, Goodheart MJ, De Geest K, Jia Y, Yang S. Endometrial cancer. Obstet Gynecol Clin North Am 2012; 39(2):255-68.
3. Sorosky JI. Endometrial cancer. Obstet Gynecol 2012; 120(2 Pt 1):383-97.
4. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer 2010; 127(12):2893-917.
5. Bazarbashi S, Al Eid H, Minguet J. Cancer incidence in Saudi Arabia: 2012 data from the Saudi Cancer Registry. Asian Pac J Cancer Prev 2017; 18(9):2437-44.
6. Morice P, Leary A, Creutzberg C, Abu-Rustum N, Darai E. Endometrial cancer. Lancet 2016; 387(10023):1094-108.
7. Amant F, Moerman P, Neven P, Timmerman D, Van Limbergen E, Vergote I. Endometrial cancer. Lancet 2005; 366(9484):491-505.
8. Dong P, Kaneuchi M, Watari H, Hamada J, Sudo S, Ju J, *et al.* MicroRNA-194 inhibits epithelial to mesenchymal transition of endometrial cancer cells by targeting oncogene BMI-1. Mol Cancer 2011; 10:99.
9. Bryan RT, Tselepis C. Cadherin switching and bladder cancer. J Urol 2010; 184(2):423-31.
10. Tran NL, Nagle RB, Cress AE, Heimark RL. N-Cadherin expression in human prostate carcinoma cell lines. An epithelial-mesenchymal transformation mediating adhesion with stromal cells. Am J Pathol 1999; 155(3):787-98.
11. Li G, Satyamoorthy K, Herlyn M. N-cadherin-mediated intercellular interactions promote survival and migration of melanoma cells. Cancer Res 2001; 61(9):3819-25.
12. Nieman MT, Prudoff RS, Johnson KR, Wheelock MJ. N-cadherin promotes motility in human breast cancer cells regardless of their E-cadherin expression. J Cell Biol 1999; 147(3):631-44.
13. Rosivatz E, Becker I, Bamba M, Schott C, Diebold J, Mayr D, *et al.* Neoexpression of N-cadherin in E-cadherin positive colon cancers. Int J Cancer 2004; 111(5):711-9.
14. Bussemakers MJ, Van Bokhoven A, Tomita K, Jansen CF, Schalken JA. Complex cadherin expression in human prostate cancer cells. Int J Cancer 2000; 85(3):446-50.
15. Yan X, Yan L, Liu S, Shan Z, Tian Y, Jin Z. N-cadherin, a novel prognostic biomarker, drives malignant progression of colorectal cancer. Mol Med Rep 2015; 12(2):2999-3006.
16. Al-Maghrabi J, Emam E, Gomaa W, Saggaf M, Buhmeida A, Al-Qahtani M, *et al.* c-MET immunostaining in colorectal carcinoma is associated with local disease recurrence. BMC Cancer 2015; 15:676.
17. Liu GL, Yang HJ, Liu T, Lin YZ. Expression and significance of E-cadherin, N-cadherin, transforming growth factor-beta1 and Twist in prostate cancer. Asian Pac J Trop Med 2014; 7(1):76-82.
18. Mariotti A, Perotti A, Sessa C, Ruegg C. N-cadherin as a therapeutic target in cancer. Expert Opin Investig Drugs 2007; 16(4):451-65.
19. Kim JB, Islam S, Kim YJ, Prudoff RS, Sass KM, Wheelock MJ, *et al.* N-Cadherin extracellular repeat 4 mediates epithelial to mesenchymal transition and increased motility. J Cell Biol 2000; 151(6):1193-206.
20. Joo YE, Rew JS, Park CS, Kim SJ. Expression of E-cadherin, alpha- and beta-catenins in patients with pancreatic adenocarcinoma. Pancreatology 2002; 2(2):129-37.
21. Hazan RB, Phillips GR, Qiao RF, Norton L, Aaronson SA. Exogenous expression of N-cadherin in breast cancer cells induces cell migration, invasion, and metastasis. J Cell Biol 2000; 148(4):779-90.
22. Hulpiau P, van Roy F. Molecular evolution of the cadherin superfamily. Int J Biochem Cell Biol 2009; 41(2):349-69.
23. Xie X, Zheng X, Wang J, Chen L. Clinical significance of Twist, E-cadherin, and N-cadherin protein expression in endometrioid adenocarcinoma. J Cancer Res Ther 2017; 13(5):817-22.
24. Tsuchiya B, Sato Y, Kameya T, Okayasu I, Mukai K. Differential expression of N-cadherin and E-cadherin in normal human tissues. Arch Histol Cytol 2006; 69(2):135-45.

25. Prudkin L, Liu DD, Ozburn NC, Sun M, Behrens C, Tang X, *et al.* Epithelial-to-mesenchymal transition in the development and progression of adenocarcinoma and squamous cell carcinoma of the lung. Mod Pathol 2009; 22(5):668-78.
26. Luo WR, Wu AB, Fang WY, Li SY, Yao KT. Nuclear expression of N-cadherin correlates with poor prognosis of nasopharyngeal carcinoma. Histopathology 2012; 61(2):237-46.
27. Tothill RW, Tinker AV, George J, Brown R, Fox SB, Lade S, *et al.* Novel molecular subtypes of serous and endometrioid ovarian cancer linked to clinical outcome. Clin Cancer Res 2008; 14(16):5198-208.
28. Quattrocchi L, Green AR, Martin S, Durrant L, Deen S. The cadherin switch in ovarian high-grade serous carcinoma is associated with disease progression. Virchows Arch 2011; 459(1):21-9.
29. Nakashima T, Huang C, Liu D, Kameyama K, Masuya D, Kobayashi S, *et al.* Neural-cadherin expression associated with angiogenesis in non-small-cell lung cancer patients. Br J Cancer 2003; 88(11):1727-33.
30. Tomita K, van Bokhoven A, van Leenders GJ, Ruijter ET, Jansen CF, Bussemakers MJ, *et al.* Cadherin switching in human prostate cancer progression. Cancer Res 2000; 60(13):3640-4.
31. Nakajima S, Doi R, Toyoda E, Tsuji S, Wada M, Koizumi M, *et al.* N-cadherin expression and epithelial-mesenchymal transition in pancreatic carcinoma. Clin Cancer Res 2004; 10(12 Pt 1):4125-33.
32. Abufaraj M, Haitel A, Moschini M, Gust K, Foerster B, Ozsoy M, *et al.* Prognostic role of N-cadherin expression in patients with invasive bladder cancer. Clin Genitourin Cancer 2017; 15:S1558-7673 (17) 30198-2.
33. Lascombe I, Clairotte A, Fauconnet S, Bernardini S, Wallerand H, Kantelip B, *et al.* N-cadherin as a novel prognostic marker of progression in superficial urothelial tumors. Clin Cancer Res 2006; 12(9):2780-7.

Original Article

# Surgical treatment of severe (Grade-C) pancreas fistula after pancreatojejunostomy by external wirsungostomy

Ozkan Subasi, Metin Ercan, Mehmet Aziret, Onur Ilhan, Cemalettin Kaan Mansiroglu, Kerem Karaman
Department of Gastroenterological Surgery, Sakarya University Teaching and Training Hospital, Sakarya, Turkey

Kuwait Medical Journal 2023; 55 (4): 329 - 335

## ABSTRACT

**Objective:** Postoperative pancreas fistula is the most feared complication after pancreaticoduodenectomy (PD). Rescue re-laparotomy may be required in patients whose pancreaticojejunal anastomosis is disrupted to a large extent. Besides, the most appropriate surgical strategy has not been determined yet. We aimed to present our wirsungostomy experience for postoperative grade-C pancreas fistula and its outcomes.
**Design:** A retrospective study
**Setting:** Department of Gastroenterological Surgery, Sakarya University Teaching and Research Hospital
**Subjects:** All patients on whom PD was applied between January 2015 and December 2019 were retrospectively analyzed.
**Intervention:** Among the 60 patients who received PD, external wirsungostomy was applied in re-laparotomy on six patients due to symptomatic grade-C fistula.
**Main outcome measures:** Data such as operation types, ductus diameter in the pancreas after resection, postoperative pathology results and fistula grades were recorded retrospectively.
**Results:** Grade-C pancreas fistula diagnosis was made for six of the 60 patients who received PD, and external wirsungostomy was applied on these patients with re-laparotomy. Re-pancreatojejunostomy was applied only in one of the six patients. In the other five patients, the external polyethylene tube catheter was removed from the pancreatic duct after a mean time of 96 days (58-150 days). The mean time of hospitalization was 63 days (36-82 days). The 3-month mortality rate was 0%.
**Conclusion:** In grade-C pancreas fistulae, for the purpose of preventing mortality-associated total pancreatectomy, the practice of pancreas-protective external wirsungostomy may be categorized as a life-saving procedure.

**KEY WORDS:** external wirsungostomy, pancreatic fistula, pancreaticojejunostomy

## INTRODUCTION

Although standardization of pancreaticoduodenectomy (PD) has been achieved, while the mortality rate at experienced centers is fewer than 5%, morbidity rates up to 50% have been reported[1-3]. The most significant cause of mortality and morbidity is postoperative pancreatic fistula[4]. The clinically significant postoperative pancreatic fistula (PPF) rate was reported between 2% and 20%[4,5].

An international consensus on PPF grading was introduced for the first time in 2005 by the International Study Group on Pancreatic Surgery (ISGPS), while it was updated in 2016[4,6]. Grade-B and grade-C PPF was defined as clinically significant PPF that requires intervention and even re-laparotomy. Although the definition and grading of PPF have been well-determined, there is still no consensus on the optimal treatment strategy[7-9].

Even though most PPF patients can be treated conservatively, re-laparotomy may be required for pancreatic fistulae complicated with intraabdominal abscess, peritonitis or uncontrolled bleeding[10-12]. For a long period of time, completion pancreatectomy had been accepted as the standard treatment for severe PPF[13]. However, its high mortality and morbidity rates and permanent exocrine and endocrine failure make this procedure suitable only for selected cases[13,14].

It is seen that pancreas-protective procedures are not only easier to apply and less invasive than completion pancreatectomy, but they also provide

*Address correspondence to:*
*Ozkan Subasi, MD, Department of Gastroenterological Surgery, Sakarya University Teaching and Research Hospital, Adnan Menderes Caddesi Sağlık Sokak No: 195 Adapazarı, 5400, Sakarya, Turkey. Tel: +90 5053842109; E-mail: osubasi25@hotmail.com*

more positive results in terms of morbidity, mortality and long-term protection of endocrine and exocrine functions[7,15,16].

As selection of pancreas-protective procedures would vary based on the preferences and experiences of surgeons and the general status of the patient, it seems impossible to form a universal consensus.

The aim of the present retrospective study was to examine the outcomes of external wirsungostomy which was applied with the aim of preserving pancreas function and to reduce perioperative morbidity and mortality in grade-C PPF after PD.

## SUBJECTS AND METHODS

### Patients and definitions of clinical parameters

With the approval of the non-invasive Studies Ethics Committee of Sakarya University, all patients on whom PD was applied between January 2015 and December 2019 in Sakarya University Teaching and Research Hospital's department of Gastroenterological Surgery Clinic were determined. Clinical data were retrospectively collected and analyzed. Gastroenterology surgery clinic was established in Ankara Yüksek İhtisas Training and Research Hospital in the early 1990s. Our experienced team here established the Gastroenterogy Surgery clinic in Sakarya University Faculty of Medicine in 2013. Active work started in 2015. The surgeries and data of the patients treated by the team has been included in the study . For this reason, the data we used in our study was included since 2015.

According to the ISGPS criteria revised in 2016[6]: for pancreas fistula, the necessary threshold is that the amylase level in the drain fluid accumulated in the pancreatic head is 3 times higher than the serum amylase level after the 3rd postoperative day. In addition to this, it should be clinically significant to be defined as PPF. In the new definition, grade-A PPF was defined as "biochemical leak". It does not have clinical significance, and thus, it is not accepted as an actual pancreatic fistula. Grade-B PPF is clinically significant, it may leave pancreatic drains where they are for a long time, and percutaneous or endoscopic interventional drainage may be necessary. If PPF-related bleeding or aneurism occurs, transfusion and/or angiography are required. Grade-C PPF was defined as a pancreatic fistula that requires re-laparotomy or involves PPF-related multi-organ failure and/or causes mortality.

Information was collected on demographic characteristics, risk factors for PPF, surgical parameters such as degree and type of PPF-related complications, pancreatic anastomosis technique, and surgery time and re-laparotomy outcomes.

Re-laparotomy indications were determined as sepsis continuing despite maximum conservative treatment, septic intraabdominal collections that cannot be drained by noninvasive methods and uncontrolled massive bleeding.

Postoperative complications were categorized retrospectively for all patients based on the Clavien-Dindo classification.

**Table 1:** Demographic data and clinical features

| Parameters | n (%) |
|---|---|
| Sex | |
| Male | 43 (71.6) |
| Female | 17 (28.3) |
| Age (year) | 61.7 (29 - 84) |
| ASA score | |
| I | 2 (3.3) |
| II | 28 (46.6) |
| III | 29 (48.3) |
| IV | 1 (1.6) |
| Co-morbidity | |
| Diabetes mellitus | 23 (38.3) |
| Hypertension | 24 (40) |
| Coronary artery disease | 5 (8.3) |
| Chronic obstructive pulmonary disease | 5 (8.3) |
| Elevated total bilirubin level (>5 mg/dL) | 39 (65) |
| Preoperative biliary drainage | |
| Nasobiliary drainage | 6(10) |
| ERCP stent placement | 24 (40) |
| PTC stent placement | 5(8.3) |
| Pancreaticojejunostomy technique | |
| Duct-to-mucosa (Wirsung Jejunostomy) | 44 (73.3) |
| Invagination (Dunking) | 16 (26.6) |
| Texture of the pancreas | |
| Soft | 22 (36.6) |
| Hard | 28 (46.6) |
| Normal | 10 (16.6) |
| Diameter of the main pancreatic duct (mm) | 4.2 (2-11) |
| Portal vein invasion | 7 (11.6) |
| Resection | |
| R0 | 54 (90) |
| R1 | 6(10) |
| R2 | 0 |
| Definitive pathology | |
| Pancreatic adenocarcinoma | 19 (31.6) |
| Ampulla vateri adenocarcinoma | 9 (15) |
| Duodenal adenocarcinoma | 6 (10) |
| Intraductal papillary mucinous neoplasm | 3 (5) |
| Pancreatic neuroendocrine neoplasm | 3 (5) |
| Bile duct carcinoma | 8 (13.3) |
| Serous cystic neoplasm | 2 (3.3) |
| Pancreatic mucinous cystic neoplasms | 4 (6.6) |
| Others | 6 (10) |
| PPF | 10 (16.6) |
| Biochemical leak | 5(8.3) |
| Grade B | 4(6.6) |
| Grade C | 6(10) |
| 30-day mortality | 4(6.6) |

ASA: American Society of Anesthesiologists; ERCP: endoscopic retrograde cholangio pancreatography; PTC: percutaneous transhepatic cholangiography; PPF: postoperative pancreatic fistula

**Surgical strategy**

The surgical procedure in re-laparotomy involved checking all anastomoses after abdominal explorations, achieving debridement of all necrotic and septic tissues and collections by washing and aspiration, and achieving hemostasis by determination of the focus of bleeding. After fixing the separation in the pancreaticojejunal anastomosis, the jejunal stump was closed by using a linear GIA stapler. Afterwards, to achieve drainage of pancreatic fluid, the main pancreatic duct in the remaining pancreas tissue was cannulated with a polyethylene catheter. The catheter was fixed on the pancreas tissue by a 4/0 PDS suture, the free end was taken outside the abdomen from the top right quadrant of the abdomen and fixed on the skin, and external drainage was achieved. Two intra-abdominal silicone drains were placed. The first one was placed behind the hepaticojejunostomy, and the other was placed at the inferior of the remaining pancreas tissue. The abdomen was closed in a standard manner.

Postoperative leukocytosis, C-reactive protein and biochemistry assessment was systematically made during hospitalization. Antibiotics therapy was determined based on bacterial culture results. Parenteral nutrition was started as soon as possible, and it was replaced by enteral and oral nutrition after the gastrointestinal ileus was fixed. The silicone drains that were placed into the abdominal cavity were removed when their daily yield dropped below 30 ml.

**Statistical analysis**

The statistical analyzes were performed using SPSS (Statistical Package for the Social Sciences ver. 21.0, SPSS Inc, Chicago, Illinois, USA). Continuous variables were shown as mean±SD or median (min-max), where applicable. Nominal data were expressed as number of cases and percentages.

**RESULTS**

PD was applied on 60 patients due to different periampullary region pathologies. Forty-three of these patients were male, 17 were female. Their mean age was 61.7 years (range: 29-84). One-month mortality rate was 6.6%. Three patients died due to cardiac arrest and one patient died due to pulmonary embolism. Demographic characteristics, surgical technique, intraoperative findings and pathological diagnoses are shown in Table 1.

There was PPF in 10 of the 60 patients who were given PD (16.6%). While four patients with grade-B PPF were conservatively treated, external wirsungostomy with re-laparotomy was applied on six patients with grade-C PPF. In the re-laparotomy, the indication was development of a life-threatening complication in PPF. The re-laparotomy rate among the PPF patients was 60% (6 of 10 patients). No organ failure was observed before re-laparotomy in any patient. The re-laparotomy was carried out after a mean time of 13 days (range: 5-26 days) by following emergency procedures. In the exploration, no symptom of failure in biliary anastomosis was observed in any patients. The mean duration of surgery was 110 minutes (range: 80-150 min). All patients required treatment at the intensive care unit.

All six patients on whom external wirsungostomy was applied were male. Their mean age was 64.5 years (range: 56-76 years). Table 2 shows medical comorbidities and preoperative patient characteristics based on American Society of Anesthesiologists scores and PD indications.

In the six patients on whom PD was applied, pancreaticojejunal anastomosis was made by wirsungojejunostomy in four patients and dunking procedure in two patients. Re-laparotomy was applied due to massive hemorrhage in four patients and secondary peritonitis in two. Among the four patients in whom massive hemorrhage was determined during re-laparotomy, the bleeding was in the gastroduodenal artery stump in one patient, hepatic artery branch in one and pancreas tissue in one, while the focus of bleeding could not be found in one patient. Indications and surgical findings are given in detail in Table 3.

The mean duration of hospitalization was 63 days (range: 36-82 days). No patients died in the early postoperative period. The patients who were discharged

**Table 2:** Preoperative features of patients undergoing external wirsungostomy

| Patient no./ sex/age | ASA score | Comorbidity | Preoperative albumin | Postoperative pancreatitis | Drain amylase output | Definitive pathology |
|---|---|---|---|---|---|---|
| 1/ M / 61 | 2 | HT | 4.3 | Yes | Low | Pancreatic adenocarcinoma |
| 2/ M / 60 | 2 | HT and DM | 3.5 | No | High | Adenocarcinoma of the ampulla of Vater |
| 3/ M / 71 | 3 | HT and CAD | 3.2 | No | High | Low-grade dysplasia |
| 4/ M / 63 | 2 | --- | 2.7 | No | High | Adenocarcinoma of the ampulla of Vater |
| 5/ M / 76 | 3 | HT and CAD | 3.4 | Yes | High | Duodenal adenocarcinoma |
| 6/ M / 56 | 2 | HT and COPD | 4 | No | Low | Adenocarcinoma of the ampulla of Vater |

M: male; ASA: American Society of Anesthesiologists; HT: hypertension; DM: diabetes mellitus; CAD: coronary artery disease; COPD: chronic obstructive pulmonary disease

**Table 3:** Indications for re-laparotomy in external wirsungostomy and intraoperative findings

| Patient no./sex/age | Indications for re-laparotomy | Pancreaticojejunostomy technique | Pancreatic consistency | Diameter of the main pancreatic duct (mm) |
|---|---|---|---|---|
| 1/ M / 61 | Hemorrhage | Wirsungo-jejunostomy | Soft | 3 |
| 2/ M / 60 | Sepsis | Dunking | Soft | 2 |
| 3/ M / 71 | Sepsis | Dunking | Soft | 3 |
| 4/ M / 63 | Hemorrhage | Wirsungo-jejunostomy | Hard | 7 |
| 5/ M / 76 | Hemorrhage | Wirsungo-jejunostomy | Hard | 2 |
| 6/ M / 56 | Hemorrhage | Wirsungo-jejunostomy | Hard | 3 |

M: male; mm: millimeter

were called for routine polyclinic checkups, and when the daily yield of the external wirsungostomy catheter in five patients dropped below 5 cc, the drainage catheter was gradually pulled back and removed, and the wirsungostomy spontaneously closed. The mean catheter follow-up process was 96 days (58-150 days). Another patient was re-operated on after 110 days, secondary pancreatojejunostomy reconstruction was made, and no complication developed in his follow-ups. Oral pancreatic enzyme replacement treatment was required for all patients. The 90-day mortality rate was 0%. One patient died in the 8th month after surgery due to ischemic cerebrovascular disease, while one patient died of relapse in the 14th month.

## DISCUSSION

In PD surgery, a leak in the pancreaticojejunal anastomosis is a high-risk complication associated with a specific morbidity rate of up to 30-50%, increased hospitalization and higher hospital costs. Additionally, it was shown that it leads to mortality due to uncontrolled retroperitoneal sepsis or massive hemorrhage in 20-40% of this patient group[17].

The pancreatic fistula rates reported by centers experienced in pancreatic surgery still vary between 2.1% and 25%[16,18,19]. According to the revised pancreatic fistula classification of the ISGPS[6], the post-PD pancreatic fistula rate at our clinic was 16.6%.

It is accepted that, in PPF, conservative treatment is effective in 40% to 70% of patients[14,20,21]. Conservative treatment involves somatostatin or analogues to reduce pancreatic secretion, percutaneous drainage by guidance of computerized tomography, target-oriented antibiotics treatment and enteral and parenteral nutrition[22]. In the case of septic status continuing despite conservative treatment, symptomatic intraabdominal abscess that cannot be accessed by percutaneous drainage, radiological embolization or bleeding continuing despite stenting, intervention must be made by re-laparotomy[12].

For many years, in severe PPF requiring re-laparotomy after PD, completion pancreatectomy (CP) was the preferred treatment method. Studies have shown that post-CP mortality rates vary between 20% and 71%[23-27]. In addition to this, it was reported that the technical difficulty and extension of the duration of surgery increase the mortality rate[5,13]. In cases complicated with peritonitis, severe sepsis or massive hemorrhage, "damage control" is important, and selecting a less invasive procedure may be better. In recent years, pancreas-protective procedures have gained popularity. As they are less invasive and more easily applicable in patients who are not hemodynamically stable, have less blood loss and short operation times, the pancreas' endocrine and even exocrine function may be preserved.

In a systematic review including 140 patients on whom pancreas-protective surgical strategies such as simple drainage, pancreatic duct occlusion, subtotal pancreatectomy, internal-external wirsungostomy and pancreaticogastrostomy were applied, it was shown that the success rate in grade-C PPF after PD was approximately 94%, while the re-intervention rate was 25%[28]. However, there is still no consensus on the optimal pancreas protection strategy for PPF. Efforts of standardizing the surgical approach in grade-C PPF become more difficult as every medical center manages PPF differently, and every surgeon applies their own preference in different intraoperative cases.

Simple drainage is the most frequently used one among protective techniques, and in recent studies, its mortality rates were reported between 11% and 67%[14,15,23]. This is similar to the mortality rate of CP. The disadvantage of this technique is that it increases the risk of permanent sepsis by contamination of the peritoneal cavity by uncontrolled pancreatic and gut content and requires repeated advanced surgical interventions. It is believed that subtotal pancreatectomy may reduce the probability of pancreas endocrine failure. However, its morbidity and mortality rates are even higher than those of CP[15].

Pancreaticogastrostomy may be an alternative strategy[27]. Nevertheless, it was not completely assessed in any studies. Additionally, it has technical difficulties in the face of severe local inflammation and fragile pancreatic tissue.

There are studies which have proposed external wirsungostomy as a better alternative to CP in

terms of mortality and morbidity[16,29-32]. External wirsungostomy prevents the risk of chemical irritation of surrounding blood vessels and tissues by evacuating the pancreas fluid from the surgical region. As the remaining pancreas tissue is preserved, another advantage of it is that the pancreas endocrine function is not disrupted, and spleen function is protected. Additionally, as this procedure is simple, fast and less invasive in hemodynamically unstable patients, it may be accepted as a reasonable treatment option. It provides treatment opportunities in the early period for patients who will receive adjuvant chemotherapy.

The disadvantages of external wirsungostomy include that pancreatojejunostomy may require elective reconstruction. Upon observing that there was no yield from the wirsungostomy catheters in five of our patients, the catheters were removed. These patients without pancreatojejunostomy reconstruction were followed-up asymptotically. Ma *et al* reported two similar cases[33]. In these five patients, there was no finding of pancreatitis, intraabdominal fluid collection, pseudocyst or peritonitis. This implies that an internal fistula may form between the pancreatic duct and the bowels during this process. However, to confirm this and make sure of the underlying mechanism, studies with more patients are needed.

In one other patient of ours, as the yield from the drainage catheter did not decrease, elective reconstruction of pancreatojejunostomy was carried out, and the follow-up of the patient continued without any early or late complications.

In the study by Paye *et al*, external wirsungostomy was applied on 12 patients due to grade-C PPF, and elective reconstruction of pancreatojejunostomy was applied on nine of these patients. The postoperative mortality rate was reported as 12%[29].

In the study by Wronski *et al*, for grade-C PPF, simple drainage in 16 patients, CP in 17 patients and external wirsungostomy in 10 patients were applied. The mortality rates were reported as 56.3% for simple drainage, 47.1% for CP and 50% for external wirsungostomy[34]. Ribero *et al*[32] reported nine patients on whom external wirsungostomy was applied who had no postoperative mortality. Similarly, there was no postoperative mortality in our study. This positive outcome is dependent on close and careful monitoring of patients who have grade-C PPF and making the re-laparotomy decision before multi-organ failure develops in patients. We think that the main factor predicting mortality is dependent on the presence of organ failure before re-operation.

Our study had some limitations. First of all, as it was a retrospective study, randomization could not be performed. Second of all, it did not include a group for another pancreas-protective procedure to make a comparison. It was a good option to compare the results with the patient group who received a different approach. However, we did not find it appropriate to use the follow-up methods and data of the surgical teams in this patient group before our gastroenterology surgery clinic was established. As the number of cases was low, it is needed to confirm these results with a larger sample and define other possible outcomes that will not show a significant difference from our study. On the other hand, the results are promising and seem to be effective in terms of a damage control surgery.

## CONCLUSION

Although the current literature has proposed several different surgical treatment options for grade-C pancreatic fistula after PD, the difficulty in clinical management continues. Patients with PPF should be closely monitored, and the re-laparotomy decision must be made before multi-organ failure develops. In critical patients who are hemodynamically unstable, during emergency re-laparotomy, CP should only be preferred in cases with pancreatic necrosis and situations where pancreas-protective procedures are technically not possible, and it should not be the first treatment option. Additionally, the usefulness of aggressive surgery against the risk of postoperative morbidity and mortality is questionable. For this reason, simple, less invasive pancreas-protective procedures with shorter operation times should be preferred. It is difficult to determine which procedure is the most suitable. The final decision needs to be dependent on the experience and preference of the surgeon. According to our clinical results, in grade-C PPF, external wirsungostomy may be preferable with its acceptable morbidity and mortality rates, and it may be categorized as a life-saving procedure in emergency re-laparotomy.

## ACKNOWLEDGMENT

**Author contributions:**

- Conception and design, or analysis and interpretation of data: Oskan Subasi, Metin Ercan, Kerem Karaman , Mehmet Aziret.
- Drafting the article or revising it critically for important intellectual content: Oskan Subasi, Metin Ercan, Kerem Karaman, Mehmet Aziret, Cemalettin Kaan Mansiroglin, Onur Ilhan.
- Final approval of the version to be published: Oskan Subasi, Metin Ercan, Kerem Karaman.
- Statistical analysis: Mehmet Aziret, Cemalettin Kaan Mansiroglin, Onur Ilhan..
- Study supervision: Metin Ercan, Kerem Karaman.

**Conflict of interest:** The authors declare no conflict of interest.

**Funding:** None.

## REFERENCES


1. Addeo P, Delpero JR, Paye F, Oussoultzoglou E, Fuchshuber PR, Sauvanet A, *et al*. Pancreatic fistula after a pancreaticoduodenectomy for ductal adenocarcinoma and its association with morbidity: a multicentre study of the French Surgical Association. HPB (Oxford) 2014; 16(1):46-55.
2. Pessaux P, Sauvanet A, Mariette C, Paye F, Muscari F, Cunha AS, *et al*. External pancreatic duct stent decreases pancreatic fistula rate after pancreaticoduodenectomy: prospective multicenter randomized trial. Ann Surg 2011; 253(5):879-85.
3. De Oliveira ML, Winter JM, Schafer M, Cunningham SC, Cameron JL, Yeo CJ, *et al*. Assessment of complications after pancreatic surgery: a novel grading system applied to 633 patients undergoing pancreaticoduodenectomy. Ann Surg 2006; 244(6):931-7; discussion 937-9.
4. Bassi C, Dervenis C, Butturini G, Fingerhut A, Yeo C, Izbicki J, *et al*. International Study Group on Pancreatic Fistula Definition. Postoperative pancreatic fistula: an international study group (ISGPF) definition. Surgery 2005; 138(1):8-13.
5. Nentwich MF, El Gammal AT, Lemcke T, Ghadban T, Bellon E, Melling N, *et al*. Salvage completion pancreatectomies as damage control for post-pancreatic surgery complications: a single-center retrospective analysis. World J Surg 2015; 39(6):1550-6.
6. Bassi C, Marchegiani G, Dervenis C, Sarr M, Hilal MA, Adham M, *et al*. The 2016 update of the International Study Group (ISGPS) definition and grading of postoperative pancreatic fistula: 11 years after. Surgery 2017; 161(3):584-91.
7. Dellaportas D, Tympa A, Nastos C, Psychogiou V, Karakatsanis A, Polydorou A, *et al*. An ongoing dispute in the management of severe pancreatic fistula: pancreatospleenectomy or not? World J Gastrointest Surg 2010; 2(11):381-4.
8. Malleo G, Pulvirenti A, Marchegiani G, Butturini G, Salvia R, Bassi C. Diagnosis and management of postoperative pancreatic fistula. Langenbecks Arch Surg 2014; 399(7):801-10.
9. McMillan MT, Vollmer Jr CM, Asbun HJ, Ball CG, Bassi C, Beane JD, *et al*. The characterization and prediction of ISGPF grade C fistulas following pancreatoduodenectomy. J Gastrointest Surg 2016; 20(2):262-76.
10. Gueroult S, Parc Y, Duron F, Paye F, Parc R. Completion pancreatectomy for postoperative peritonitis after pancreaticoduodenectomy: early and late outcome. Arch Surg 2004; 139(1):16-9.
11. Tamijmarane A, Ahmed I, Bhati CS, Mirza DF, Mayer AD, Buckels JAC, *et al*. Role of completion pancreatectomy as a damage control option for post-pancreatic surgical complications. Dig Surg 2006; 23(4):229-34.
12. Blanc T, Cortes A, Goere D, Sibert A, Pessaux P, Belghiti J, *et al*. Hemorrhage after pancreaticoduodenectomy: when is surgery still indicated? Am J Surg 2007; 194(1):3-9.
13. Farley DR, Schwall G, Trede M. Completion pancreatectomy for surgical complications after pancreaticoduodenectomy. Br J Surg 1996; 83(2):176-9.
14. Haddad LB, Scatton O, Randone B, Andraus W, Massault PP, Dousset B, *et al*. Pancreatic fistula after pancreaticoduodenectomy: the conservative treatment of choice. HPB (Oxford) 2009; 11(3):203-9.
15. de Castro SMM, Busch ORC, van Gulik TM, Obertop H, Gouma DJ. Incidence and management of pancreatic leakage after pancreatoduodenectomy. Br J Surg 2005; 92(9):1117-23.
16. Denost Q, Pontallier A, Rault A, Ewald JA, Collet D, Masson B, *et al*. Wirsungostomy as a salvage procedure after pancreaticoduodenectomy. HPB (Oxford) 2012; 14(2):82-6.
17. Seetharam P, Rodrigues GS. Postoperative pancreatic fistula: A surgeon's nightmare! An insight with a detailed literature review. JOP 2015; 16(2):115-24.
18. Daskalaki D, Butturini G, Molinari E, Crippa S, Pederzoli P, Bassi C. A grading system can predict clinical and economic outcomes of pancreatic fistula after pancreaticoduodenectomy: results in 755 consecutive patients. Langenbecks Arch Surg 2011; 396(1):91-8.
19. Schmidt CM, Choi J, Powell ES, Yiannoutsos CT, Zyromski NJ, Nakeeb A, *et al*. Pancreatic fistula following pancreaticoduodenectomy: clinical predictors and patient outcomes. HPB Surg 2009; 2009:404520.
20. Reid-Lombardo KM, Farnell MB, Crippa S, Barnett M, Maupin G, Bassi C, *et al*; Pancreatic Anastomotic Leak Study Group. Pancreatic anastomotic leakage after pancreaticoduodenectomy in 1,507 patients: a report from the Pancreatic Anastomotic Leak Study Group. J Gastrointest Surg 2007; 11(11):1451-9.
21. Kazanjian KK, Hines OJ, Eibl G, Reber HA. Management of pancreatic fistulas after pancreaticoduodenectomy: results in 437 consecutive patients. Arch Surg 2005; 140(9):849-56.
22. Klek S, Sierzega M, Turczynowski L, Szybinski P, Szczepanek K, Kulig J. Enteral and parenteral nutrition in the conservative treatment of pancreatic fistula: a randomized clinical trial. Gastroenterology 2011; 141(1):157-63.
23. Balzano G, Pecorelli N, Piemonti L, Ariotti R, Carvello M, Nano R, *et al*. Relaparotomy for a pancreatic fistula after a pancreaticoduodenectomy: a comparison of different surgical strategies. HPB (Oxford) 2014; 16(1):40-5.
24. Cullen JJ, Sarr MG, Ilstrup DM. Pancreatic anastomotic leak after pancreaticoduodenectomy: incidence, significance, and management. Am J Surg 1994; 168(4):295-8.
25. Xu J, Dai X, Bu X, Gao F, Zhang X. Pancreaticojejunal bridge-anastomosis: a novel option for surgeon to preserve pancreatic body and tail in urgent reoperation for intra-abdominal massive hemorrhage after pancreaticoduodenectomy. World J Surg 2010; 34(10):2457-62.

26. Erdem H, Çetinkünar S, Aziret M, Reyhan E, Sözütek A, Sözen S, *et al*. Can isolated pancreaticojejunostomy reduce pancreas fistula after pancreaticoduodenectomy with Roux-en-Y reconstruction? Turk J Surg 2016; 32(4):248-51.
27. Bachellier P, Oussoultzoglou E, Rosso E, Scurtu R, Lucescu I, Oshita A, *et al*. Pancreatogastrostomy as a salvage procedure to treat severe postoperative pancreatic fistula after pancreatoduodenectomy. Arch Surg 2008; 143(10):966-70.
28. Bouras AF, Marin H, Bouzid C, Pruvot FR, Zerbib P, Truant S. Pancreas-preserving management in reinterventions for severe pancreatic fistula after pancreatoduodenectomy: a systematic review. Langenbecks Arch Surg 2016; 401(2):141-9.
29. Paye F, Lupinacci RM, Kraemer A, Lescot T, Chafaï N, Tiret E, *et al*. Surgical treatment of severe pancreatic fistula after pancreaticoduodenectomy by wirsungostomy and repeat pancreatico-jejunal anastomosis. Am J Surg 2013; 206(2):194-201.
30. Horvath P, Beckert S, Nadalin S, Königsrainer A, Königsrainer I. Pancreas-preserving surgical management of grade-C pancreatic fistulas after pancreatic head resection by external wirsungostomy. Langenbecks Arch Surg 2016; 401(4):457-62.
31. Königsrainer I, Zieker D, Beckert S, Glatzle J, Schroeder TH, Heininger A, *et al*. A pancreas-preserving technique for the management of symptomatic pancreatic anastomotic insufficiency refractory to conservative treatment after pancreas head resection. Langenbecks Arch Surg 2010; 395(6):693-6.
32. Ribero D, Amisano M, Zimmitti G, Giraldi F, Ferrero A, Capussotti L. External tube pancreatostomy reduces the risk of mortality associated with completion pancreatectomy for symptomatic fistulas complicating pancreaticoduodenectomy. J Gastrointest Surg 2013; 17(2):332-8.
33. Ma T, Bai X, Chen W, Li G, Lao M, Liang T. Pancreas-preserving management of grade-C pancreatic fistula and a novel bridging technique for repeat pancreaticojejunostomy: an observational study. Int J Surg 2018; 52:243-7.
34. Wroński M, Cebulski W, Witkowski B, Guzel T, Karkocha D, Lech G, *et al*. Surgical management of the grade C pancreatic fistula after pancreatoduodenectomy. HPB (Oxford) 2019; 21(9):1166-74.

Original Article

# Prevalence of osteoarthritis in Korean patients with chronic obstructive pulmonary disease: a cross-sectional study

Jae Hyun Jung[1,2], Ji Hyun Lim[1,3], Hongdeok Seok[4], Gwan Gyu Song[1,5], Sung Jae Choi[1,2]
[1]Department of Internal Medicine, Korea University College of Medicine, 73 Goryeodae-ro, Seongbuk-gu, Seoul, 02841, Republic of Korea
[2]Division of Rheumatology, Department of Internal Medicine, Korea University Ansan Hospital, 123 Jeokgeum-ro, Danwon-gu, Ansan-si, Gyeonggi-do, 15354, Republic of Korea
[3]Department of Internal Medicine, Soksiwon Clinic, 688 Michuhol-ro, Michuhol-gu, Incheon, 22140, Republic of Korea
[4]Department of Occupational and Environmental Medicine, Busan Adventist Hospital, Sahmyook Medical Centre, 170 Daeti-ro, Seo-gu, Busan, 49230, Republic of Korea
[5]Division of Rheumatology, Department of Internal Medicine, Korea University Guro Hospital, 148 Gurodong-ro, Guro-gu, Seoul, 08307, Republic of Korea

Kuwait Medical Journal 2023; 55 (4): 336 - 342

## ABSTRACT

**Objective:** Chronic obstructive pulmonary disease (COPD) is an inflammatory disease associated with physical disability and various comorbidities. The disease often leads to musculoskeletal weakness and may be associated with the prevalence of osteoarthritis (OA). Here, we aimed to investigate the prevalence of OA among patients with COPD and the relationship between COPD and OA.
**Design:** Cross-sectional study
**Setting:** Nationwide
**Subjects:** Participants (4324 men and 5499 women) who underwent pulmonary function tests, knee and hip radiography, and health surveys.
**Intervention:** Comparison of the prevalence of OA between patients with and without COPD, adjusted for age, body mass index, smoking status, hypertension, diabetes mellitus, dyslipidemia and occupation.
**Main outcome measures:** The odds ratios (ORs) and 95% confidence intervals (CIs) were used to determine the prevalence of OA in patients with COPD.
**Results:** The overall prevalence of COPD in Korea was 1.6% (3.6% men; 0.1% women). The prevalence of OA among male patients with COPD was 11%, which is higher than that among those without COPD (6.6%). However, a significant difference in OA prevalence was not found between the COPD and non-COPD groups (OR: 1.50; 95% CI: 0.87-2.57).
**Conclusion:** The prevalence of OA was higher among males with COPD than among those without COPD; however, no significant relationship was found between the presence of COPD and the prevalence of OA.

**KEY WORDS:** chronic obstructive pulmonary disease, Korea, osteoarthritis, prevalence

## INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is characterized by limited airflow and persistent respiratory symptoms; it results from exposure to harmful substances such as tobacco[1]. COPD is associated with chronic symptoms that lead to the development of physical disabilities, decreased quality of life, increased global disease burden and increased mortality rates[2]. COPD also affects various other diseases, such as cardiovascular disease, musculoskeletal disease, metabolic syndrome and mental illness[3]. Patients with COPD often develop musculoskeletal diseases associated with bone and muscle loss, such as osteoporosis, cachexia and muscle dysfunction. The evaluation of a patient with COPD involves an assessment of the patient's ability to exercise; decreased muscle strength resulting from a decreased ability to exercise can lead to musculoskeletal disorders[4].

*Address correspondence to:*
*Sung Jae Choi, MD, PhD, Division of Rheumatology, Department of Internal Medicine, Korea University Ansan Hospital, 123 Jeokgeum-ro, Danwon-gu, Ansan-si, Gyeonggi-do, 15354, Republic of Korea. Tel: +82 314124982; Mob: +82 1052062268; E-mail: csjmd888@korea.ac.kr*

Osteoarthritis (OA) is the most commonly encountered musculoskeletal disease among the elderly and primarily begins with degenerative changes in the cartilage and progresses to bone damage and weakening of the surrounding muscles and ligaments[5]. Damage to the cartilage, bone and muscle may lead to the development of chronic pain and joint deformation which, in turn, leads to the development of physical disabilities and increased disease burden. OA is also closely related to diseases other than musculoskeletal disorders, including cardiovascular disease, metabolic syndrome and mental illness[6,7].

As both OA and COPD are associated with chronic symptoms, physical disabilities, various other diseases and high medical cost burdens, investigating the association between them is important for improving the patients' quality of life[8]. In addition, as irreversible organ structural changes are noted in patients with these diseases, management of both diseases is important. OA and COPD cause inflammation of the joints and lungs, respectively; however, factors related to systemic inflammatory responses, such as levels of reactive oxygen species and tumor necrosis factor (TNF)-$\alpha$, are also increased in both diseases[9,10]. Reactive oxygen species increase with age and TNF-$\alpha$ is a pro-inflammatory cytokine involved in the inflammatory process. Since both OA and COPD are more common in older individuals and are characterized by chronic inflammation, the two disorders may be related. Previous studies have reported a high prevalence of OA among patients with COPD[11]. However, to the best of our knowledge, COPD studies based on diagnostic criteria (e.g., pulmonary function tests [PFTs] results, symptoms and medical histories), and OA studies based on symptoms and radiological findings have not been conducted to date. In addition, risk factors, such as age, are common between the diseases; hence, whether COPD is associated with a high prevalence of OA remains unclear. The prevalence of both COPD and OA increase with age, and their prevalence and disease characteristics vary according to sex. The prevalence and mortality rates associated with COPD are higher among men than among women, but exacerbations are more commonly observed in women[12]. The prevalence of OA, predominantly in the knee joint, is higher among women than among men; women also present with more severe pain and greater functional decline. Men are more likely to develop cervical spine disorders, and the incidence of mental disorders is higher among men[7,13,14]. Thus, the prevalence of OA among patients with COPD and the relationship between COPD and OA are expected to differ between the sexes. In this study, we diagnosed COPD on the basis of the PFT results, presence of chronic cough or sputum, and smoking status; OA was diagnosed based on chronic pain and the radiological evidence of joint space narrowing. We investigated the prevalence of OA among patients with COPD according to sex and assessed whether OA was significantly associated with COPD.

## SUBJECTS AND METHODS

### Study design and setting

We conducted a cross-sectional study using the 2009-2013 Korea National Health and Nutrition Examination Survey (KNHANES) data. The KNHANES is a nationally representative, cross-sectional survey administered to a sample of the non-institutionalized, civilian population of Korea[15]. Households were randomly selected for participation and were sampled using multi-stage stratifications based on geographical areas.

### Participants

All KNHANES participants signed informed consent forms. This research was approved by the institutional review board of the authors' government-affiliated organizations (approval numbers: 2009-01CON-03-2C, 2010-02CON-21-C, 2011-02CON-06-C, 2012-01EXP-01-2C and 2013-07CON-03-4C). The survey was conducted in accordance with the principles of the Declaration of Helsinki 2000.

According to the 2009–2013 KNHANES data, radiography of the knee and hip joints was performed for participants >50 years and PFTs were performed for participants aged 40-80 years. A total of 10,576 participants underwent knee or hip joint radiography and PFTs; among them, participants not completing the health survey were excluded. The final study sample included 9823 participants (4324 men; 5499 women).

### Main variables and covariates

The participants with COPD were identified as follows: 1) those with forced expiratory volume in 1 second/forced vital capacity <0.7; 2) those with chronic cough or sputum production for >3 months; and 3) those with a smoking history of ≥10 pack-years. PFTs were conducted using digital computed spirometry (Vyntus Spiro, Vyaire Medical, Nettawa, IL, USA) and repeated 3-8 times; chronic cough and sputum production and smoking history were evaluated using the participants' self-reports.

Knee/hip OA was defined on the basis of symptoms and joint radiographic changes. Joint pain was self-reported in response to the following question: "Have you experienced knee/hip pain for 30 or more days over the past 3 months?" The radiographic criterion was a knee/hip joint Kellgren-Lawrence grade of ≥2.

Sex, age, body mass index, smoking status, hypertension (HTN), diabetes mellitus (DM),

**Table 1:** Demographic characteristics of male participants with and without chronic obstructive pulmonary disease (COPD; n =4324)

| Characteristic | COPD (n =154) | | Non-COPD (n=4170) | | *P*-value |
|---|---|---|---|---|---|
| | n | % | n | % | |
| Age (years) | | | | | <0.001 |
| 50–59 | 38 | 24.7 | 1685 | 40.4 | |
| 60–69 | 54 | 35.1 | 1504 | 36.1 | |
| 70–79 | 62 | 40.2 | 981 | 23.5 | |
| Obesity | | | | | 0.742 |
| Underweight | 4 | 2.6 | 89 | 2.1 | |
| Normal | 102 | 66.2 | 2667 | 64.0 | |
| Obese | 48 | 31.2 | 1414 | 33.9 | |
| Smoking status | | | | | <0.001 |
| Never | 0 | 0.0. | 673 | 16.1 | |
| Past | 84 | 54.6 | 2191 | 52.5 | |
| Light | 0 | 0.0 | 201 | 4.8 | |
| Moderate | 23 | 14.9 | 460 | 11.1 | |
| Heavy | 47 | 30.5 | 645 | 15.5 | |
| Hypertension | | | | | 0.264 |
| Normal | 40 | 26.0 | 938 | 22.5 | |
| Prehypertension | 47 | 30.5 | 1140 | 27.3 | |
| Hypertension | 67 | 43.5 | 2092 | 50.2 | |
| Diabetes mellitus | | | | | 0.359 |
| Normal | 73 | 47.4 | 2089 | 50.1 | |
| Impaired fasting glucose | 44 | 28.6 | 1273 | 30.5 | |
| Diabetes mellitus | 37 | 24.0 | 808 | 19.4 | |
| Dyslipidemia | 86 | 55.8 | 2446 | 58.7 | 0.506 |
| Occupational cluster | | | | | 0.002 |
| None | 0 | 0.0 | 6 | 0.1 | |
| White-collar | 12 | 7.8 | 679 | 16.3 | |
| Pink-collar | 39 | 25.3 | 1149 | 27.6 | |
| Blue-collar | 57 | 37.0 | 1524 | 36.5 | |
| Green-collar | 39 | 25.3 | 746 | 17.9 | |
| Soldier | 7 | 4.6 | 66 | 1.6 | |
| Physical activity | | | | | |
| Intense | 22 | 14.3 | 684 | 16.4 | 0.579 |
| Moderate | 13 | 8.4 | 411 | 9.9 | 0.679 |
| Walking | 65 | 42.2 | 1764 | 42.3 | 1.000 |
| Osteoarthritis | 17 | 11.0 | 275 | 6.6 | 0.047 |

dyslipidemia, occupation and physical activity were considered potential confounding variables that affect the incidence of COPD and OA. According to the guidelines of the Korea Center for Disease Control and Prevention, the low-weight group comprised individuals with BMI <18.5 kg/m$^2$, the normal-weight group included those with BMIs ≥18.5 and <25 kg/m$^2$; and individuals in the obese group had BMI ≥25 kg/m$^2$. Each participant was classified a never-smoker, past smoker and current smoker. Among the current smokers, those who smoked <10, 10-20 and >20 cigarettes/day were identified as light, moderate and heavy smokers, respectively[16-18]. HTN was defined as an average systolic blood pressure ≥140 mmHg or a diastolic blood pressure ≥90 mmHg or having a prescription for antihypertensive drugs. Participants assigned a pre-HTN status were those with systolic blood pressures ≥120 mmHg or diastolic blood pressures ≥80 mmHg without HTN. DM was defined as a fasting plasma glucose level ≥126 mg/dL, DM diagnosed by a clinician, or having a prescription for oral hypoglycemic agents and/or insulin. Impaired fasting glucose was defined as a fasting plasma glucose level ≥100 and ≤126 mg/dL, without a DM diagnosis. A diagnosis of dyslipidemia was based on total cholesterol levels ≥200 mg/dL, triglyceride levels ≥150 mg/dL, high-density lipoprotein cholesterol levels <40 mg/dL (men) or <50 mg/dL (women), or current use of any anti-dyslipidemia drugs. Based on the International Standard Classification of Occupations, occupations were clustered as follows: white-collar for managers and professionals; pink-collar for clerks and service/sales workers; blue-collar for craft/trade workers, machine operators, assemblers and elementary manual workers; green-collar for agricultural/fishery workers; and soldiers[19]. Physical activity was classified as intense (≥20 min/session, ≥3 times/week), moderate (≥30 min/session, ≥5 times/week) and walking (≥30 min/session, ≥5 times/week).

**Statistical analysis**

We calculated the odds ratios (ORs) and 95% confidence intervals (CIs) for knee/hip OA in accordance with the presence of COPD. A logistic regression model was used to assess the association between COPD and knee/hip OA, adjusting for age, obesity, smoking status, HTN, DM, dyslipidemia, occupational type and physical activity. SPSS (ver. 23.0, SPSS, Chicago, IL, USA) was used for all statistical analyses; a *P*-value ≤0.05 was considered significant.

**RESULTS**

The overall prevalence of COPD among the study participants was 1.6%. Of the 4324 men, 154 (3.6%) met the COPD definition; however, only 3 (0.1%) of the 5499 women satisfied the definition. The overall prevalence of OA was 13.3% (6.8% men; 18.5% women). The prevalence of OA was 11% among men with COPD and 6.6% among men without COPD; OA was not observed in the three female patients with COPD.

**Table 2:** Odds ratios (ORs) and 95% confidence intervals (CIs) for the development of osteoarthritis in men with chronic obstructive pulmonary disease

| Model | Crude | | Adjusted* | |
|---|---|---|---|---|
| Outcome | OR | 95% CI | OR | 95% CI |
| Osteoarthritis | 1.76 | 1.05–2.95 | 1.50 | 0.87–2.57 |

*Adjusted for age, obesity, smoking status, hypertension, diabetes mellitus, dyslipidemia, occupation and physical activity

Table 1 shows the demographic characteristics, according to the prevalence of COPD, of the male participants. The participants with COPD were older than those without COPD, and their smoking frequency was significantly higher. The white-collar occupational cluster was less commonly noted in the COPD group than in the non-COPD group. Moreover, individuals classified as soldiers or in the blue- and green-collar occupational clusters were more commonly found in the COPD group than in the non-COPD group. As only three women were identified as having COPD in this study, we did not analyze the prevalence of OA in the female population of the cohort.

In the crude analysis model, the prevalence of OA was significantly higher in the COPD group than in the non-COPD group (OR: 1.76; 95% CI: 1.05-2.95). However, significant difference in the prevalence of OA was not observed between the two groups, after adjusting for the confounding variables (OR: 1.50; 95% CI: 0.87-2.57; Table 2).

**DISCUSSION**

Chronic inflammation is noted in patients with COPD (lungs) and in those with OA (joints). This chronic inflammation leads to the secretion and activation of various inflammatory response-related substances, including pro-inflammatory cytokines that are associated with other chronic inflammatory diseases[20]. In patients with COPD, sputum and peripheral blood TNF-$\alpha$ levels are increased, compared to those in healthy individuals; such increases are associated with cachexia or skeletal muscle apoptosis in some severe diseases. TNF-$\alpha$ also activates nuclear factor-κB, which amplifies the inflammatory response[10]. In addition, the levels of interleukin (IL)-17 increase in the sputa and airways of patients with COPD[21]. IL-1β and TNF-$\alpha$ are the key cytokines that are active during the more advanced stages of OA and play crucial roles in osteophyte formation. IL-6 activates and enhances the inflammatory response. The IL-17 level is also elevated in the sera and synovial fluids of patients with OA; consequently, the synthesis of proteoglycans is inhibited in these individuals[22]. As noted in previous studies, this study showed that the prevalence of OA was higher among men with COPD than among those without COPD[11]. However, because COPD and OA share various risk factors, COPD does not have a significant association with the high prevalence of OA. Therefore, OA and COPD may exist independently. In the present study, the prevalence of OA among women was more than double that observed among men. However, only three participants in our study had COPD, also indicating that OA and COPD can exist independently.

This study estimated the overall prevalence of COPD in Korea to be 1.6%. This is lower than the prevalence of 5-13% reported in other studies[23-25]. Most previous studies defined COPD using only the spirometer criteria (forced expiratory volume in 1 second/forced vital capacity <0.7); however, we suggest that individuals presenting with chronic coughs and sputa, with a history of smoking, should be included in the COPD definition; therefore, the prevalence of COPD was lower in this study. The prevalence of COPD in our study was similar to that reported in a study that defined COPD using chronic sputa, dyspnea and spirometry results as indicators[26]. In our study, COPD was defined using the patient's smoking history, chronic symptoms and PFT results; thus, our criteria were close to those defined by the Global Initiative for Chronic Obstructive Lung Disease classification[27]. In a previous study that used a national sample cohort from Korea's National Health Insurance Service, the overall prevalence of COPD was 2.4%, which was also higher than that reported in this study. However, the prevalence of COPD among

men was 3%, which was lower than that noted in this study[28]. In the present study, the prevalence of COPD among female participants was 0.1%, possibly because 93.5% of the female participants were never-smokers and were not classified as having COPD. The low prevalence of COPD among female participants seems to have decreased the overall prevalence of COPD. In a previous study, only patients who had visited the clinic because of symptoms were diagnosed as having COPD based on their PFT results. However, in this study, PFT was also performed outside the clinic, and the prevalence of COPD was higher among male participants.

The prevalence of COPD increased with advancing age; patients in the COPD group were significantly older than those in the non-COPD group. Considering that the strongest risk factor for OA is age and that advancing age is also a risk factor for COPD, the prevalence of OA among patients with COPD was anticipated to be high. Occupational classifications also showed significant differences in COPD[19]. Although individuals involved in certain occupations may be exposed to toxic substances that are associated with COPD development, resulting in an increased prevalence of COPD, differences in the smoking status among the occupational clusters may also account for the differences. In a previous study, the prevalence of OA was lower among white-collar workers and higher among blue- and green-collar workers[19], mimicking the COPD pattern. The high prevalence of OA in the COPD group may have been affected by the patients' occupational clusters after exposure to the common risk factors for the development of OA and COPD.

Smoking, a critical risk factor for COPD, has been shown to either not be related to OA development or associated with a reduced OA risk[29,30]. Nevertheless, the prevalence of OA was high among COPD patients, suggesting that various factors, such as physical activity, may also contribute to its prevalence. In patients with COPD, physical activity is restricted; thus, these patients cannot exercise easily, resulting in weakening of the muscles and skeleton[31]. Physical disabilities and weaknesses are expected to be associated with OA. However, in this study, there were no differences in physical activity between the participants with and without COPD. This may be due to inflammation-related factors in both the lungs and joints, such as oxidative stress or carboxyhemoglobin levels[9,10,32]. The prevalence of OA among patients with COPD was significantly higher than among those without COPD, suggesting that the coexistence of the two diseases should be considered during the diagnosis of each disease. Nevertheless, we did not find a significant association between OA and COPD, after adjusting for the participants' smoking statuses, which would be the examined risk factor that was most relevant to COPD. Although systemic factors such as inflammatory cytokines affect OA and COPD, both diseases cause localized inflammation in their respective target organs. This is thought to explain the absence of an independent association between OA and COPD, indicating that localized treatment of each disease, such as intra-articular injection or surgery for OA and inhalant therapy for COPD, may be more effective than systemic treatment.

This study has some strengths. First, this study was based on authoritative, nationwide data; thus, it presented the diagnoses of COPD and OA in the Korean population and recorded data useful for determining the prevalence of both diseases and their relationship. As the sample was taken from the entire population, using a multi-level cluster probability sampling method, it represents the general population of Korea. Second, COPD was defined using chronic symptoms and smoking status as well as PFT results, and OA was defined based on both symptoms and radiological findings. These definitions included both objective examinations and symptomatic criteria. Third, spirometry and plain radiography were performed by trained technicians and conducted using the same equipment. The review center reviewed all spirometry data and provided feedback to the technicians, and data from participants with two or more adequate spirometric curves were analyzed[33]. Radiographs were read by two radiologists who worked at a university hospital, and the final radiological grade was decided by one examiner[34]. Fourth, various confounding factors that may affect COPD and/or OA, including smoking status, were included in the adjustments.

This study is limited by cross-sectional design that prevented the determination of a causal relationship between COPD and OA. However, because a significant relationship between the two diseases was not observed, assessing a causal relationship was not important. Additionally, the number of female participants with COPD was too small to allow for the analysis of a relationship between COPD and OA among women. The low prevalence of COPD among women is believed to be due to the low frequency of smoking among the female participants. Approximately 10% of patients with COPD were nonsmokers. In addition to direct smoking, second-hand smoking; inhalation of noxious vapors, gases or dust; and less frequently, hereditary alpha-1 antitrypsin deficiencies are COPD risk factors[35]. In addition to physical activity and obesity, OA is affected by joint structure,

malalignment and trauma; however, an investigation of these factors was not conducted[36]. Finally, the disease durations or severities of COPD and OA were not considered; the medications used in the treatment of the diseases were also not examined.

## CONCLUSION

The prevalence of COPD in Korea was found to be 1.6% and was higher among men than among women. The prevalence of OA was higher in male participants with COPD than in those without COPD. However, a significant relationship was not observed between the presence of COPD and the prevalence of OA. Both OA and COPD are affected by various factors; since the associated comorbidities, including anemia and osteoporosis, are diverse, further large-scale studies that include these factors are needed.

## ACKNOWLEDGMENT

**Author's contribution:** JHJ and JHL contributed to the study design; the acquisition, analysis, and interpretation of the data; and drafted the manuscript. They contributed equally to this work. HS contributed to the study design and to the acquisition and analysis of the data, and helped critically revise the manuscript for important intellectual content. GGS contributed to the data analysis and interpretation and critically revised the manuscript for important intellectual content. SJC contributed to the study conception, data acquisition and interpretation, and critical revision of the manuscript for important intellectual content. All authors approved the final version of the manuscript submitted for publication and each agrees to be accountable for all aspects of the study.

**Conflict of Interest:** The authors report no conflicts of interest. This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

## RERERENCES

1. Vogelmeier CF, Criner GJ, Martinez FJ, Anzueto A, Barnes PJ, Bourbeau J, *et al*. Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease 2017 report. GOLD executive summary. Eur Respir J 2017;49(3):1700214.
2. GBD 2015 Chronic Respiratory Disease Collaborators. Global, regional, and national deaths, prevalence, disability-adjusted life years, and years lived with disability for chronic obstructive pulmonary disease and asthma, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet Respir Med 2017; 5(9):691-706.
3. Warwick E, Scourfield A, Quint J. Systemic manifestations of chronic obstructive pulmonary disease. Br J Hosp Med (Lond) 2015; 76(6):324-9.
4. Zainuldin R, Sasiadek KM, Abdul Raub NA, Tay NW. An evaluation on the effects of inpatient pulmonary rehabilitation following acute exacerbation of chronic obstructive pulmonary disease in a Singapore hospital. Ann Acad Med Singap 2016; 45(4):169-71.
5. Litwic A, Edwards MH, Dennison EM, Cooper C. Epidemiology and burden of osteoarthritis. Br Med Bull 2013; 105:185-99.
6. Mathieu S, Couderc M, Tournadre A, Soubrier M. Cardiovascular profile in osteoarthritis: a meta-analysis of cardiovascular events and risk factors. Joint Bone Spine 2019; 86(6):679-84.
7. Jung JH, Seok H, Kim JH, Song GG, Choi SJ. Association between osteoarthritis and mental health in a Korean population: a nationwide study. Int J Rheum Dis 2018; 21(3):611-9.
8. Radnaabaatar M, Kim YE, Go DS, Jung Y, Yoon S-J. Burden of disease in coastal areas of South Korea: an assessment using health insurance claim data. Int J Envion Res Public Health 2019; 16(17):3044.
9. Abramoff B, Caldera FE. Osteoarthritis: pathology, diagnosis, and treatment options. Med Clin North Am 2020; 104(2):292-311.
10. Barnes PJ. Inflammatory mechanisms in patients with chronic obstructive pulmonary disease. J Allergy Clin Immunol 2016; 138(1):16-27.
11. Wshah A, Guilcher SJ, Goldstein R, Brooks D. Prevalence of osteoarthritis in individuals with COPD: a systematic review. Int J Chron Obstruct Pulmon Dis 2018; 13:1207-16.
12. Lisspers K, Larsson K, Janson C, Stallberg B, Tsiligianni I, Gutzwiller FS. Gender differences among Swedish COPD patients: results from the ARCTIC, a real-world retrospective cohort study. NPJ Prim Care Respir Med 2019; 29(1):45.
13. Boyan BD, Tosi L, Coutts R, Enoka R, Hart DA, Nicolella DP, *et al*. Sex differences in osteoarthritis of the knee. J Am Acad Orthop Surg 2012; 20(10):668-9.
14. O'Connor MI. Osteoarthritis of the hip and knee: sex and gender differences. Orthop Clin North Am 2006; 37(4):559-68.
15. Kweon S, Kim Y, Jang MJ, Kim Y, Kim K, Choi S, *et al.* Data resource profile: the Korea National Health and Nutrition Examination Survey (KNHANES). Int J Epidemiol 2014; 43(1):69-77.
16. Cho MH, Lee K, Park SM, Chang J, Choi S, Kim K, *et al.* Effects of smoking habit change on all-cause mortality and cardiovascular diseases among patients with newly diagnosed diabetes in Korea. Sci Rep 2018; 8(1):5316.
17. Choi S, Chang J, Kim K, Park SM, Lee K. Effect of smoking cessation and reduction on the risk of cancer in Korean men: a population based study. Cancer Res Treat 2018; 50(4):1114-20.
18. Song YM, Sung J, Cho HJ. Reduction and cessation of cigarette smoking and risk of cancer: a cohort study of Korean men. J Clin Oncol 2008; 26(31):5101-6.
19. Seok H, Choi SJ, Yoon JH, Song GG, Won JU, Kim JH, *et al*. The association between osteoarthritis and occupational clusters in the Korean population: a nationwide study. PLoS One 2017; 12(1):e0170229.

20. Sivalingam SP, Thumboo J, Vasoo S, Thio ST, Tse C, Fong KY. In vivo pro- and anti-inflammatory cytokines in normal and patients with rheumatoid arthritis. Ann Acad Med Singap 2007; 36(2):96-9.
21. De Grove KC, Provoost S, Verhamme FM, Bracke KR, Joos GF, Maes T, *et al*. Characterization and quantification of innate lymphoid cell subsets in human lung. PLoS One 2016; 11(1):e0145961.
22. Wojdasiewicz P, Poniatowski LA, Szukiewicz D. The role of inflammatory and anti-inflammatory cytokines in the pathogenesis of osteoarthritis. Mediators Inflamm 2014; 2014:561459.
23. Zha Z, Leng R, Xu W, Bao H, Chen Y, Fang L, *et al*. Prevalence and risk factors of chronic obstructive pulmonary disease in Anhui Province, China: a population-based survey. BMC Pulm Med 2019; 19(1):102.
24. Wijnant SRA, Lahousse L. Prevalence of asthma and COPD and blood eosinophil count in a middle-aged Belgian population. J Clin Med 2019; 8(8):1122.
25. Park HJ, Leem AY, Lee SH, Song JH, Park MS, Kim YS, *et al*. Comorbidities in obstructive lung disease in Korea: data from the fourth and fifth Korean National Health and Nutrition Examination Survey. Int J Chron Obstruct Pulmon Dis 2015; 10:1571-82.
26. North CM, Kakuhikire B, Vorechovska D, Hausammann-Kigozi S, McDonough AQ, Downey J, *et al*. Prevalence and correlates of chronic obstructive pulmonary disease and chronic respiratory symptoms in rural southwestern Uganda: a cross-sectional, population-based study. J Glob Health 2019; 9(1):010434.
27. Mittal R, Chhabra SK. GOLD Classification of COPD: Discordance in criteria for symptoms and exacerbation risk assessment. COPD 2017; 14(1):1-6.
28. Park HY, Kang D, Lee H, Shin SH, Kang M, Kong S, *et al*. Impact of chronic obstructive pulmonary disease on mortality: a large national cohort study. Respirology 2020; 25(7):726-34.
29. Hui M, Doherty M, Zhang W. Does smoking protect against osteoarthritis? Meta-analysis of observational studies. Ann Rheum Dis 2011; 70(7):1231-7.
30. Lee YH. Causal association between smoking behavior and the decreased risk of osteoarthritis: a Mendelian randomization. Z Rheumatol 2019; 78(5):461-6.
31. Mantoani LC, Dell'Era S, MacNee W, Rabinovich RA. Physical activity in patients with COPD: the impact of comorbidities. Expert Rev Respir Med 2017; 11(9):685-98.
32. Yasuda H, Sasaki T, Yamaya M, Ebihara S, Maruyama M, Kanda A, *et al*. Increased arteriovenous carboxyhemoglobin differences in patients with inflammatory pulmonary diseases. Chest 2004; 125(6):2160-8.
33. Kim DS, Kim YS, Jung KS, Chang JH, Lim CM, Lee JH, *et al*. Prevalence of chronic obstructive pulmonary disease in Korea: a population-based spirometry survey. Am J Respir Crit Care Med 2005; 172(7):842-7.
34. Jung JH, Bang CH, Song GG, Kim C, Kim JH, Choi SJ. Knee osteoarthritis and menopausal hormone therapy in postmenopausal women: a nationwide cross-sectional study. Menopause 2018; 26(6):598-602.
35. Tee AK. Chronic obstructive pulmonary disease (COPD): "not a cigarette only pulmonary disease." Ann Acad Med Singap 2017; 46(11):415-6.
36. O'Neill TW, McCabe PS, McBeth J. Update on the epidemiology, risk factors and disease outcomes of osteoarthritis. Best Pract Res Clin Rheumatol 2018; 32(2):312-26.

Case Report

# Endovascular thrombectomy prior to decompressive craniectomy in acute ischemic stroke with low ASPECTS

Jingmin Zhao[1,2], Guangxian Nan[1], Songji Zhao[3,4]
[1]Department of Neurology, China-Japan Union Hospital of Jilin University, Changchun, China
[2]Department of Radiology and Nuclear Medicine, Fukushima Medical University, Fukushima, Japan
[3]Advanced Clinical Research Center, Fukushima Global Medical Science Center, Fukushima Medical University, Fukushima, Japan
[4]Basic Medical College of Jilin University, Changchun, China

Kuwait Medical Journal 2023; 55 (4): 343 - 348

## ABSTRACT

The impact of endovascular thrombectomy on patients with a low initial Alberta Stroke Program Early Computer Tomography Score (ASPECTS) remains controversial. In this report, we describe the case of a patient in whom endovascular thrombectomy prior to decompressive craniectomy in acute ischemic stroke with a low ASPECTS had a favorable outcome, recovering to functional independence (modified Rankin Scale = 2) after 90 days. We also discuss the clinical benefits of thrombectomy in acute ischemic stroke patients with even low ASPECTS.

**KEY WORDS:** acute ischemic stroke, collateral circulation, decompressive craniectomy, endovascular thrombectomy, low Alberta stroke program early computer tomography score

## INTRODUCTION

Endovascular thrombectomy (EVT) is beneficial for patients with acute ischemic stroke caused by an occlusion of the proximal anterior circulation[1]. However, this benefit is based on common inclusion criteria of previous trials, which apply to patients with an Alberta Stroke Program Early Computed Tomography Score (ASPECTS) of 6 or higher; hence, the American Heart Association recommends mechanical thrombectomy in acute stroke patients with an ASPECTS of >5[2]. The SWIFT-PRIME and ESCAPE trials used an ASPECTS of ≤5 determined from baseline non-contrast computed tomography (CT) images as an exclusion criterion. The treatment recommendations of the American Heart Association/ American Stroke Association in 2015 (Class I; level of evidence A) also defined an ASPECTS of ≤5 as unfavorable[3]. Other studies have defined an ASPECTS of ≤6 as unfavorable[4,5]. However, few actual data that indicate the effects of vessel recanalization on patients with a lower ASPECTS exist[1,6-10]. The potential clinical benefit or harm of mechanical thrombectomy in patients with a low initial ASPECTS therefore remains a controversial subject[8,11-13]. We describe here a case of EVT prior to decompressive craniectomy (DC) in acute ischemic stroke with low ASPECTS and discuss the reasons for a good clinical outcome (*i.e.*, improvement of modified Rankin Scale (mRS) score from 0 to 2).

## CASE REPORT

A 60-year-old woman who had a history of atrial fibrillation was admitted to our hospital with slurred speech and paralysis on the left side, which began 30 minutes before hospitalization. Neurologic examination revealed dysarthria, left gaze paralysis, left facial paralysis, left hemiplegia, a positive Babinski sign and a muscle power of the left limb of grade 0. Her National Institutes of Health Stroke Scale score was 14/42. Brain CT images showed low-density shadows in the right middle cerebral artery region (Figure 1). Her ASPECTS was 4/10. She then

***Address correspondence to:***
*Guangxian Nan, MD, PhD, Department of Neurology, China-Japan Union Hospital of Jilin University, 126 Xian Tai Street, Changchun, 130031, Jilin, China. Tel: +86 431 84995606; E-mail: nangx@jlu.edu.cn*

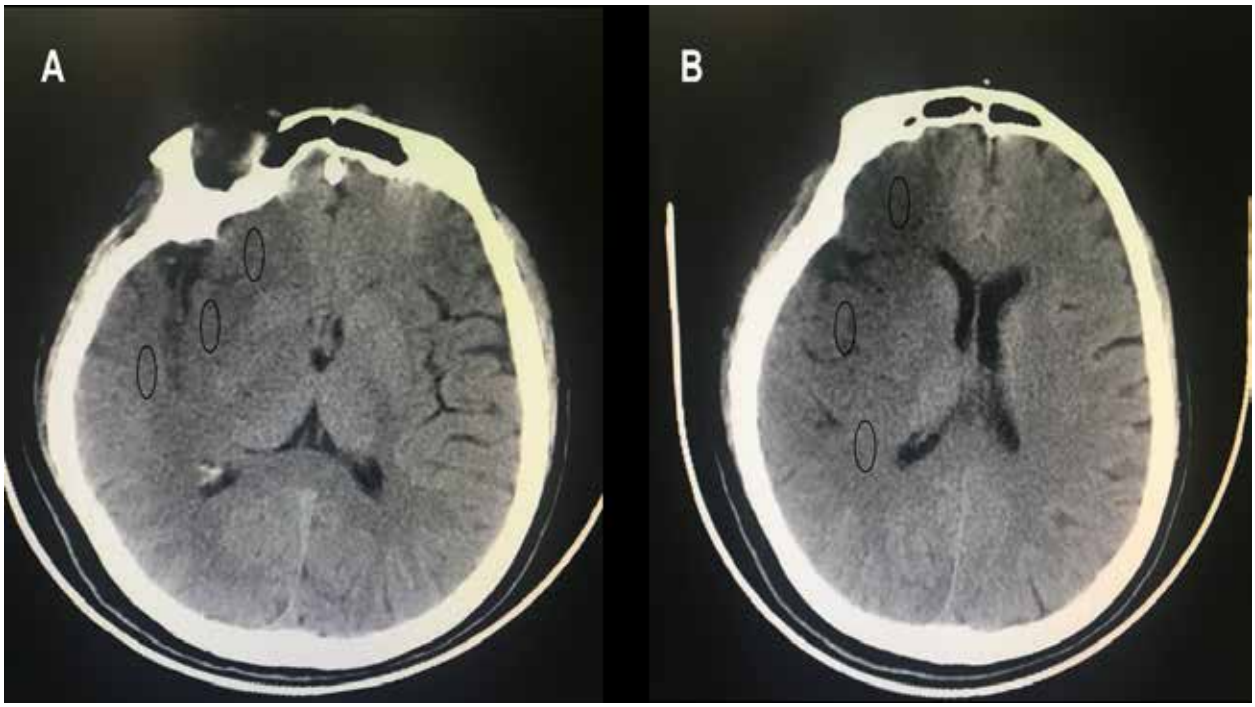


**Figure 1:** CT images of 60-year-old female with cerebral infarction at one-hour onset. **Findings:** Unenhanced brain CT imaging, axial section at level of basal ganglia on left image and at supraganglionic level on right image. There is hypodensity in the insular cortex, M1, M2, M4, M5, and M6 regions on the left side, resulting in ASPECTS of 4.

underwent brain digital subtraction angiography (DSA), which showed no abnormalities in the left internal carotid artery (ICA) or basilar artery (Figure 2A, 2B) but showed occlusion of the right ICA (Figure 2C). DSA also showed the right anterior cerebral artery collateral through the anterior communicating artery (Figure 2A) and the right middle cerebral artery collateral through the branch of the right posterior cerebral artery (Figure 2B). On the basis of the collateral circulation grading system from the American Society of Interventional and Therapeutic Neuroradiology/American Society of Interventional Radiology (ASITN/SIR), the class of leptomeningeal compensation is evaluated as grade 0 to 4. This patient's ASITN/SIR score was 2/4. Although her ASPECTS was low, the time from onset was short and the collateral was acceptable. After signing a written informed consent, we performed EVT to open the occluded right ICA (thrombolysis in cerebral infarction (TICI) scale score of 2b) (Figure 2D). The onset-to-recanalization time was 120 minutes. Immediate postoperative examination of the nervous system showed no changes. However, on the first day after surgery, the patient's level of consciousness declined. Re-examination by head CT showed swelling of the right cerebral hemisphere, a large-area hypodensity shadow accompanied by a hyperdensity shadow, and a midline shift (Figure 3). The patient was immediately subjected to neurosurgery and DC was performed. After one month of systemic treatment, the weakness of the left limb improved and neurologic examination revealed that her left limb increased to grade 2 from grade 0 at the onset. Brain CT performed after 90 days showed that the low-density shadow of the right middle cerebral artery blood supply area has formed a stroke sac (Figure 4). The patient achieved functional independence with mRS of 2 after 90 days, which is a considerable improvement from mRS of 5 at the onset.

## DISCUSSION

In the meta-analysis of Highly Effective Reperfusion evaluated in Multiple Endovascular Stroke Trials collaborators, a low baseline ASPECTS is strongly associated with low rates of favorable outcome[1]. However, neurosurgeons and interventional neuroradiologists need to decide every day whether to treat patients with acute stroke and large necrotic cores, and patients in the real world are not always the ideal "trial" candidates for thrombectomy. These patients were treated during the re-ventilation time window and had accessible blood clots for thrombectomy. There is no standard guideline available for this condition. Although there are various reasons for treating these patients, such as younger age, a short interval after the onset of symptoms, or the specific desires or wishes of family members, the decision to treat still depends on the patient's personal factors and the experience of the interventional neuroradiologist on duty. In our

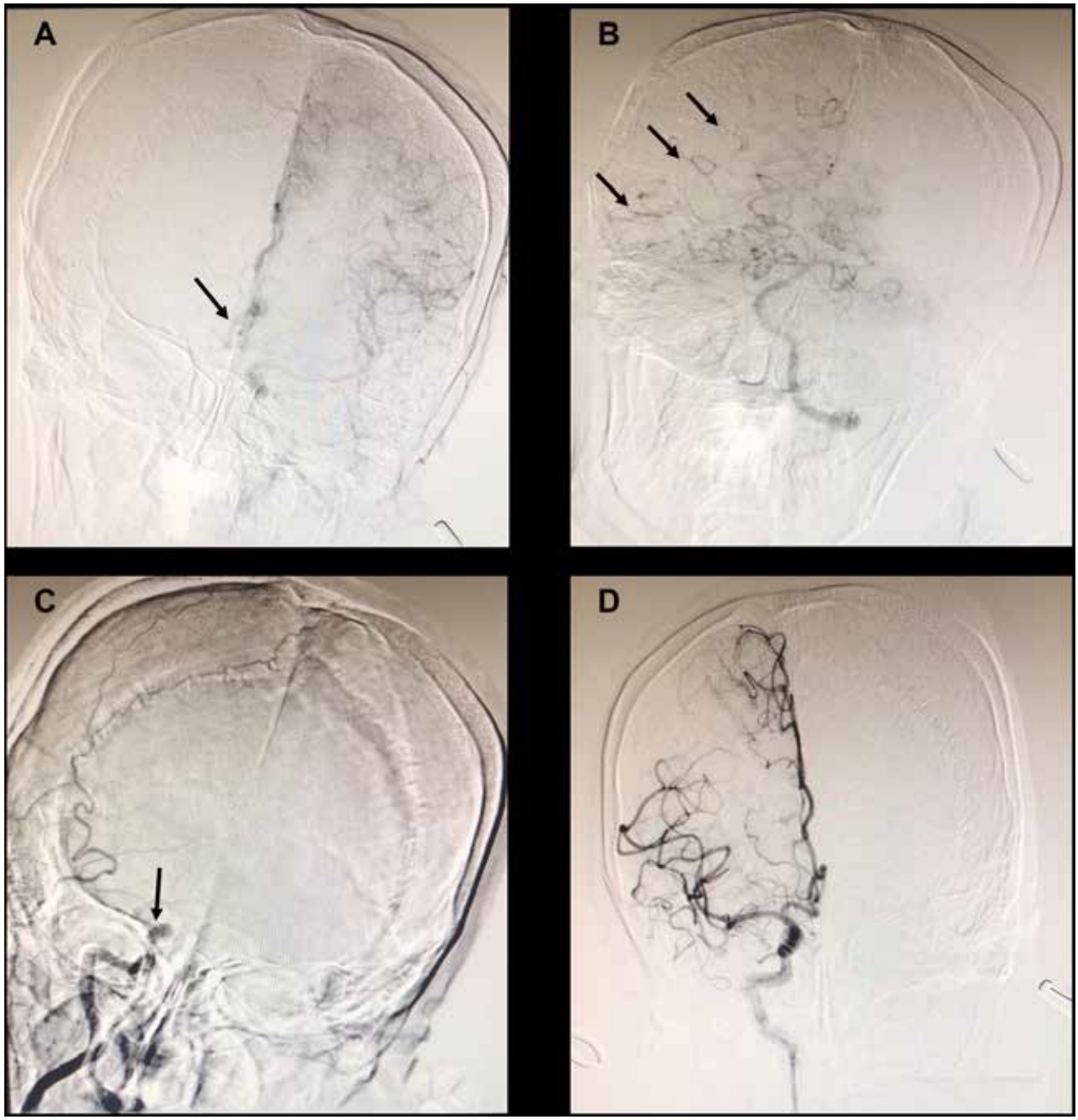


**Figure 2:** DSA images of 60-year-old female with cerebral infarction. **Findings:** DSA showed no abnormalities in the left ICA, the right anterior cerebral artery collateral through the anterior communicating artery **(Fig. 2A)** or the basilar artery (BA), which is the right middle cerebral artery collateral through the branch of the right posterior cerebral artery **(Fig. 2B)**. The patient's ASITN/SIR score was2/4. DSA also showed occlusion of the right ICA **(Fig. 2C)**, and endovascular thrombectomy was performed to open the occluded right ICA (TICI scale 2b) **(Fig. 2D)**. Onset-to-recanalization time was 120 minutes.

current case, the patient had a good prognosis, and we analyzed the following three factors: (1) the onset-to-recanalization time of the patient was short (120 min) and we successfully opened the occluded right ICA (TICI scale 2b); (2) the collateral circulation was good; and (3) DC was timely. Mourand *et al* demonstrated that endovascular therapy can safely and efficiently be applied to patients with ischemic stroke with an ASPECTS of ≤5 on admission (based on diffusion-weighted imaging findings and radiological-clinical mismatch). These patients should not automatically be excluded from receiving EVT, especially if they are aged <70 years[7]. When chosen carefully, patients with core infarcts on brain CT images involving the basal ganglia or multiple territories (ASPECT ≤6) at presentation can achieve good clinical outcomes, similarly to patients who had an entirely reversible penumbra at presentation[14]. Desilles *et al* described

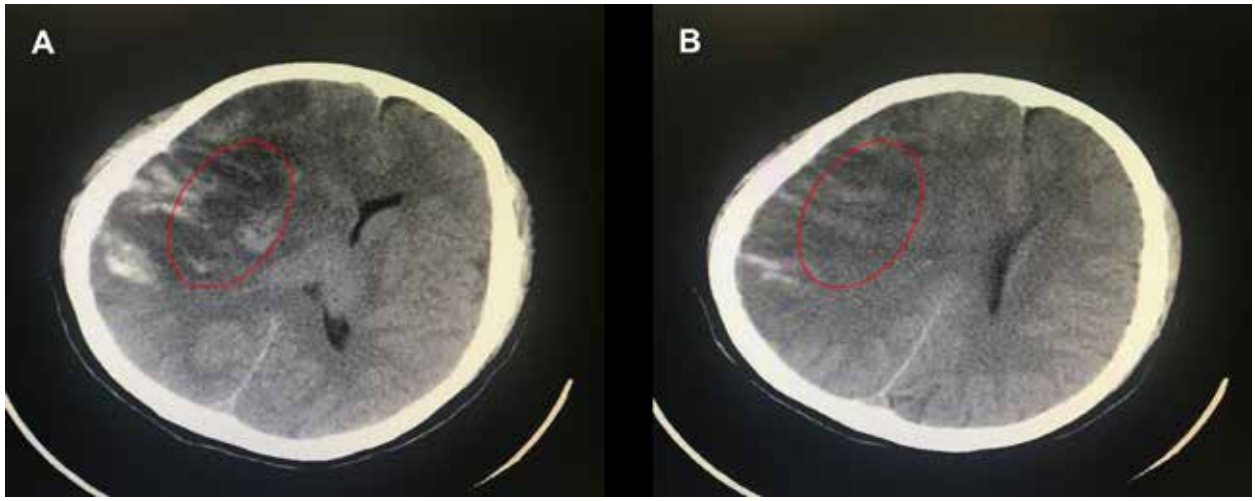


**Figure 3:** CT images of 60-year-old female with cerebral infarction one day after surgery.

a positive although non-significant trend towards better functional outcome (23.1% vs 9.5%), lower mortality rate (45.7% vs 57.1%), and lower rate of sICH (23.9% vs 45.5%) in successfully reperfused patients compared with non-reperfused patients of the diffusion-weighted imaging-ASPECTS 0-4 subgroup[15]. Broocks *et al* demonstrated that in stroke patients with large vessel occlusion and a low initial ASPECTS of 5, vessel recanalization was associated with substantially reduced ischemic brain water uptake on early follow-up[9]. The observed effect of vessel recanalization on edema progression was directly related to favorable effects on clinical endpoints with a decreased rate of malignant infarctions and improved mRS scores[9]. The results encourage prospective studies on the robust potential benefits of EVT in patients with a low ASPECTS[9]. The patient's age in this case was 60, and there were no other high-risk factors other than atrial fibrillation, and the brain CT images showed that there was still no low-density shadow in the basal ganglia at presentation. Moreover, the onset time of the patient was short (30 min) and we successfully opened the occluded right ICA (TICI scale score of 2b), which was one factor for the good outcome. On the other hand, collateral status may be relevant to the clinical

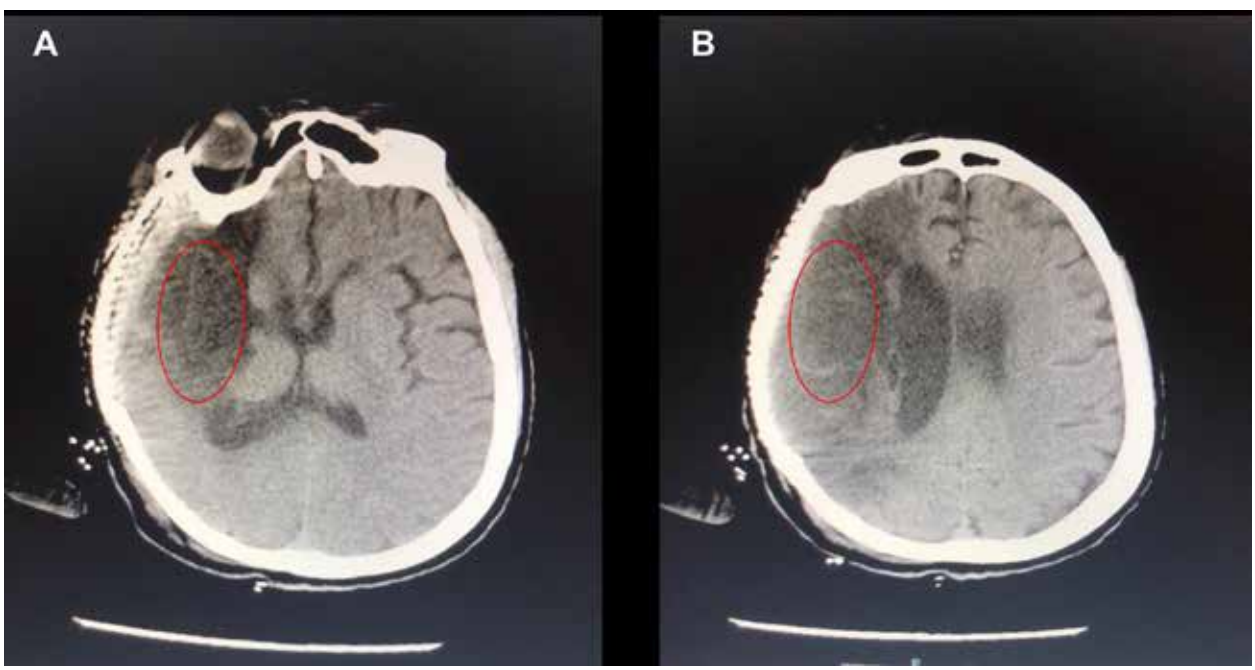


**Figure 4:** CT images of 60-year-old female with cerebral infarction three months after onset.

outcome in acute ischemic stroke patients, despite an initially low ASPECTS of ≤5[16]. Moreover, poor intracranial collaterals were directly associated with aggravated edema formation and impaired clinical outcome, whereas better collaterals attenuated ischemic brain edema with improved outcome[16]. Broocks *et al* demonstrated that collateral status could serve as a selection criterion for the treatment of low-ASPECTS patients[16]. In the current case, the DSA also showed the right anterior cerebral artery collateral through the anterior communicating artery and the right middle cerebral artery collateral through the branch of the right posterior cerebral artery (Figures 3 and 4). The patient's ASITN/SIR score was 2, which maybe another factor for the patient's good prognosis. However, Göttsche *et al* demonstrated that even successful EVT does not exclude all patients from life-threatening postsurgical clinical courses requiring decompressive craniectomy[17]. The outcome of EVT depends on various factors. In addition to the timing and success of the revascularization, some patients also experience very early severe infarct edema, which is not reversible despite thrombectomy[18,19]. Göttsche *et al* also demonstrated that the clinical parameters of patients who had undergone thrombectomy prior to surgery did not differ from those of patients without EVT. Furthermore, an endovascular treatment performed prior to craniectomy did not lead to a delay of the surgery as there were no significant differences in the timing of the operation between patient groups[17]. Therefore, timely DC in this case is very important, and endovascular treatment did not lead to a delay of DC.

## CONCLUSION

By choosing carefully and treating properly, we can expect patients with low ASPECTS to achieve good clinical outcomes.

## ACKNOWLEDGMENTS

**Authors contribution:** JZ: writing manuscript and design; GN: critical review; SZ: literature search
**Consent:** Written informed consent was obtained from patient.
**Conflict of Interest:** No conflict of interest was declared by the authors.
**Financial Disclosure:** None.

## REFERENCES

1. Goyal M, Menon BK, van Zwam WH, Dippel DW, Mitchell PJ, Demchuk AM, *et al.* Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. Lancet 2016; 387(10029):1723-31.
2. Gupta AC, Schaefer PW, Chaudhry ZA, Leslie-Mazwi TM, Chandra RV, Gonzalez RG, *et al.* Interobserver reliability of baseline noncontrast CT Alberta Stroke Program Early CT Score for intra-arterial stroke treatment selection. AJNR Am J Neuroradiol 2012; 33(6):1046-9.
3. Powers WJ, Derdeyn CP, Biller J, Coffey CS, Hoh BL, Jauch EC, *et al.* 2015 American Heart Association/American Stroke Association focused update of the 2013 guidelines for the early management of patients with acute ischemic stroke regarding endovascular treatment: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2015; 46(10):3020-35.
4. Jovin TG, Chamorro A, Cobo E, de Miquel MA, Molina CA, Rovira A, *et al.* Thrombectomy within 8 hours after symptom onset in ischemic stroke. N Engl J Med 2015; 372(24):2296-306.
5. Logan C, Maingard J, Phan K, Motyer R, Barras C, Looby S, *et al.* Borderline Alberta Stroke programme early CT score patients with acute ischemic stroke due to large vessel occlusion may find benefit with endovascular thrombectomy. World Neurosurg 2018; 110:e653-8.
6. Yoo AJ, Berkhemer OA, Fransen PSS, van den Berg LA, Beumer D, Lingsma HF, *et al.* Effect of baseline Alberta Stroke Program Early CT Score on safety and efficacy of intra-arterial treatment: a subgroup analysis of a randomised phase 3 trial (MR CLEAN). Lancet Neurol 2016; 15(7):685-94.
7. Mourand I, Abergel E, Mantilla D, Ayrignac X, Sacagiu T, Eker OF, *et al.* Favorable revascularization therapy in patients with ASPECTS ≤ 5 on DWI in anterior circulation stroke. J Neurointerv Surg 2018; 10(1):5-9.
8. Román LS, Menon BK, Blasco J, Hernandez-Perez M, Davalos A, Majoie CB *et al.* Imaging features and safety and efficacy of endovascular stroke treatment: a meta-analysis of individual patient-level data. Lancet Neurol 2018; 17(10):895-904.
9. Broocks G, Hanning U, Flottmann F, Schonfeld M, Faizy TD, Sporns P, *et al.* Clinical benefit of thrombectomy in stroke patients with low ASPECTS is mediated by oedema reduction. Brain 2019; 142(5):1399-407.
10. Bracard S, Ducrocq X, Mas JL, Soudant M, Oppenheim C, Moulin T, *et al.* Mechanical thrombectomy after intravenous alteplase versus alteplase alone after stroke (THRACE): a randomised controlled trial. Lancet Neurol 2016; 15(11):1138-47.
11. von Kummer R. Early CT score to establish stroke treatment. Lancet Neurol 2016; 15(7):651-3.
12. Desai SM, Haussen DC, Aghaebrahim A, Al-Bayati AR, Santos R, Nogueira RG, *et al.* Thrombectomy 24 hours after stroke: beyond DAWN. J Neurointerv Surg 2018; 10(11):1039-42.
13. Goyal N, Tsivgoulis G, Frei D, Turk A, Baxter B, Froehler MT, *et al.* A multicenter study of the safety and effectiveness of mechanical thrombectomy for patients with acute ischemic stroke not meeting top-tier evidence criteria. J Neurointerv Surg 2018; 10(1):10-6.

14. Hungerford JP, Hyer M, Turk AS, Turner RD, Chaudry MI, Fargen KM, *et al.* Impact of ASPECT scores and infarct distribution on outcomes among patients undergoing thrombectomy for acute ischemic stroke with the ADAPT technique. J Neurointerv Surg 2017; 9(9):823-9.
15. Desilles JP, Consoli A, Redjem H, Coskun O, Ciccio G, Smajda S, *et al.* Successful reperfusion with mechanical thrombectomy is associated with reduced disability and mortality in patients with pretreatment diffusion-weighted imaging-Alberta Stroke Program early computed tomography score ≤6. Stroke 2017; 48(4):963-9.
16. Broocks G, Kniep H, Schramm P, Hanning U, Flottmann F, Faizy T, *et al.* Patients with low Alberta Stroke Program Early CT Score (ASPECTS) but good collaterals benefit from endovascular recanalization. J Neurointerv Surg 2020; 12(8):747-52.
17. Göttsche J, Flottmann F, Jank L, Thomalla G, Rimmele DL, Czorlich P, *et al.* Decompressive craniectomy in malignant MCA infarction in times of mechanical thrombectomy. Acta Neurochir (Wien) 2020; 162(12):3147-52.
18. Peng G, Huang C, Chen W, Xu C, Liu M, Xu H, *et al.* Risk factors for decompressive craniectomy after endovascular treatment in acute ischemic stroke. Neurosurg Rev 2020; 43(5):1357-64.
19. Rocha M, Jovin TG. Fast versus slow progressors of infarct growth in large vessel occlusion stroke: clinical and research implications. Stroke 2017; 48(9):2621-7.

Case Report

# A pregnant woman with COVID-19 complicated by superior sagittal sinus thrombosis

Bahadir Yazicioglu[1], Huri Guvey[2], Canan Soyer Caliskan[3]
[1]Department of Family Medicine, University of Health Sciences, Samsun Education and Research Hospital, Samsun, Turkey
[2]Department of Obstetrics and Gynecology, Private Clinic, Kutahya, Turkey
[3]Department of Obstetrics and Gynecology, University of Health Sciences, Samsun Education and Research Hospital, Samsun, Turkey

Kuwait Medical Journal 2023; 55 (4): 349 - 353

## ABSTRACT

Coronavirus disease 2019 (COVID-19) is a pandemic that affects people around the world. Among those affected are pregnant women, a particularly worrisome group who can show various clinical presentations of COVID-19. In this case, a woman at 33 weeks of gestation was admitted to the hospital with abdominal pain and shortness of breath. She had a seizure in the hospital inpatient clinical follow-up, and she was taken for an emergency cesarean section. Magnesium sulfate infusion was started during and after cesarean section due to the pre-diagnosis of eclampsia. After the postoperative diagnosis of COVID-19, hydroxychloroquine treatment was administered. The patient had a second seizure on the fifth postoperative day. After neurological examination and cranial MR venogram imaging, a thrombus in the upper sagittal sinus was revealed. Due to continuing uncontrolled seizures, she was intubated and started on lopinavir, ritonavir and enoxaparin treatment. The patient received COVID-19 plasma therapy and was later weaned. As a result, being aware of the increased rate of thromboembolic events in pregnant women who are positive for COVID-19 is of vital importance to reach differential diagnoses in complex clinical cases.

**KEY WORDS**: COVID-19, pregnancy, seizure, thrombosis

## INTRODUCTION

The new coronavirus infection that emerged in Wuhan City, China in December 2019 quickly spread all over the world and turned into a pandemic with massive public health impact[1]. This ribonucleic acid virus, which was isolated as a factor, was first named as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) and then as Coronavirus Disease-19 (COVID-19). Symptoms were fever, cough, fatigue, myalgia and dyspnoea. It was observed that it could develop slowly, as well as rapidly and severely, leading to pneumonia[2,3]. According to data obtained from small case series and case reports, pregnancy and delivery do not increase susceptibility to COVID-19 infection and do not aggravate clinical presentations of COVID-19[4]. However, COVID-19 has been shown to increase pregnancy-related complications such as miscarriage, preeclampsia, emergency cesarean operation and preterm delivery[5]. In addition to these complications, the tendency to thrombosis increases during pregnancy. Intravascular inflammation rate increases secondary to infection and thrombosis in pregnant women. These risks are higher in pregnant women who contract COVID-19[6]. In this case report, the clinical characteristics of a pregnant woman diagnosed with COVID-19 positively complicated by superior sagittal sinus thrombosis (SSST) is shared.

## CASE REPORT

A primigravid female patient at the age of 25 at the 33rd week of pregnancy (according to the first day of her last menstrual period) was admitted to the emergency service of Health Sciences University Samsun Training and Research Hospital with complaints of abdominal

*Address correspondence to:*
*Huri Guvey, Obstetrics and Gynecology Specialist, Private Clinic, Dumlupinar Square, Sehit Er Bahtiyar Yalinca Street, Number 15/8, Kutahya, Turkey. Tel: +90 5335655358; E-mail: huriguvey@gmail.com; ORCID number: 0000-0002-8603-6981*

pain and shortness of breath. Since her husband tested positive for COVID-19 and her body temperature was 38.2 °C, a nasopharyngeal sample was taken from the patient with a swab to detect possible COVID-19. The patient was isolated and hospitalized until the results were known. The reverse transcription polymerase chain reaction (RT-PCR) test result of the nasopharyngeal specimen was positive for COVID-19. According to the results of the routine blood test dated April 16, 2020, hemoglobin level was 8.8 mg/dL (↓), white blood cell count was $10.9x10^9$/L (↑), C-reactive protein level was 47.1 mg/dL (↑) and fibrinogen was 567 mg/dL (↑). Serum biochemistry, blood tests measuring blood coagulation profile (prothrombin time, partial thromboplastin time and international normalization ratio), and urine analysis were normal. Arterial blood pressure was found to be 140/100 mmHg. During her inpatient follow-up in the clinic, the patient had a tonic-clonic seizure.

After the seizure, the patient was taken for an emergency cesarean operation. A baby girl weighing 2349 grams were delivered. The baby's Apgar score was seven in the first minute and eight in the fifth minute. During the operation, 4 g of magnesium sulfate was given intravenously to the mother for 10 minutes. Due to the pre-diagnosis of eclampsia, magnesium sulfate treatment was continued as an infusion at a dose of 2 g/hour. Postoperative computed thorax tomography (CT) of the patient with dyspnea was planned. CT evaluation revealed increased density and ground-glass opacities suggestive of COVID-19 pneumonia in the lower and posterior zones of both lungs (Figure 1). The treatment was started with 2 x 200 mg hydroxychloroquine orally.

On the fifth postoperative day, the patient had another seizure. Despite intravenous administration of 10 mg diazepam, seizure control could not be achieved and therefore the patient was intubated. The patient was transferred to the intensive care unit (ICU). Treatment was continued with lopinavir 400 mg/ ritonavir 100 mg. In her examination, there was no obvious pathological finding of the neurological system. Cranial CT followed by cranial magnetic resonance imaging and MR venogram was performed to reveal the etiology of the seizures. Imaging procedures revealed superior sagittal sinus thrombosis (Figures 2 and 3). To treat thrombosis, subcutaneous 2x1 enoxaparin 6000 U/l treatment was initiated. To control the seizures, 100 mg of levetiracetam and 25 mg of quetiapine fumarate were administered. There was no history of coagulopathy in the patient or family. Abnormal laboratory findings obtained from the tests performed in the intensive care unit on April 22, 2020, hemoglobin of 8.8 mg/dL (↓),white blood cell count of $15.8x10^9$/L (↑) and D-dimer of 6.78 ng/mL (↑). After the third day of intubation, the patient was extubated because of the clinical findings that improved. However, after weaning, the patient's breathing deteriorated again. To improve respiratory functions, immune plasma was applied to the patient from the person who had COVID-19. After plasma treatment, the patient was successfully weaned. After four days of treatment with 10 L/m nasal oxygen, the patient was transferred from the ICU to the COVID-19 clinic. Three days after she was transferred from the ICU, C-reactive protein, fibrinogen and D-dimer levels decreased to normal limits. Laboratory findings of the patient are summarized in Table 1.

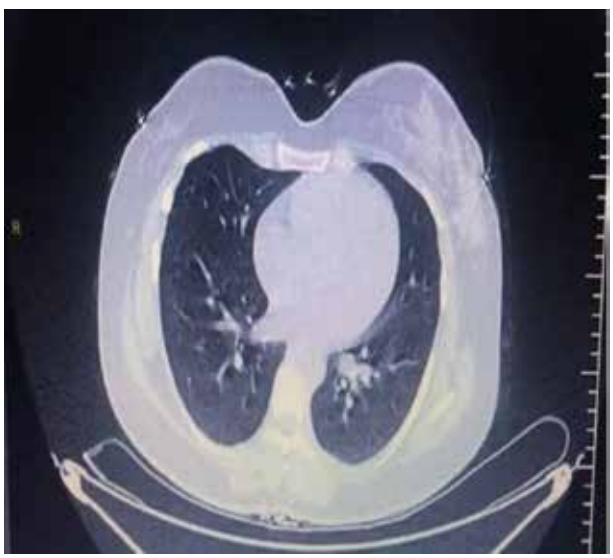

**Figure 1:** Chest computerized tomography displaying dependant densities and ground-glass opacities in lower and posterior sites of lung.

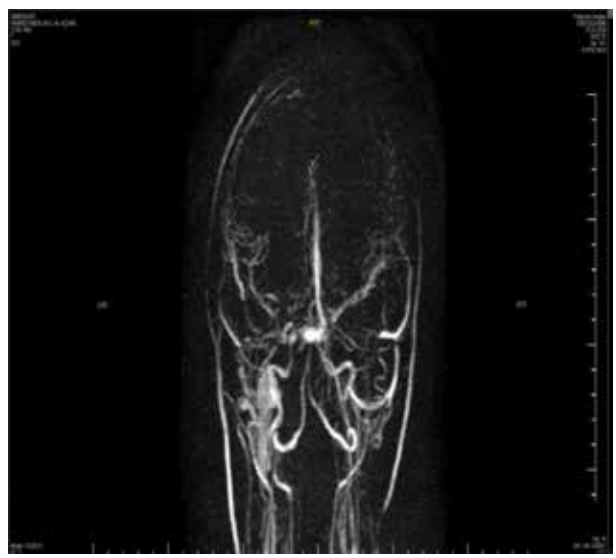

**Figure 2:** Brain magnetic resonance venogram showing superior sagittal sinus thrombosis.

**Table 1:** Changes in patient's laboratory findings in the timeline

| Laboratory findings variable | Laboratory findings value | | |
|---|---|---|---|
| | At admission to hospital (16.04.2020) | In ICU (22.04.2020) | Three days after discharge from ICU (29.04.2020) |
| Hb (mg/dL) | 8.8(↓) | 8.8(↓) | 8.4(↓) |
| WBC (x10$^9$/L) | 10.9(↑) | 15.8(↑) | 8.3 |
| Neutrophil count (x10$^9$/L) | 9.3(↑) | 14.1(↑) | 6.4 |
| CRP (mg/dL) | 47.1(↑) | 60(↑) | 4.75 |
| Urea (mg/dL) | 15.2 | 22 | 29 |
| Creatinine (mg/dL) | 0.44(↓) | 0.7 | 0.4(↓) |
| ALT (U/L) | 12.9 | 15 | 18 |
| AST (U/L) | 7.6 | 10 | 20 |
| PT (seconds) | 10.95 | 11.4 | 12.3 |
| aPTT (seconds) | 19.95 | 24.5 | 18 |
| INR | 0.95 | 1 | 1.08 |
| Fibrinogen (mg/dL) | 567(↑) | 249 | 181 |
| D-Dimer (ng/mL) | 4.81(↑) | 6.78(↑) | 0.4 |

ICU: intensive care unit; ALT: alanine aminotransferase; AST: aspartate aminotransferase; aPTT: activated partial thromboplastin time; CRP: C-reactive protein; CVST: cerebral vein sinus thrombosis; DIC: disseminated intravascular coagulopathy; ICU: intensive care unit; INR: international normalization ratio; WBC: white blood cell

RT-PCR test was repeated on the 14$^{th}$ day of hospitalization. The test was negative for SARS-CoV-2. RT-PCR test of her baby was also negative. For this case, it has been shown that SARS-CoV-2 has no vertical transmission. The patient was discharged when the patient's treatment was completed and his clinical condition and laboratory tests returned to normal levels.

There is no history of coagulopathy in the patient or family. In laboratory tests, normal results of anti-cardiolipin antibody (IgM=6.1 U/mL, IgG=5 U/mL), anti-phospholipid antibody (negative), lupus anticoagulant (35 seconds), anti-thrombin-3 ( 95%), Factor V Leiden (negative), prothrombin gene mutation (negative), protein C (80 U/dL) and protein S (70U/dL) testing are shown. In this case, the cause of SSST is thought to be hypercoagulation in pregnancy aggravated by COVID-19.

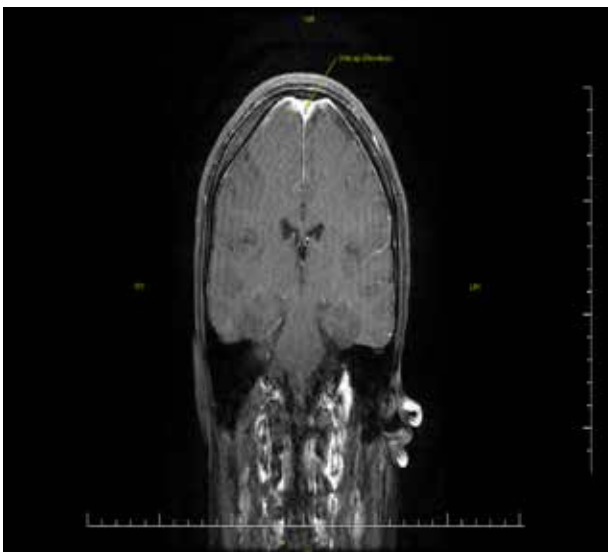

**Figure 3:** Brain magnetic resonance imaging showing superior sagittal sinus thrombosis as delta sign in coronal view.

## DISCUSSION

COVID-19 can be complicated by a complication such as SSST, as noted in this case, apart from the typical and widely known development of pneumonia. Cerebral sinus venous thrombosis (CVST) is a very rare disease seen in 1 in 5 million people[7]. A retrospective study by Cantu *et al* reported that 59% of CVST cases were pregnant or postpartum. In this study, the prothrombotic state due to hormonal effect during pregnancy and postpartum period was stated as the cause[8]. Some of the prominent symptoms of CVST in pregnancy and puerperium are headache (74%), seizure (50%), motor weakness (38%), coma (45%) and visual changes (24%)[9]. In this case, CVST is presented with a seizure. In a pregnant CVST case reported by Farzi *et al*, eclampsia was first considered as in this case, but when magnesium sulfate treatment failed, neuroimaging methods were applied. Similarly, the diagnosis was made as in this case[10]. It is thought that the current COVID-19 may contribute to CVST by affecting coagulation pathways in patients. Cytokine elevation and inflammatory changes triggered by SARS-CoV-2 infection can lead to serious complications, including disseminated intravascular coagulopathy. Coagulopathy may occur with the increase of D-dimer and fibrin degradation products, and changes in prothrombin time, partial thromboplastin time and platelet count can be seen[11]. In this case, D-dimer and fibrinogen levels increased in the early stages, but this increase returned to normal following COVID-19 and anticoagulant therapy. The

patient's symptoms and clinical condition improved. CVST treatment should be arranged according to the patient's clinical presentation, pregnancy and breastfeeding status. Enoxaparin is safe and effective as it does not cross the placenta and breast milk[7,9]. In this case, enoxaparin sodium 0.6 cc 2x1 treatment was applied and a response was obtained. In the treatment of COVID-19, COVID-19 treatment guidelines emphasize that no drug has been proven to be completely safe and effective. In a cross-sectional study involving 48 COVID-19 patients by Ren *et al*, lower extremity deep vein thrombosis was detected at a rate of 85.4%[12]. In a case series by Cavalcanti[13] and colleagues and cases by Hughes *et al*[14], Klein *et al*[15] and Sugiyama *et al*[16], cerebral venous thrombosis was reported in COVID-19 patients. Supportive therapy and isolation are recommended for patients requiring it. While there is no adequate evidence for the effectiveness of hydroxychloroquine treatment, in severe cases whose $SpO_2$ <94%, remdesivir is recommended. The therapeutic effectiveness of lopinavir and ritonavir couldn't be proven and not recommended for COVID-19 treatment. However, these studies had small sampling and no blindness. There are insufficient data to recommend either for or against the use of COVID-19 convalescent plasma for treatment. Yet the safety of lopinavir and ritonavir is proven because they are used for human immunodeficiency virus infection in pregnant women. Also, the importance of thromboprophylaxis is highlighted in COVID-19 treatment[17]. Hydroxychloroquine was administered first in this case because the clinical findings of the patient were not severe, but lopinavir and ritonavir were administered to the patient due to the severity of the disease after intubation. When the patient could not tolerate weaning, immune plasma therapy was administered and a response was obtained.

## CONCLUSION

In conclusion, COVID-19 can present different clinical situations in pregnant. Also, awareness of thromboembolic events in pregnancy with COVID-19 is vital to make a differential diagnosis in complex clinical states.

## ACKNOWLEDGMENT

**Author contribution:** BY: acquisition and interpretation of the data for the work; HG: drafting the work critically for intellectual content; CSC: final approval of the version to be published.

The address of the institution at which the work was carried out together: University of Health Sciences, Samsun Education and Research Hospital, Obstetrics and Gynecology Department, Samsun, Turkey

**Disclosure:** There is no conflict of interest and there is no financial support to declare.

## REFERENCES

1. World Health Organization. Director-General's remarks at the media briefing on 2019-nCoV on 11 February 2020. https://www.who.int/dg/speeches/detail/who-director-general-s-remarks-at-the-media-briefing-on-2019-ncov-on-11-february-2020 (Accessed on May 22, 2020).
2. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, *et al*. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA 2020; 322(11):1061-9.
3. World Health Organization. Director-General's remarks at the media briefing on 2019-nCoV on 11 February 2020. https://www.who.int/dg/speeches/detail/who-director-general-s-remarks-at-the-media-briefing-on-2019-ncov-on-11-february-2020 (Cited on May 22, 2020).
4. Elshafeey F, Magdi R, Hindi N, Elshebiny M, Farrag N, Mahdy S, *et al*. A systematic scoping review of COVID-19 during pregnancy and childbirth. Int J Gynaecol Obstet 2020; 150(1):47-52.
5. Di Mascio D, Khalil A, Saccone G, Rizzo G, Buca D, Liberati M, *et al*. Outcome of coronavirus spectrum infections (SARS, MERS, COVID-19) 1 during pregnancy: a systematic review and meta-analysis. Am J Obstet Gynecol MFM 2020; 2(2):1001107.
6. Di Renzo GC, Giardina I. Coronavirus disease 2019 in pregnancy: consider thromboembolic disorders and thromboprophylaxis. Am J Obstet Gynecol 2020; 223(1):135.
7. Luo Y, Tian X, Wang X. Diagnosis and treatment of cerebral venous thrombosis: A review. Front Aging Neurosci 2018; 10:2.
8. Cantú C, Barinagarrementeria F. Cerebral venous thrombosis associated with pregnancy and puerperium: Review of 67 cases. Stroke 1993; 24(12):1880-4.
9. Kashkoush AI, Ma H, Agarwal N, Panczykowski D, Tonetti D, Weiner GM, *et al*. Cerebral venous sinus thrombosis in pregnancy and puerperium: A pooled, systematic review. J Clin Neurosci 2017; 39:9-15.
10. Farzi F, Abdollahzadeh M, Faraji R, Chavoushi T. Seizure in pregnancy following cerebral venous sinus thrombosis. Anesth Pain Med 2015; 5(3):e26866.
11. Connors JM, Levy JH. COVID-19 and its implications for thrombosis and anticoagulation. Blood 2020; 135(23):2033-40.
12. Ren B, Yan F, Deng Z, Zhang S, Xiao L, Meng Wu, *et al*. Extremely high incidence of lower extremity deep venous thrombosis in 48 patients with severe COVID 19 in Wuhan. Circulation 2020; 142(2):181-3.
13. Cavalcanti DD, Raz E, Shapiro M, Dehkharghani S, Yaghi S, Lilemmoe K, *et al*. Cerebral venous thrombosis associated with COVID-19. Am J Neuroradiol 2020; 41(8):1370-6.

14. Hughes C, Nichols T, Pike M, Subbe C, Elghenzai S. Cerebral venous thrombosis as a presentation of COVID-19. Eur J Case Rep Intern Med 2020; 7(5):001691.
15. Klein DE, Libman R, Kirsch C, Arora R. Cerebral venous thrombosis: a typical presentation of COVID-19 in the young. J Stroke Cerebrovasc Dis 2020; 29(8):104989.
16. Sugiyama Y, Tsuchiya T, Tanak R, Ouchi R, Motoyama A, Takamoto T, *et al*. Cerebral venous thrombosis in COVID-19 associated coagulopathy: A case report. J Clin Neurosci 2020; 79:30-2.
17. COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institute of Health Availeble at: https://www.covid19treatmentguidelines.nih.gov/.(Cited on 22 May 2020).

Case Report

# Successful treatment of a rare retroperitoneal necrotizing soft tissue infection due to cranial spread of necrotizing perianal infection in COVID positive patient: a case report

Khaled M Albassam[1], Aliasgar I Kachwala[1], Obaid M Alharbi[1,2]
[1]Department General Surgery, Farwaniya Hospital, Kuwait
[2]Faculty member at KIMS, Kuwait

Kuwait Medical Journal 2023; 55 (4): 354 - 358

## ABSTRACT

Retroperitoneal necrotizing soft tissue infections (NSTI) are rare and a lethal disease. Delay in diagnosis and initiating treatment can lead to disastrous outcomes.

This is a case of a 38-year-old young COVID positive male with retroperitoneal NSTI possibly due to cranial spread of ischiorectal necrotizing infection by E.coli, *Salmonella enterica* and bacteroides. On presentation, patient had high grade fever with left flank pain for three days and perianal discomfort for 10 days. Laboratory evaluation of unexplained sepsis revealed leucocytosis and acute kidney injury. Emergency computerized tomography scan of the abdomen showed gas in soft tissue, tracking along left psoas muscle. Initial emergency perianal debridement for source control relieved sepsis, but not abdominal pain. After initial improvement, patient deteriorated again. Further serial debridements by lumbotomy without contaminating peritoneal cavity lead to improvement. Wound closure was achieved by negative pressure wound therapy (NPWT) and secondary closure.

Ischiorectal infection can spread to retroperitoneum, even in the absence of any definite fistulous connections. Once in preperitoneal space, it can spread rapidly to retroperitoneum and can cause profound sepsis. Early diagnosis, broad spectrum antibiotics and thorough debridement with adequate wound drainage can be lifesaving. NPWT can be very useful in patients with extensive wounds in COVID positive patients.

**KEY WORDS:** necrotizing soft tissue infections, negative pressure wound therapy, retroperitoneal

## INTRODUCTION

Necrotizing soft tissue infections (NSTI) are uncommon and life-threatening diseases. It is defined as infection and necrotizing changes within any layer of the soft tissue compartments[1]. Typical sites are lower extremities, abdomen and perineum[2,3]. Necrotizing fasciitis involving retroperitoneum is quite uncommon as per our knowledge. True risk factors for necrotizing fasciitis has not been identified, yet certain conditions more commonly associated with are injection drug abuse, diabetes mellitus, obesity, HIV infections and other causes leading to immunosuppression[4-6]. In a majority of cases with risk factors, type I infection – polymicrobial are common, while in young healthy male Type II, monomicrobial infections are more common[7]. Due to absence of specific signs and symptoms, it often leads to delay in diagnosis and poor outcome. The principle management of NSTI includes source control by serial debridements, antimicrobial therapy, support and monitoring. Studies have shown that only microbial therapy with support may result in 100% mortality. Thorough serial debridements lead to control of infection and allows future recovery. We report a successfully treated rare case of extended retroperitoneal NSTI caused by possible cranial extension of perianal NSTI.

## CASE REPORT

A 38-year-old male truck driver was referred from clinic to emergency department with provisional diagnosis of urinary tract infection. The patient presented with complaints of perianal discomfort for

*Address correspondence to:*
*Dr. Aliasgar Kachwala, Department of General Surgery, Farwaniya Hospital, Kuwait. Mob: +965 65681544; E-mail: dr.aliasgar@yahoo.co.in*

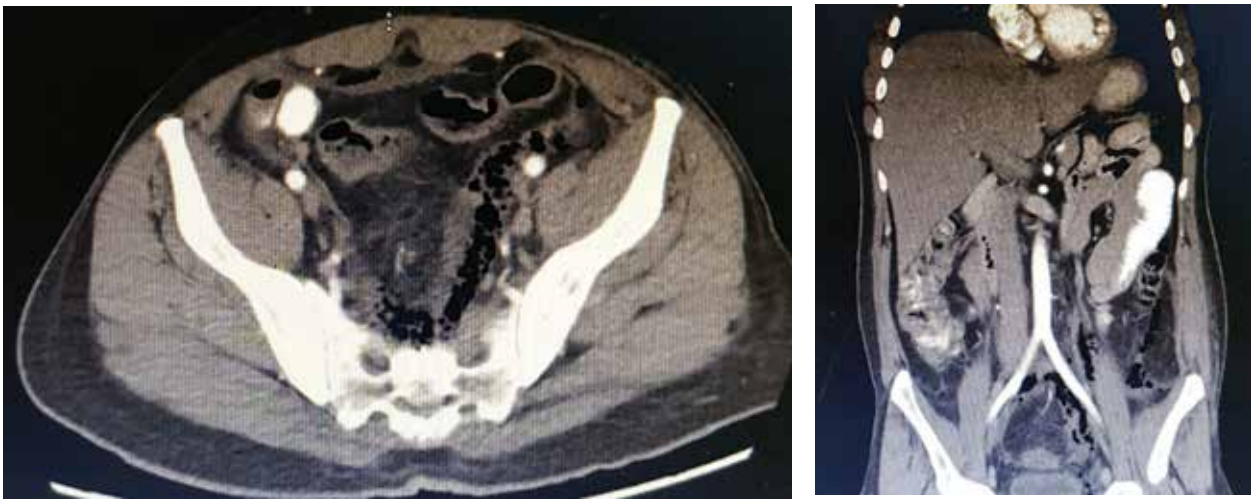

**Figure 1, 2:** Preoperative CT images showing extensive air in pararectal, presacral, parailiac, pararenal air tracking along left psoas muscle.

10 days, which he neglected and attributed to nature of his prolonged sitting while driving long distances, severe left flank pain for three days and generalized profound weakness for three days.

On assessment, patient was febrile with temperature of 39 °C, heart rate of 118/min, blood pressure of 108/76 mmHg, respiratory rate of 16/min and $SpO_2$ of 98% on room air. Chest auscultation revealed bilateral equal breath sounds. Abdominal examination revealed tender abdomen, more on left flank with severe tenderness on per rectal examination. Proctoscopy was not attempted due to severe pain. There were no bullae or crepitus over abdomen or perineal region. The patient was admitted for further evaluation. His blood test revealed total count (TC) of $15.1x10^9$/L, raised serum creatinine of 247 umol/L, blood sugar of 8.14 mmol/L, high C-reactive protein of 442 mg/L and lactic acid of 2.77 mmol/L. Urine examination showed nitrite positive and microscopy showed presence of granular and hyaline cast. Chest X-ray was normal with no evident findings suggestive of pneumonia. His nasopharyngeal swab for COVID PCR was positive. After admission, patient received intravenous fluid hydration with 2 liters of normal saline, intravenous piperacillin + tazobactum 2.25 gm and metronidazole 500 mg. Emergency computerized tomography (CT) of the abdomen with oral, rectal and intravenous contrast was performed, which showed presence of multiple extensive air loculi in soft tissues of pre sacral, left para rectal, recto sigmoid, left paracolic, left para renal soft tissues reaching up to perisplenic, para aortic and parailiac vessel regions along the left psoas muscles. Mild amount of free fluid in pelvic cavity was noticed. Both kidneys and parinephric spaces were normal and there was no extravasation of oral or rectal contrast (Figures 1 and 2). Preoperative CT images showed extensive air in pararectal, presacral, parailiac and pararenal air tracking along left psoas muscle.

The patient was taken for emergency examination of perianal region under general anesthesia in COVID designated operation theatre with all personal protective equipment precautions. On exploration, we found left ischiorectal abscess with necrotic tissues pointing towards pelvirectal space, horse-shoe extension to right side and necrotizing facsitis over inner side of left thigh. Extension of debridement towards pelvirectal space drained large amount of yellowish-brown foul-smelling frothy fluid. Large incisions with debridement of necrotic tissues, lavage with betadine, $H_2O_2$ and saline were done. Malecott drains into pelvirectal space were kept for irrigation and patient was returned to COVID isolation bed for postoperative care. The patient was continued on antibiotics and drain irrigation with betadine saline every eight hours. Patient improved initially with creatinine of 107 umol/L, TC of $11.4x10^9$/L and C-reactive protein of 208mg/L. However, he still had persistent complaint of left flank pain. Pus cultures from previous surgery showed heavy growth of E.coli, Salmonella enterica and bacteroides fragilis, which were sensitive to antibiotics prescribed. On the 5$^{th}$ postoperative day, patient had a fever spike of 39 $^0$C and elevated TC of $18.4x10^9$/L. CT scan abdomen with triple contrast was repeated, which showed regressive but persistent air loculi in parasacral, left paracolic, left paranephric spaces reaching to left side of diaphragm along left psoas muscle. The patient was taken for second look debridement in COVID designated operation theatre with all personal protective equipment precautions. On exploration of the perineal wound, it showed significant amount of retained purulent fluids communicating to retroperitoneal tissue. Left lumbotomy incision was kept and foul smelling brownish frothy fluid was drained. After retracting peritoneum medially, communication of left para rectal collection with retroperitoneal collection

**Figure 3** - Postoperative image before secondary suturing of lumbotomy wound after NPWT discontinuance.

was identified and thorough debridement was done. Wounds were packed with betadine gauze and drains were placed for irrigation. The patient was shifted to intensive care unit on mechanical ventilation. Histopathology of tissues taken revealed necrotic adipose tissues. After 36 hours, debridement was done again in COVID designated operation theatre. Postoperatively, the patient was shifted to intensive care unit on mechanical ventilation. Patient responded to management and became afebrile with improving laboratory parameters. Patient was extubated on 5$^{th}$ postoperative day and shifted to isolation ward as per COVID protocol of hospital. After regular flushing of drains and dressing change at every 8 hours, wounds started developing healthy granulation tissue. Negative pressure wound therapy (NPWT) for abdominal wound was applied. Antibiotics were discontinued after a total of three weeks. On the 23$^{rd}$ day, abdomen wounds were secondarily sutured and patient was discharged after 28 days (Figure 3).

## DISCUSSION

Necrotizing fasciitis is rare, with a documented incidence of 3 cases per 100,000 people per year[8]; fulminant, rapidly progressing necrotizing soft tissue disease with high mortality rate especially if the diagnosis is inaccurate or delayed[9]. Early diagnosis, intravenous antibiotics and thorough surgical debridement are the keys to decrease the mortality in NSTI[9]. Clinical features that aid in early diagnosis are: pain which is out of proportion to clinical findings, unexplained sepsis /organ failure, failure to respond to broad spectrum antibiotics, bullae on skin and imaging like x-ray / CT-scan showing gas in soft tissues[10]. Our patient presented with high grade fever, sepsis and acute kidney injury. Diagnosis of retroperitoneal necrotizing infection was achieved by CT scan in our case. CT scan plays an important role in demonstrating early findings with reported sensitivity and specificity of 100% and 81% respectively[11]. It helps in assessing the extent of disease, determining the best surgical approach, identifying the primary source of infection and also for evaluating the response to treatment. Common CT scan findings include fascial thickening and enhancement, muscular edema, fat stranding, fluid collections and abscess formations. Gas tracking along fascial planes and asymmetric involvement of the retroperitoneal fascial planes are the hallmark of retroperitoneal fasciitis, which was diagnostic in our case also. Indirect tracking and transgression of fascial planes indicates more severe infection[11].

Broad spectrum antibiotics should be administered as soon as necrotizing fasciitis is suspected clinically[12]. NSTI has been classified microbiologically into 2 types: type 1 (polymicrobial) which is more common and the culture yields are usually a mixture of aerobic and anaerobic organisms; and type 2 (monomicrobial)[7]. Polymicrobial infections typically occur in the perineum and trunk and the isolates reflect normal skin commensals adjacent to the site of infection. The etiologic isolates consist of Gram-positive organisms like Staphylococcus aureus, S. pyogenes and enterococci; Gram-negative aerobes like Escherichia coli and Pseudomonas species; and anaerobic organisms like bacteroides or clostridium species[13]. E. coli, Salmonella enterica and bacteroides fragilis were identified as pathogenic bacteria on two consecutive cultures, sensitive to antibiotics administered in our case. Type 1 NSTI is more common in immunocompromised individuals[5-7]. In our case, necrotizing infection in the absence of risk factors in healthy young male may be due to transient immunosuppression during active phase of infection leading to COVID, or may be vice versa.

The pelvic floor represents a musculo-aponeurotic barrier to the cranial extension of an abscess below the levators. The crossing of this barrier can either be due to chronic supralevator fistula completely asymptomatic or by a local infectious destruction of the muscle fibers at the level of the ischio-rectal compartment due to virulence of the organisms involved. An anatomical condition seems to be necessary; however, it is the

congenital opening of the caudal portion of the cone of the peri-renal fascia providing communication between the sub peritoneal spaces with the retroperitoneal space[14]. The rapid spread of the infection is due to the loose and non-partitioned nature of the areolar fatty tissue in retroperitoneum[14-17].

Timely and thorough surgical debridement removing all necrotic tissue and pus collection is an essential part of treatment and must be performed as soon as possible, since a delay in treatment beyond 12 hours can prove fatal[18]. To perform extensive surgical debridement of NSTI in COVID positive patient with high risk for transmission to care givers was surgically challenging[19]. Access of retro peritoneum through midline laprotomy can lead to significant morbidity in perioperative period. Inoculation of peritoneal cavity must be avoided if it is not the primary source of infection. The iliac route allows better exposure to the Retzius and Bogros space, but the access to the upper compartment of the retroperitoneum remains very limited. Lumbotomy is therefore the only approach that allows complete exposure of the entire retroperitoneal space to achieve wide excision of gangrenous tissue and adequate toilet, but it does not allow access to the Retzius if it is involved in the gangrene. This choice should be made according to the direction of the extension of the sub and retroperitoneal gangrene and according to CT data[20]. Daily assessment of wound for necrotic tissue and wound flushing with copious betadine saline is vital in postoperative period. By removing debris and blood clots which provides medium for bacterial proliferation, source control can be achieved. We do not use any topical antibiotics or topical wound solutions in our practice. Depending on the vital signs and clinical course of necrosis, surgical debridement must be repeated after 24 hours or later[21].

Therapeutic regimens of antibiotics can be adjusted according to culture reports. The duration of antibiotics therapy should be decided depending on clinical condition and laboratory tests. The average duration of antibiotics therapy is around 4-6 weeks[18].

Hyperbaric oxygen administration for necrotizing fasciitis can offer many benefits, including direct anaerobic bacterial effect, reduced endotoxin activity, increased leukocytic phagocytosis and decreased free radical production. However, due to COVID positive status in our patient, it was not attempted[22].

NPWT is a revolutionary technique in terms of wound closure. It improves local blood flow, induces macro deformation, granulation and angiogenesis and reduces edema and bacterial colonization[23]. With the help of NPWT, skin and soft tissue defects can be sutured directly without need for skin grafts and flaps in many cases. The dressing change interval every 3-4 days or sometimes longer is a boon, especially in COVID patients, as contact with body fluids is reduced, which can transmit COVID-19 virus.

## CONCLUSION

Necrotizing fasciitis as such is an uncommon lethal infection. Retroperitoneal necrotizing infection probably due to cranial spread of perianal infections is hardly documented as per our knowledge. Spread of perianal infection to retroperitoneum is rare and must be suspected in cases of perianal infections with unexplained abdominal tenderness, sepsis and organ failure. Successful treatment of this patient with retroperitoneal necrotizing infection with COVID infection can be attributed to early diagnosis aided by CT scan, sensitivity of microorganisms to antibiotics prescribed, timely, serial and thorough debridement without contaminating peritoneal cavity and good supportive care. State of immunosuppression during severe infection probably led to COVID infection in this patient, or maybe viral infection led to state of immunosuppression resulting in flourishing sepsis. Advanced wound closure techniques like NPWT are very useful in the time of COVID.

## ACKNOWLEDGMENT

The authors declare that there are no conflicts of interest regarding the publication of this paper.

The clinical case was managed successfully as a teamwork. The case report was prepared by Aliasgar I Kachwala with guidance of Khaled M Albassam and Obaid M Alharbi.

## REFERENCES

1. Anaya DA, Dellinger EP. Necrotizing soft-tissue infection: diagnosis and management. Clin Infect Dis 2007; 44(5):705-10.
2. Anaya DA, McMahon K, Nathens AB, Sullivan SR, Foy H, Bulger E. Predictors of mortality and limb loss in necrotizing soft tissue infections. Arch Surg 2005; 140(2):151-7.
3. Morgan MS. Diagnosis and management of necrotizing fasciitis: a multiparametric approach. J Hosp Infect 2010; 75(4):249-57.
4. Wall DB, Klein SR, Black S, de Virgilio C. A simple model to help distinguish necrotizing fasciitis from nonnecrotizing soft tissue infection. J Am Coll Surg 2000; 191(3):227-31.
5. Wong C-H, Khin L-W, Heng K-S, Tan K-C, Low C-O. The LRINEC (laboratory risk indicator for necrotizing fasciitis) score: a tool for distinguishing necrotizing fasciitis from other soft tissue infections. Crit Care Med 2004; 32(7):1535-41.
6. Singh G, Sinha SK, Adhikary S, Babu KS, Ray P, Khanna SK. Necrotising infections of soft tissues - a clinical profile. Eur J Surg 2002; 168(6):366-71.

7. Elliot D, Kufera JA, Myers RA. The microbiology of necrotizing soft tissue infections. Am J Surg 2000; 179(5):361-6.
8. Vilallonga R, Mazarro A, Rodriguez-Luna MR, Caubet E, Fort JM, Armengol M, *et al*. Massive necrotizing fasciitis: a life threatening entity. J Surg Case Rep 2019; 2019(11):rjz269.
9. Takakura Y, Ikeda S, Yoshimitsu M, Hinoi T, Sumitani D, Takeda H, *et al*. Retroperitoneal abscess complicated with necrotizing fascitis of the thigh in a patient with sigmoid colon cancer. Would J Surg Oncol 2009; 7:74.
10. Goh T, Goh LG, Ang CH, Wong CH. Early diagnosis of necrotizing fasciitis. Br J Surg 2014; 101(1):e119-25.
11. ChingKoe CM, Jahed A, Loreto MP, Sarrazin J, McGregor CT, Blaichman JI, *et al*. Retroperitoneal fasciitis: Spectrum of CT findings in the abdomen and pelvis. Radiographics 2015; 35(4):1095-107.
12. Sudarsky LA, Laschinger JC, Coppa GF, Spencer FC. Improved results from a standardized approach in treating patients with necrotizing fasciitis. Ann Surg 1987; 206(5):661-5.
13. File TM Jr, Tan JS, DiPersio JR. Group A streptococcal necrotizing fasciitis. Diagnosing and treating the "flesh-eating bacteria syndrome". Cleve Clin J Med 1998; 65(5):241-9.
14. Mindell HJ, Mastromatteo JF, Dickey KW, Sturtevant NV, Shuman WP, Oliver CL, *et al*. Anatomic communications between the three retroperitoneal spaces: determination by CT-guided injections of contrast material in cadavers. AJR Am J Roentaenol 1995; 164(5):1173-8.
15. Amitai A, Sinert R. Necrotizing fasciitis as the clinical presentation of a retroperitoneal abscess. J Emerg Med 2008; 34(1):37-40.
16. Elliott DC, Kufera JA, Myers RA. Necrotizing soft tissue infections. Risk factors for mortality and strategies for management. Ann Surg 1996: 224(5):672-83.
17. Cadot P Rouquette I, Szym P, Andre JL. [Life-threatening cellulitis, or Fournier's gangrene of the perineum]. J Chir (Paris) 2003; 140(1):22-32. Article in French.
18. Misiakos EP, Bagias G, Patapis P, Sotiropoulos D, Kanavidis P, Machairas A. Current concepts in the management of necrotizing fascitis. Front Surg 2014; 1:36.
19. Yenigun A, Ozturan O, Dagistanli N, Koc MM, Koytak A. Surgical precautions and algorithmic decision-making for surgical procedures during the COVID-19 pandemic. J Am Coll Surg 2020; 231(6):787-9.
20. Daldoul S, Massoudi I, Mabrouk A, Ksontini I, Abid W, Moussa MB. An unexpected cause of retroperitoneal gangrene. Tunis Med 2017; 95(2):152-5.
21. Roje Z, Roje Z, Matic D, Librenjak D, Dokuzovic S, Varvodic J. Necrotizing fasciitis: literature review of contemporary strategies for diagnosis and management with three case reports: torso, abdominal wall, upper and lower limbs. World J Emerg Surg 2011; 6(1):46.
22. Tejada S, Batle JM, Ferrer MD, Busquets-Cortes C, Monserrat-Mesquida M, Nabavi SM, *et al*. Therapeutic effects of hyperbaric oxygen in the process of wound healing. Curr Pharm Des 2019; 25(15):1682-93.
23. Hasan MY, Teo R, Nather A. Negative pressure wound therapy for management of diabetic foot wounds: a review of the mechanism of action, clinical applications, and recent developments. Diabet Foot Ankle 2015; 6:27618.

Case Report

# Mechanical intestinal obstruction cause which mimic rectum tumor: Endometriosis

Mehmet Onur Gul, Serdar Gumus
Surgical Oncology, Department of Surgical Oncology, Cukurova University, Balcali Training and Research Hospital, Adana, Turkey

Kuwait Medical Journal 2023; 55 (4): 359 - 363

## ABSTRACT

Endometriosis is a disease that frequently affects women of reproductive age. The estimated incidence of intestinal endometriosis in women with endometriosis is between 5.3% - 12%. Most of the time, bowel endometriosis is asymptomatic and often clinically insignificant. However, serious complications can occur, such as complete bowel obstruction. A 45-year-old patient with endometriosis which caused mechanical bowel obstruction was radiologically and clinically similar to upper rectum cancer. Emergency laparotomy was performed on the patient due to mechanical intestinal obstruction. In the rectosigmoid of the colon, a tumoral structure invading the uterus and surrounding tissues was detected. The patient was evaluated in the multidisciplinary oncology council. The decision was made to perform total abdominal hysterectomy with bilateral salmingo oophorectomy (TAH + BSO) with low anterior resection, and total abdominal hysterectomy since the differentiation of the rectosigmoid colon cancer and deep endometriosis could not be made with the available examinations. Endometriosis may not always be diagnosed with current clinical methods and practices and may be confused with the diagnosis of colorectal cancer.

**KEY WORDS:** endometriosis, mechanical intestinal obstruction, rectal bleeding

## INTRODUCTION

Endometriosis is a relatively common disease affecting 10% of women of reproductive age[1]. Its incidence is as high as 50% among adolescents with pelvic pain[1,2]. Endometriosis is common in women of reproductive age, on average, around 37 years old[3]. The disease is generally associated with multiple lesions, including the abdominal-pelvic peritoneum and visceral organs. Intestinal endometriosis's estimated incidence in women with endometriosis is between 5.3-12%[1,4]. Most of the time, bowel endometriosis is asymptomatic and often clinically insignificant. However, serious complications can occur, such as complete bowel obstruction[5]. Progestin-based hormone therapy and gonadotropin-releasing hormone analogs have become the standard therapy for endometriosis. However, many patients experience systemic side effects associated with these treatments[6]. Besides, response to hormonal therapy may not be sufficient in all women with endometriosis, especially in those with the deep infiltrating disease.

This article aims to present a case of endometriosis that causes mechanical bowel obstruction, which is radiologically and clinically similar to upper rectum cancer.

## CASE REPORT

A 45-year-old woman was referred to our clinic with complaints of abdominal pain, nausea and vomiting, which started one week ago and gradually increased for the last two days. She had dysmenorrhea and rectal bleeding during her menstrual periods in the last two months in her detailed medical history. There was no history of drug use.

In physical examination, there was distension and generalized tenderness in the abdomen. Intestinal sounds increased, and the ampulla of the rectum examination was empty. Diffuse small intestine and colonic air-fluid levels were seen on standing plain radiography, and there was no free air. In the laboratory values, leukocyte was $11.4x10^3/\mu l$, hematocrit was 41.6%, platelets were 336,103/µl, and no pathology was

*Address correspondence to:*
*Mehmet Onur Gul, MD, Fellow of Surgical Oncology, Department of Surgical Oncology, Cukurova University, Balcali Training, and Research Hospital, Adana, Turkey. Tel: +90 555 6806729; Fax: +90 322 3386945; E-mail: mehmetonurgul@hotmail.com*

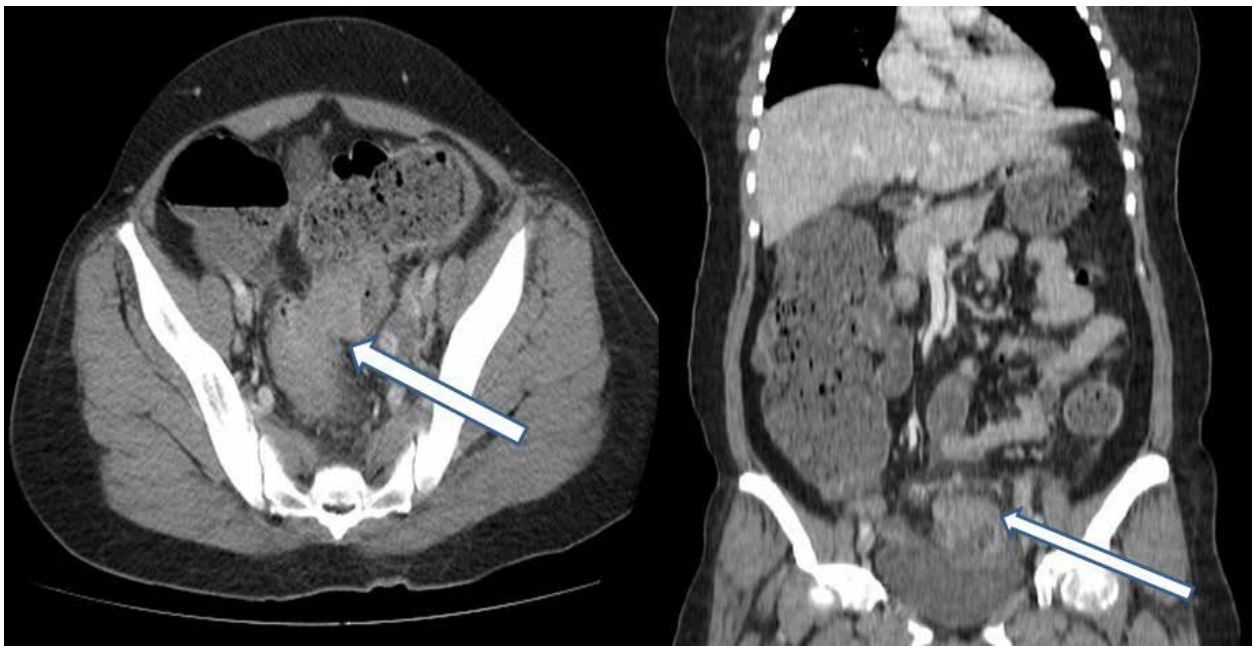

**Figure 1:** CT images: Rectosigmoid colon tumor and secondary mechanical intestinal obstruction images.

found in biochemical values. Intravenous contrast-enhanced computed tomography (CT) performed to investigate the ileus' etiology revealed a mass involving the rectosigmoid corner and invading the uterus (Figure 1). Rectosigmoidoscopy was performed under emergency conditions, and it was found that the rectosigmoid colon was completely occluded. Endoscopic biopsies were taken from the area causing the obstruction.

Emergency laparotomy was performed for the patient due to mechanical bowel obstruction. Invasive tumor structure was detected in the rectosigmoid colon, uterus and surrounding tissues in the colon. The cecum and small intestines were greatly enlarged. The obstructive pathology in the patient was observed to be a rectosigmoid tumor. A sigmoid loop colostomy was opened for diversion, and biopsy was taken from areas thought to overflow into the serosa. As a result of histopathological examination of intraoperative and endoscopic biopsies, mixed-type inflammatory cells containing abundant eosinophil leukocytes were seen, but no malignancy was found. The carcinoembryonic antigen value was 9.45 ng/ml and carbonic anhydrase 125 was 118.4 U/ml.

In the postoperative period, the patient underwent lower abdominal magnetic resonance imaging (MRI),

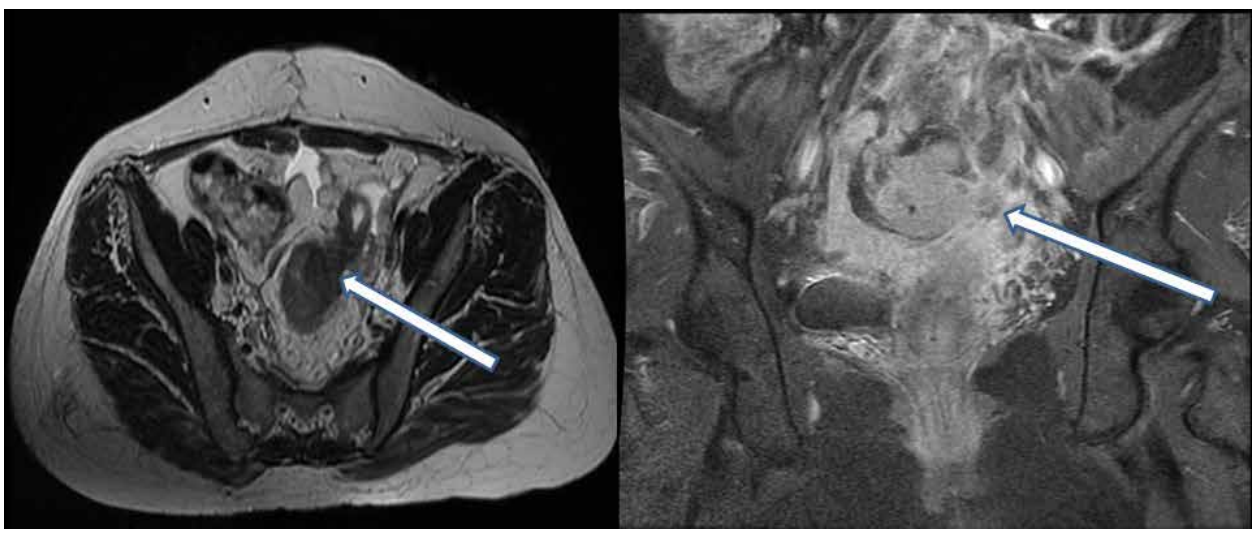

**Figure 2:** MRI imaging: Mass lesion T4b, which is thought to have invaded the uterus, starting from the rectosigmoid region and extending to the middle part of the rectum associated with the right lateral uterus.

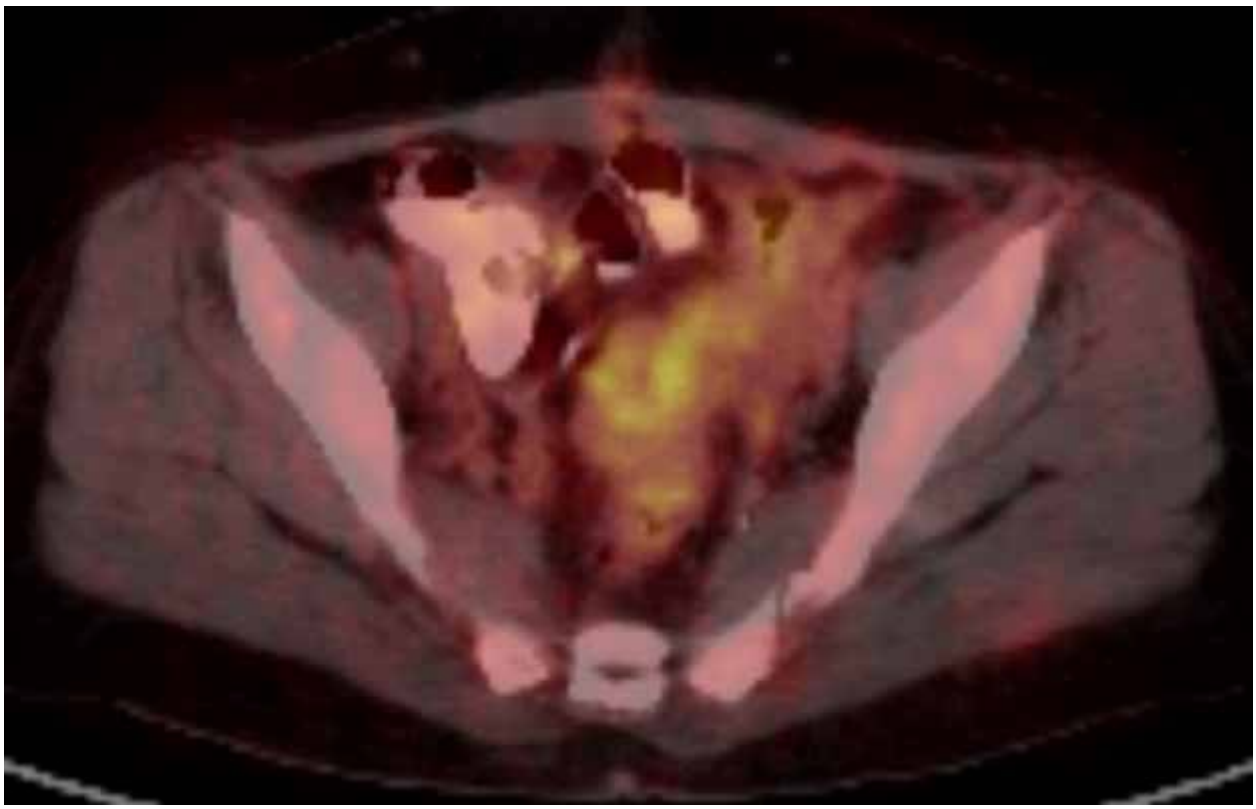

**Figure 3:** PetCT imaging: Hypermetabolic irregular wall thickening at the rectosigmoid colon level.

and the mass was evaluated as a rectosigmoid-derived malignancy (Figure 2). In positron emission tomography (PET-CT), the SUVmax value of the gathering was assessed as 8.31 (Figure 3). Pancolonoscopy was performed and no additional pathology was found.

The patient was evaluated in the multidisciplinary oncology council. It was decided to perform bilateral oophorectomy (total abdominal hysterectomy with bilateral salpingo-oophorectomy, TAH + BSO) with low anterior resection. The distinction could not be made between rectosigmoid colon cancer and deep endometriosis with available examinations, despite being a virgin.

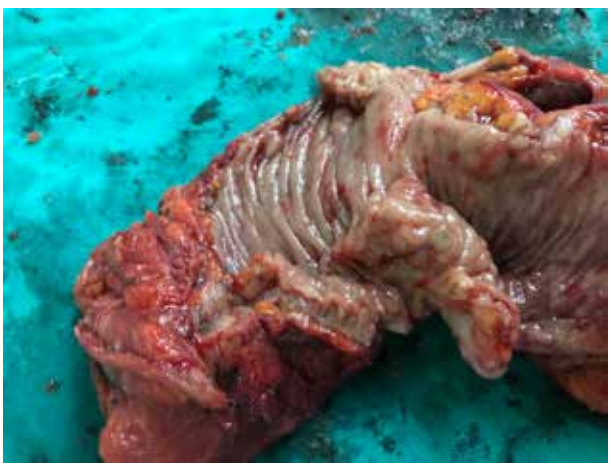

**Figure 4:** View of the specimen opened after resection.

After obtaining the patient's consent, the second operation was performed 30 days after the first operation. Loop ileostomy was conducted by performing TAH + BSO with low anterior resection. On the back table, it was determined that the lesion originated from the uterus and occupied the rectal serosa and the colonic mucosa was intact (Figure 4).

In histopathological examination, she had extensive deep endometriosis, which was 5.5x3x3 cm in size, occupying the rectum wall externally. The patient was discharged without any complications. In the postoperative 4$^{th}$ month, the loop ileostomy was closed and intestinal continuity was achieved.

## DISCUSSION

Endometriosis was first described in 1860 by von Rokitansky[7]. It is a benign, non-neoplastic gynecological lesion that is mainly seen in women of reproductive age and characterized by functional endometrial tissue outside of the uterus[8,9]. Endometriosis diagnosis should be kept in mind in premenopausal women who present with cyclic abdominal pain, especially during menstrual periods[9].

The first case of digestive system involvement in patients with endometriosis was reported by Sampson in 1924 and defined the presence of sigmoid participation as a part of common endometriotic lesions[10]. Intestinal endometriosis often begins as asymptomatic small serosal implants[11]. Diarrhea and other digestive complaints such as constipation, cramping and rectal bleeding have been reported in approximately 15, 26 and 33% of patients[8,12]. The severity of symptoms and the probability of diagnosis increase with age and peaks at around 40 years of age[3]. The case we presented was in the 4th decade following the literature and presented with signs of cyclic rectal bleeding and obstruction.

Abdominal ultrasonographic imaging and MRI are the alternatives preferred by clinicians for diagnosis[13]. MRI sensitivity in intestinal endometriosis diagnosis is high (77%-93%)[8]. However, laparoscopy is increasingly used to confirm the presence of endometriosis before laparotomy[14]. According to the European Society of Human Reproductive and Embryology guidelines, the gold standard for endometriosis diagnosis is the histological demonstration of endometrial tissue presence by a biopsy performed by laparoscopy[15]. However, in intestinal-related endometriosis, endoscopic biopsies taken from the intestinal lumen for histology are insufficient to diagnose endometriosis because mostly non-specific chronic mucosal changes are detected in these biopsies. Endometriosis usually causes symptoms by invading the intestinal wall's deep layers, not the mucosa[9]. In endoscopic intestinal biopsy, mucosal changes include impaired intestinal glands, blunting of the intestinal villi, pyloric metaplasia, polypoid granulation tissue, and deep cracks be found in inflammatory bowel disease, ischemic bowel and chronic enteritis[16]. In our case, preoperative intravenous CT was performed because there were signs of mechanical intestinal obstruction, but the differential diagnosis of endometriosis and rectosigmoid could not be achieved. Biopsies were performed by performing laparotomy instead of diagnostic laparoscopy due to obstruction, but histopathological diagnosis could not be confirmed. Postoperative MRI and PetCT could not distinguish between endometriosis and rectosigmoid cancer. Endoscopic biopsies were also interpreted in favor of inflammation findings under the literature.

Intestinal endometriosis's estimated incidence in women with endometriosis is between 5.3-12%[1,4]. In centers where cases are common, the incidence of patients with deep pelvic endometriosis can be as high as 35%[17]. Complete colon obstruction is a rare complication of endometriosis occurring in less than 1% of cases[5]. The issue of endometriosis causing complete obstruction by colon involvement is much less common[18,19]. Rectosigmoidal involvement is more common in intestinal endometriosis[20].

Cyclic rectal bleeding has traditionally been accepted as an almost pathognomonic sign of mucosal involvement in intestinal endometriosis. However, recent data confirmed by biopsies that most patients who underwent recto-sigmoidoscopy during their menstruation had normal mucosa, and luminal abnormalities other than stenosis were not detected[21]. Endometriosis may end with fibrosis due to the inflammatory reaction caused by cyclic bleeding during the healing process, which can cause fibrosis of the intestinal wall, lumen stenosis and even varying degrees of obstruction that may require resection[9].

Vercellini *et al*[1] reported that both progestins alone and when combined with low-dose estrogen reduced dysmenorrhea, dyspareunia and dyschezia symptoms[22]. Ferrero *et al* reported that low-dose norethindrone (2.5 mg/day) could significantly reduce diarrhea, cramps and cyclic rectal bleeding in women with histologically proven endometriosis, and 53% of 40 participants provided adequate improvement in gastrointestinal symptoms. At the end of the 12-month study period, 33% of patients chose to undergo surgical treatment for intestinal endometriosis due to persistent irritating symptoms[23]. Vercellini *et al* stated that medical treatments could be considered in the absence of suspicion of an adnexal mass, obstructive uropathy or intestinal stenosis[24]. There was an obstructive endometriosis case with tumor suspicion in our study, and surgical treatment was considered the first choice as in other large series[24,25].

Vercellini *et al* reported that 84 right-sided colon resections, 245 left-sided colon resections and eight bilateral colon resections were performed in a study of 336 patients in which the topography of pelvic viscera involvement was examined in patients with obstructive colonic endometriosis[24]. de Jong *et al* in their study applied diversion colostomy to all patients to eliminate the acute condition due to complete bowel obstruction. Later, they stated that they needed a second, and in some cases, a third laparotomy to resect the obstructed bowel and maintain bowel continuity[25]. In our case, the patient's emergency was eliminated with a diversion colostomy that removed the obstruction, and definitive treatment was provided by performing colon resection and TAH-BSO with the second session of surgery.

## CONCLUSION

Excluding the differential diagnosis of endometriosis with imaging methods may not always be possible, as in our case. Patients can also present with mechanical intestinal obstruction. Intestinal endometriosis should be kept in mind in the

differential diagnosis in the presence of a mass causing cyclic rectal bleeding in premenopausal women.

**ACKNOWLEDGMENT**

**Conflict of interest**: There is no conflict of interest and financial funding for this study. Corresponding author is not a recipient of a research scholarship for this study.

Mehmet Onur Gul contributed to the design and implementation of the case report, to the analysis of the case, and to the writing of the manuscript. Serdar Gumus discussed the results and contributed to the final manuscript.

**REFERENCES**

1. Weed JC, Ray JE. Endometriosis of the bowel. Obstet Gynecol 1987; 69(5):727-30.
2. Chapron C, Chopin N, Borghese B, Foulot H, Dousset B, Vacher-Lavenu MC, *et al*. Deeply infiltrating endometriosis: pathogenetic implications of the anatomical distribution. Hum Reprod 2006; 21(7):1839-45.
3. Vigano P, Parazzini F, Somigliana E, Vercellini P. Endometriosis: epidemiology and aetiological factors. Best Pract Res Clin Obstet Gynecol 2004; 18(2):177-200.
4. MacAfee CH, Greer HL. Intestinal endometriosis: a report of 29 cases and a survey of the literature. J Obstet Gynecol Br Emp 1960; 67:539-55.
5. Jubanyik KJ, Comite F. Extrapelvic endometriosis. Obstet Gynecol Clin North Am 1997; 24(2):411-40.
6. Ferrero S, Alessandri F, Racca A, Maggiore UL. Treatment of pain associated with deep endometriosis: alternatives and evidence. Fertil Steril 2015; 104(4):771-92.
7. Bagchi S, Gupta AK, Alwadhi K, Sah S. Caesarean scar endometriosis: a rare site of extra pelvic endometriosis. Int J Reprod Contra cept Obstet Gynecol 2015; 4(5):1639-41.
8. De Ceglie A, Bilardi C, Blanchi S, Picasso M, di Muzio M, Trimarchi A, *et al*. Acute small bowel obstruction caused by endometriosis: A case report and review of the literature. World J Gastroenterol 2008; 14(21):3430-4.
9. Chhabra P, Rao C, Singh H, *et al*. Endometriosis causing small bowel obstruction. Trop Gastroenterol 2013; 34:188-91.
10. Sampson JA. Benign and malignant endometrial implants in the peritoneal cavity, and their relation to certain ovarian tumors. Surg Gynecol Obstet 1924; 38:287-311.
11. Nezhat C, Hajhosseini B, King LP. Laparoscopic management of bowel endometriosis: Predictors of severe disease and recurrence. JSLS 2011; 15(4):431-8.
12. Thomassin I, Bazot M, Detchev R, Barranger E, Cortez A, Darai E. Symptoms before and after surgical removal of colorectal endometriosis that are assessed by magnetic resonance imaging and rectal endoscopic sonography. Am J Obstet Gynecol 2004; 190(5):1264-71.
13. Morassutto C, Monasta L, Ricci G, Barbone F, Ronfani L. Incidence and estimated prevalence of endometriosis and adenomyosis in Northeast Italy: a data linkage study. PLoSOne 2016; 11(4):e0154227.
14. Lin YH, Kuo LJ, Chuang AY, Cheng TI, Hung CF. Extra pelvic endometriosis complicated with colonic obstruction. J Chin Med Assoc 2006; 69(1):47-50.
15. Nnoaham KE, Hummelshoj L, Webster P, d'Hooghe T, de Cicco Nardone F, de Cicco Nardone C; World Endometriosis Research Foundation Global Study of Women's Health consortium. Impact of endometriosis on quality of life and work productivity: A multicenter study across ten countries. Fertil Steril 2011; 96(2):366-73.
16. Yantiss RK, Clement PB, Young RH. Endometriosis of the intestinal tract: a study of 44 cases of a disease that may cause diverse challenges in clinical and pathologic evaluation. Am J Surg Pathol 2001; 25(4):445-54.
17. Bazot M, Darai E, Hourani R, Thomassin I, Cortez A, Uzan S, *et al*. Deep pelvic endometriosis: MR imaging for diagnosis and prediction of extension of disease. Radiology 2004; 232(2):379-89.
18. Arafat S, Alsabek MB, Almousa F, Kubtan MA. Rare manifestation of endometriosis causing complete rectosigmoid obstruction: A case report. Int J Surg Case Rep 2016; 26:30-3.
19. Bacalbasa N, Balescu I, Filipescu A. Ileocecal obstruction due to endometriosis- A case report and literature review. In Vivo 2017; 31(5):999-1002.
20. Beltrán MA, Tapia TF, Araos F, Martinez H, Cruces KS. [Ileal endometriosis as a cause of intestinal obstruction. Report of two cases]. Rev Med Chil 2006; 134(4):485-90. Article in Spanish.
21. Mijatovic V, Hompes PGA, vanWaesberghe JHTM, *et al*. A sign of intestinal endometriosis? Evaluation by MRI and rectosigmoidoscopy. Gastrointest Endosc 2006; 63:AB206.
22. Vercellini P, Pietropaolo G, De Giorgi O, Pasin R, Chiodini A, Crosignani PG. Treatment of symptomatic rectovaginal endometriosis with an estrogen-progestogen combination versus low-dose norethindrone acetate. Fertil Steril 2005; 84(5):1375-87.
23. Ferrero S, Camerini G, Ragni N, Venturini PL, Biscaldi E, Remorgida V. Norethisterone acetate in the treatment of colorectal endometriosis: a pilot study. Hum Reprod 2010; 25(1):94-100.
24. Vercellini P, Chapron C, Fedele L, Gattei U, Daguati R, Crosignani PG. Evidence for asymmetric distribution of lower intestinal tract endometriosis. BJOG 2004; 111(11):1213-7.
25. de Jong MJ, Mijatovic V, van Waesberghe JH, Cuesta MA, Hompes PG. Surgical outcome and long-term follow-up after segmental colorectal resection in women with a complete obstruction of the rectosigmoid due to endometriosis. Dig Surg 2009; 26(1):50-5.

Brief Communication

# Millennial-minded approach for the management of presbyopia

Marianne L Shahsuvaryan
Department of Ophthalmology, Yerevan State Medical University, Yerevan, Armenia

Kuwait Medical Journal 2023; 55 (4): 364 - 365

## INTRODUCTION

Presbyopia or age-related farsightedness is a natural condition manifested by the gradual loss of the human eye's ability to focus on near located objects, causing difficulties with reading small prints, especially in poor light and doing any job near-hand. No person is immune to it, since it accompanies the aging process. Taking into account the increased life expectancy in many parts of the world, prevalence of presbyopia is exponentially growing. It is estimated that the number of persons with presbyopia will reach 1.9 billion in 2050[1].

Commonly, presbyopia is correctable by various optical means (bifocal or reading glasses), but currently it is evidenced that the population is eager to reach glasses-independence in modern life.

In an effort to overcome this challenge, multiple approaches have been developed directed to cause a constriction of pupil producing a "pinhole effect," increasing the depth of focus; or restore accommodation; or restore lens flexibility[2].

Pilocarpine hydrochloride 1.25% eye drops (Vuity) is the first pharmacotherapeutic agent to be approved by the FDA in 2021 for the management of presbyopia[3]. The effects of Vuity are related to its pupil constriction and contraction of the ciliary body. It should be noted that pilocarpine is accompanied by multiple undesirable side effects, such as chronic inflammation, stationary pupil unresponsive to light, with adhesions to the lens, obstructing pupil dilation for fundus exam and/or cataract surgery, myopic shift in refraction with subsequent decrease in distance vision and lens opacifications. The latest one has the most deteriorating effect on vision.

Conceptually, in presbyopia, the lens substance "hardens" so that even when zonular tension is relaxed by contraction of the ciliary muscle, the lens does not change shape.

At present, it was documented that presbyopia, as the earliest observable symptom, is a precursor of cataract, characterized by lens opacifications changing its transparency[4]. Cataract is the major cause of reversible blindness worldwide, currently treatable only surgically with a significant economic burden, representing a medico-social challenge. In order to overcome this challenge, millennial-minded approach for the management of presbyopia should be directed to restore lens flexibility and prevent cataract formation simultaneously. Different substances have been used. An attempt was made to present the most relevant updates on the topic.

Topical lipoic acid choline ester (UNR844, 1.5%) ophthalmic solution was tested for safety and efficacy in a prospective, randomized, double-masked, multicenter clinical trial[5]. The effect of the drug is related to its ability to reduce lens disulfide bonds. It has been shown that tested topical treatment revealed good safety and tolerability profiles in twice-daily dosing. It is noteworthy that bilateral distance-corrected near visual acuity improved in 53.1% of subjects maintaining improvement in 5-7 months period after discontinuation of therapy. Researchers reported no clinically relevant changes in intraocular pressure, pupil size, distance visual acuity or cessation of therapy due to adverse events. Despite this promising initial finding, in a recent phase 2b study, the drug failed to meet its primary endpoint at month 3. The company Novartis abandoned development of the compound[6].

Among other lens proteins, the protein alpha-crystallin plays an important role in maintaining transparency and flexibility of lens, and recently serving as a new druggable target for presbyopia and cataract management[7]. In a preclinical study of mouse models of cataracts, Molnar *et al*[8] have evaluated an ability of an oxysterol, VP1-001 to bind and stabilize

***Address correspondence to:***
*Marianne L Shahsuvaryan, 85 Hanrapetutyan St., Yerevan, Armenia. Tel: +374 98533569; E-mail: mar_shah@hotmail.com*

αB-crystallin. The researchers concluded that "VP1-001 produced a statistically significant improvement in lens clarity and favorable changes in lens morphology".

Currently, different biochemical mechanisms responsible for lens opacification have been studied[4,9,10]. Panja *et al*[9] discovered that water solubility of lens proteins could be accelerated by $N^{\varepsilon}$-acetyllysine. In an effort to find a suitable candidate capable to donate an acetyl group to lysine residues in proteins in order to solubilize lens aggregated proteins, several compounds have been tested. As a result, Aggrelyte-2 (N,S-diacetyl-L-cysteine methyl ester) was chosen. The researchers evaluated Aggrelyte-2 efficacy ex vivo in cultured human and mouse lenses. Aggrelyte-2 revealed a non-toxic effect on lens epithelial cells. It was shown that the effect of Aggrelyte-2 is related to its dual mechanism of action manifesting by protein acetylation and disulfide bonds reducement. The obtained findings suggest that the Aggrelyte-2 potentially could promote protein solubility and diminish lens stiffness. It remains to be seen if the effect is repeatable experimentally in aged mice and rats. These promising results deserve further scientific investigations.

The latest research for preventing cataracts and presbyopia was conducted by Doki *et al*[10]. Taking into consideration that advanced glycation end products (AGEs) are accumulated in lens proteins accompanying aging process, the researchers have selected AGE as a druggable target. The scientific team studied the effects of hesperetin on AGEs accumulation.

The citrus flavonoid hesperetin is a bioflavonoid derived from citrus species (oranges, mandarins, and lemons) with multiple biological activities, such as anti-hypertensive, anti-diabetic, anti-inflammatory with demonstrated strong antioxidant effect. It has been reported to exert anti-cataract effects in experimental models of cataract in rats. Recently, efficacy of hesperetin was evaluated in mouse lens organ culture *ex vivo* study and *in vitro* in human lens epithelial cell lines[10]. Hesperetin has been shown to retard lens hardening *ex vivo*, preventing its sclerosis with subsequent cataract development. The effects of hesperetin are related to impact on AGE generation and transient receptor potential vanilloid channels. It should be noted that *in vitro* hesperetin prevents AGE generation. Experimental work indicates a need for in vivo studies. The researchers concluded that such novel drug compounds "hesperetin and hesperetin derived compounds are good candidates for the prevention of presbyopia and cataracts".

## CONCLUSION

Summarizing, the cases of presbyopia are exponentially growing, and it is well documented that presbyopia, as the earliest observable symptom, is a precursor of cataract, representing a medico-social challenge. In order to overcome this challenge, millennial-minded approach for the management of presbyopia requires noninvasive, cost-effective pharmacotherapy with optimized bioavailability, directed to restore lens flexibility and prevent cataract formation simultaneously. Hopefully, in the foreseen future, such a therapeutic agent should be validated.

## ACKNOWLEDGMENT

**Conflict of interest:** None
**Proprietary interest:** None
**Financial support:** None

## REFERENCES

1. Fricke TR, Tahhan N, Resnikoff S, Papas E, Burnett A, Ho SM, *et al*. Global prevalence of presbyopia and vision impairment from uncorrected presbyopia: systematic review, meta-analysis, and modelling. Ophthalmology 2018; 125(10):1492-9.
2. Orman B, Benozzi G. Pharmacological treatments for presbyopia. Drugs Aging 2023; 40(2):105-16.
3. Abbvie. Press Releases. VUITY (pilocarpine HCI ophthalmic solution) 1.25%, the first and only FDA-approved eye drop to treat age-related blurry near vision (Presbyopia), is now available. https://news.abbvie.com/news/press-releases/vuity-pilocarpine-hci-ophthalmic-solution-125-first-and-only-fda-approved-eye-drop-to-treat-age-related-blurry-near-vision-presbyopia-is-now-available.html. Accessed 20, 2023.
4. Nakazawa Y. [Study of the mechanisms of maintaining the transparency of the lens and treatment of its related diseases for making anti-cataract and/or anti-presbyopia drugs]. Yakugaku Zasshi 2020; 140(9):1095-9. Article in Japanese.
5. Korenfeld MS, Robertson SM, Stein JM, Evans DG, Rauchman SH, Sall KN, *et al*. Topical lipoic acid choline ester eye drop for improvement of near visual acuity in subjects with presbyopia: a safety and preliminary efficacy trial. Eye (Lond) 2021; 35(12):3292-300.
6. Mathis AE. Industry Briefs Presbyopia News & Notes. Presbyopia Physician 2022; 2(12):8-9.
7. Dunyak B, Su B, Molnar K, Hamilton P, Bozeman S, Li S, *et al*. Discovery of non-sterol αB-crystallin ligands as potential cataract therapeutics. Invest Ophthalmol Vis Sci 2019; 60(9):5691.
8. Molnar KS, Dunyak BM, Su B, Izrayelit Y, McGlasson-Naumann B, Hamilton PD, *et al*. Mechanism of action of VP1-001 in cryAB(R120G)-associated and age-related cataracts. Invest Ophthalmol Vis Sci 2019; 60(10):3320-31.
9. Panja S, Nahomi RB, Rankenberg J, Michel CR, Gaikwad H, Nam MH, *et al*. Aggrelyte-2 promotes protein solubility and decreases lens stiffness through lysine acetylation and disulfide reduction: Implications for treating presbyopia. Aging Cell 2023; 22(4):e13797.
10. Doki Y, Nakazawa Y, Morishita N, Endo S, Nagai N, Yamamoto N, *et al*. Hesperetin treatment attenuates glycation of lens proteins and advancedglycation end products generation. Mol Med Rep 2023; 27(5):103.

## Letter to the Editor

# The prevalence of enuresis nocturna and accompanying factors in a group of school-age children in a single-center

Mehmet Uysal
Department of Pediatric Surgery, Medical Faculty of Karamanoglu Mehmetbey University, Karaman, Turkey

Kuwait Medical Journal 2023; 55 (4): 366 - 367

**Dear Editor,**

Enuresis is defined as the voluntary or involuntary leakage of urine for at least three months in children over the age of 5[1]. Nocturnal enuresis is more common in the childhood age group. In clinical studies in European countries, the prevalence of nocturnal enuresis was found to be 9% to 19% at 5 years, 7% to 22% at 7 years, 5% to 13% at 9 years, and 1% to 2% at 16 years. In a study conducted in the United States, it was reported as 33% at 5 years, 18% at 8 years, 7% at 11 years and 0.7% at 17 years[2].

This study provides very important information in terms of making a regional contribution to previous scientific studies on the prevalence of enuresis and the examination of accompanying risk factors in the environment we live in. Therefore, I found it appropriate to write this article in order to raise awareness for future research on this subject and to contribute scientifically. We examined the clinical features of enuretic children and investigated the risk factors associated with nocturnal enuresis among school-age children.

In our study, we examined the prevalence of enuresis and accompanying risk factors in a group of children and adolescents aged 6-15 years living in Karaman. While forming the methodology of our study, we first determined the number of students studying in primary and secondary schools in the 6-15 age group in Karaman through the Provincial Directorate of National Education (51,954 students for the 2022-23 academic year), the confidence level was 94%, the estimated prevalence was 14.5%, the maximum acceptable deviation is ±1.4, and the cluster effect is 1.8, and we decided that it would be sufficient to determine the prevalence and risk factors in the province of Karaman by conducting a survey on 2964 students using appropriate statistical methods. We distributed 3490 questionnaires consisting of 40 questions, excluding the demographic data of the children, to the schools that we determined to cover all primary and secondary schools within the borders of Karaman province, through the Provincial Directorate of National Education. 2783 (79.5%) of the questionnaires were returned to our clinic after being filled in completely. We found the prevalence of enuresis nocturna to be 8.8% (n=245).

When we classify it according to age groups, we found that the prevalence of enuresis was 11.9% (n=184) for the 6-11 age group, while this rate was 3.8% (n=28) for the 12-15 age group. In terms of gender, the frequency of enuresis was higher in boys. On the other hand, we found this relationship more in lower age groups. We found that low socioeconomic conditions, inappropriate family characteristics, poor school performance and social adaptation, attention and hyperactivity disorder were more common in enuretic children, with problems in friendship communication, a decrease in school success, a history of difficulty in waking up, history of upper respiratory tract infection of allergy origin, snoring, and apnea complaints were more common in children with enuresis ($P$<0.001).

In this study, enuresis as gender was more common in boys (male/female ratio 1.7), and its incidence decreased with age, regardless of gender. There was also daytime wetting in 18% of enuretic children. There was familial in 48% of siblings and 72% of all family members. Non-enuretic children were able to urinate more spontaneously at night ($P$<0.001). Families were found to have a low relationship with the child with

***Address correspondence to:***
*Mehmet Uysal, Associate Professor, M.D. Department of Pediatric Surgery, Medical Faculty of Karamanoglu Mehmetbey University, Karaman, Turkey.*
*Tel: +90 5376912451; E-mail: drmyzuysal3@gmail.com; Orcid ID: 0000-0003-1561-6601*

enuresis, and only 754 (27.1%) families consulted a doctor for this reason.

We found that enuresis was more common in children whose parents had a history of enuresis nocturna ($P$<0.001). Enuresis was present in 26.8% (n=746) of the children with another urological problem (urinary system infection, urinary system stone disease, external genital organ anomaly, asthma and bronchitis, growth retardation). In our analysis to determine the risk factors, we found that there is a relationship between the age of the child and the mother, bad friendships, low school success, the presence of enuresis in siblings and parents, and sleep apnea and enuresis.

**ACKNOWLEDGMENT**

This study was't supported by any Research Funds.

**REFERENCES**

1. Tonkaz GY, Deliağa H, Çakır A, Tonkaz G, Özyurt G. An evaluation of parental attitudes and attachment in children with primary monosymptomatic nocturnal enuresis: A case control study. J Ped Urol 2023; 19(2):174. e1-174.e5.
2. Hansakunachia T, Ruangdaraganon N, Udomsubpayakol U, Sombuntham T, Kotchabhakdi N. Epidemiology of enuresis among school-age children in Thailand. J Dev Behav Pediatr 2005; 26(5): 356-60.

## Letter to the Editor

# *Naegleria fowleri* outbreak in Pakistan: urgent attention needed to combat *Naegleria fowleri*

Asif Mahmood[1,2], Shama[1], Wen Zhang[1]
[1]Department of Microbiology, School of Medicine, Jiangsu University, Zhenjiang, China
[2]Institute for Advanced Materials, School of Material Science and Engineering, Jiangsu University, Zhenjiang, China

Kuwait Medical Journal 2023; 55 (4): 368 - 369

**Dear Editor,**

*Naegleria fowleri*, a thermophilic single celled microscopic entity also referred to as the "brain-eating amoeba," has been an emerging problem in major cities of Pakistan like Karachi and Lahore. This specific amoeba has been responsible for causing atypical and severe brain infection termed as primary amoebic meningoencephalitis (PAM)[1]. *Naegleria fowleri* is free-living amoeba distributed globally and located in warm freshwater habitat and moist soil, particularly during the summer months. Amoeba gets into the human body via nasal route, often during water activities such as diving or swimming in warm freshwater lakes. In certain situations such as during ritual ablution, it may have increased exposure. Once inside the body, it travels through olfactory nerves and enters the brain to cause acute inflammation that destroys brain tissues, the so called brain eating-amoeba causes a devastating condition referred to as PAM[2,3]. In the early stages of infection, the initial symptoms mimic those of the typical viral illnesses such as fever, severe headache, vomiting, nausea and stiffness in the neck. However, if the infection advances, symptoms become worse, leading to meningitis including seizure, altered mental status and eventually progressing to coma and death. The infections are challenging due to its antagonistic nature and the scarce availability of effective treatments, with a mortality rate over 97% death, typically transpires within a span of 3-7 days as a result of edema and heightened intracranial pressure followed by cerebral herniation[1,3].

Over the years, Pakistan has experienced sporadic outbreaks of brain-eating amoeba infections and reported the first case of PAM in 2008[2]. According to officials, the incidence of unreported deaths due to PAM is higher in a country like Pakistan because of inadequate healthcare facilities and limited awareness. Accessible data reveals a pattern of PAM cases in recent years. In 2017, six deaths were reported, followed by one in 2018. The year 2019 observed a significant increase with 15 reported deaths[2,3]. No deaths were reported in 2020, but six deaths were reported in 2021. Moving to 2022, as of October 5$^{th}$, four cases have been reported, including the death of a 59-year-old man from Kemari district, Karachi on May 2$^{nd}$[2,3]. Additionally, another death was recorded in June, followed by two deaths in July 2022[3]. Since 2008, reports of PAM-related deaths have frequently emerged from Karachi and other parts of the country, resulting in the loss of several lives each year due to *Naegleria fowleri*. In 2023, six new cases were recorded, with the first reported death occurring in Lahore, bringing the total number of incidents across the country over the past 15 years to above 150[4]. Within the mere decade, the incidence of PAM cases in Pakistan has surpassed the number reported in the USA over the past decades, while in the USA, the majority of PAM cases were found in children under the age of 14 years, whereas in Pakistan the distribution exhibited among adults aged between 26 and 45 years, suggesting that there may be a genetically distinct strain in Pakistan[5].

The incidence of PAM is most commonly observed during the summer and preceding the rainy season in Pakistan. This emergence of *Naegleria fowleri* has sparked scientific interest in climate alteration, as prolonged periods of elevated temperature and high humidity, resulting from climate alteration, create a favorable habitat for pathogenic amoebas to thrive in aquatic environment. Interestingly, all recorded PAM incidents in Pakistan occurred in the Muslim population, with just two persons among the recorded incidents having a documented history of participating

***Address correspondence to:***
*Wen Zhang, Department of Microbiology, School of Medicine, Jiangsu University Zhenjiang, Jiangsu, China. Tel: +86 15006107319; E-mail: zhangwen@ujs.edu.cn*

in water-related recreational pursuits. This suggests that *Naegleria fowleri* is present in the household water of Karachi, and infections primarily occur during ablution, which is unexpected, considering the normally saline nature of water in the city. It is possible that in Pakistan, the strain *N. fowleri* has shown the ability to withstand or tolerate saline environment or differs from strains found elsewhere in the world.

Among the various strains of naegleria, only *N. fowleri* poses a pathogenicity towards humans. Due to the complex and potentially multifactorial nature of its pathogenesis, gaining a comprehensive insight of its genetic background could clarify the mechanisms behind its severe and rapidly fatal effects. Identifying distinctive genetic markers, novel genes, gene homologs and genes acquired through gene transduction will be crucial in unraveling the disease mechanisms triggered by *N. fowleri*. By using a genetic approach that studies *N. fowleri*'s entire genome, it becomes possible to discover instances of these novel genetic elements. The research approach presents an exciting opportunity to uncover and analyze the genomic sequence of lately identified resistant strain in Pakistan. The elucidation of the genome sequence holds great potential for improving the diagnosis and implementing early prevention of the disease.

Furthermore, there is an urgent need to raise public awareness about the significance of hot water for rinsing nose as a preventive measure against *N. fowleri* infections, considering the current public health crisis.

## REFERENCES

1. NIH (National Institute of Health) Pakistan. Field epidemiology and disease surveillance division. (2022, May) [Cited 2023 Aug 12]. Advisory for Naegleriasis. Retrieved from https://www.nih.org.pk/wp-content/uploads/2022/05/Advisory-for-Naegleriasis-May-2022.pdf.
2. Sarfraz MR, Tariq H, Rehman S, Khan S. Naegleria fowleri - The brain-eating amoeba: an emerging threat in Pakistan. Acta Biomed 2023; 94(2):e2023024.
3. Tabassum S, Naeem A, Gill S, Mumtaz N, Khan MZ, Tabassum S, *et al*. Increasing cases of Naegleria fowleri during the time of COVID 19; an emerging concern of Pakistan. Int J Surg 2022; 105:106881.
4. Brain-eating amoeba Naegleria fowleri kills another man in Karachi; death tally rises to 6 [Internet]. Daily Pakistan Global. 2023 [Cited 2023 Aug 12]. Available from: https://en.dailypakistan.com.pk/08-Jul-2023/brain-eating-amoeba-naegleria-fowleri-kills-another-man-in-karachi-death-tally-rises-to-6
5. Case Report Data & Graphs | Naegleria fowleri | CDC [Internet]. www.cdc.gov. 2020 [Cited 2023 Aug 12]. Available from: https://www.cdc.gov/parasites/naegleria/graphs.html

# Selected Abstracts of Articles Published Elsewhere by Authors in Kuwait

Kuwait Medical Journal 2023; 55 (4): 370 - 372

## Real world study of ocrelizumab in multiple sclerosis: Kuwait experience

Raed Alroughani[1], Malak AlMojel[2], Jasem Al-Hashel[3], Samar Farouk Ahmed[4]
[1]Division of Neurology, Amiri Hospital, Arabian Gulf Street, Sharq 13041, Kuwait; MS Clinic, Ibn Sina Hospital, P.O. Box 25427, Safat 13115, Kuwait.
[2]Department of Medicine, Faculty of Medicine, Kuwait University, P.O. Box 24923, Safat 13110, Kuwait.
[3]Department of Medicine, Faculty of Medicine, Kuwait University, P.O. Box 24923, Safat 13110, Kuwait; Department of Neurology, Ibn Sina Hospital, P.O. Box 25427, Safat 13115, Kuwait.
[4]Department of Medicine, Faculty of Medicine, Kuwait University, P.O. Box 24923, Safat 13110, Kuwait; Department of Neurology and Psychiatry, Minia University, P.O. Box 61519, Minia 61111, Egypt. Electronic address: samerelshayb@hotmail.com.

**Mult Scler Relat Disord. 2023 Nov:79:104941. doi: 10.1016/j.msard.2023.104941. Epub 2023 Aug 18.**

**BACKGROUND**
Ocrelizumab is a humanized anti-CD20 antibody that has been approved for the treatment of patients with multiple sclerosis (MS). Real-world data in the Middle East is very limited.

**OBJECTIVES**
To describe the effectiveness and safety of ocrelizumab treatment in MS patients in a real clinical setting.

**METHODS**
This is an observational, registry-based study. MS patients who were treated with ocrelizumab and completed at least one-year follow-up post-treatment were included. Baseline clinical and radiological characteristics were collected before ocrelizumab initiation. The relapse rate, disability measures, magnetic resonance image (MRI) activity (new T2 lesions and/or GD+ enhancing T1 lesions), and adverse events (AE) at the last follow-up visits were assessed.

**RESULTS**
Data from 447 patients were analyzed, of which 260 (58.2%) were females. The mean age and mean disease duration were 37.39 ± 11.61 and 9.38 ± 7.57 years respectively. Most of the cohort was of a relapsing form (74.3%; n = 332), whereas active secondary and primary progressive forms represented 15.4% (n = 69) and 10.3% (n = 46) respectively. In the relapsing cohort, Ocrelizumab was prescribed in 162 (48.8%) patients due to highly active disease, and in 99 (29.8%) patients due to disease breakthrough while on prior therapies. In the last follow-up visits, most of the relapsing cohort was relapse-free (95.8% vs. 27.4%; $p < 0.001$), had no evidence of MRI activity (3.6% vs. 67.5%; $p < 0.001$) while EDSS score was stable (1.80+1.22 vs. 1.87+1.16; $p < 0.104$) when compared to baseline. NEDA-3 was achieved in 302 (91%) of RRMS patients. Confirmed disability progression was 27.5% and 23.9% in SPMS and PPMS respectively. Adverse events were observed in 139 (31.1%); infusion reactions and infections represented the most.

**CONCLUSION**
This study showed that ocrelizumab is an effective and safe treatment for MS patients in a real clinical setting similar to what was observed in clinical trials.

## A Well-Differentiated Grade-3 Neuroendocrine Tumor in the Ascending Colon: A Case Report

Ali AlSaffar[1], Sarah Wood[1], Fatma AlRabiy[2], Dany Hamie[3], Salah Termos[1]
[1]Department of Surgery, Al-Amiri Hospital, Kuwait City, Kuwait.
[2]Department of Pathology, Al-Amiri Hospital, Kuwait City, Kuwait.
[3]Department of Gastroenterology, Al-Amiri Hospital, Kuwait City, Kuwait.

**Am J Case Rep. 2022 Jan 11:23:e933792. doi: 10.12659/AJCR.933792.**

**BACKGROUND**
Gastrointestinal neuroendocrine tumors (NETs) are indolent hormone-secreting pathologic illnesses that can occur throughout the whole digestive tract. They are classified by site and grade. Colon neuroendocrine neoplasm (NEN) is an unusual histologic finding that needs to be further investigated. Well-differentiated (WD) Grade-3 (G3) is a new category of NEN that falls between neuroendocrine tumor (NET) and neuroendocrine carcinoma (NEC).

**CASE REPORT**
A 60-year-old man with a past medical history of diabetes mellitus presented with severe anemia and significant weight loss. Tumor markers (CEA and CA 19.9) were unremarkable. Colonoscopy showed a large fungating mass in the proximal part of the ascending colon. Biopsy results suggested colonic adenocarcinoma. Contrast-enhanced computed tomography of the chest, abdomen, and pelvis demonstrated a 5×5 cm ascending colon mass with few locoregional lymph nodes and no distant metastasis. A laparoscopic right hemicolectomy performed and histopathologic examination revealed T4N1, WD-NET G3. Postoperative completion work-up was done. Chromogranin-A was in the normal range and nuclear scans (PET and gallium 68) showed no abnormal uptake or residual disease. Extensive review, expert opinion, and multidisciplinary meetings failed to establish guidelines for adjuvant therapy due to the paucity of data in the literature.

**CONCLUSIONS**
Well-differentiated grade 3 NETs of the ascending colon is a rare finding in a rare disease. This entity of NENs is an unmet medical issue on the border between NET and NEC that remains a matter of great debate in terms of establishing an accurate diagnosis and outlining proper management.

## Women's experiences of social support during pregnancy: a qualitative systematic review

Mona Al-Mutawtah[1,2], Emma Campbell[3], Hans-Peter Kubis[3], Mihela Erjavec[3]
[1]School of Human and Behavioural Sciences, Bangor University, Bangor, UK. Mnl18pqc@bangor.ac.uk.
[2]Community Medicine- Clinical Psychology, Kuwait University, Kuwait City, Kuwait. Mnl18pqc@bangor.ac.uk.
[3]School of Human and Behavioural Sciences, Bangor University, Bangor, UK.

**BMC Pregnancy Childbirth. 2023 Nov 10;23(1):782. doi: 10.1186/s0-06089-023-12884.**

**BACKGROUND**
Social support during pregnancy can alleviate emotional and physical pressures, improving the well-being of mother and child. Understanding women's lived experiences and perceptions of social support during pregnancy is imperative to better support women. This systematic review explores and synthesises the qualitative research on women's experiences of social support during pregnancy.

**METHODS**
Databases PubMed, CINAHL, MEDLINE, APA PsycInfo and Scopus were searched with no year limit. Eligible studies included pregnant women or women who were up to one year postpartum and were assessed on their experiences of social support during pregnancy. The data were synthesised using the thematic synthesis approach.

**RESULTS**
Fourteen studies were included with data from 571 participating women across ten countries; two studies used focus groups, and 12 used interviews to collect their data. Four main themes were developed ('a variety of emotional support', 'tangible and intangible instrumental support', 'traditional rituals and spiritual support', and 'the all-encompassing natal home'), and six sub-themes ('female network connections', 'care and affection from the husband', 'dissatisfaction with relationships', 'financial support from the husband and family', 'practical support from family and friends', 'health information support').

**CONCLUSIONS**
This systematic review sheds light on women's experiences of social support during pregnancy. The results indicate a broad variety of emotional support experienced and valued by pregnant women from different sources. Additionally, women expressed satisfaction and dissatisfaction with tangible and intangible support forms. It was also highlighted that spirituality played an essential role in reducing stress and offering coping mechanisms for some, whereas spirituality increased stress levels for others.

# Forthcoming Conferences and Meetings

Compiled and edited by
**Vineetha Elizabeth Mammen**

Kuwait Medical Journal 2023; 55 (4): 373 - 380

International Conference on **Medical Health Science, Pharmacology & Bio Technology**
Jan 01, 2024
*United States of America*, New York
Email: papers.issrd@gmail.com

International Conference on Recent Advances in **Medical and Health Sciences**
Jan 01, 2024
*United Arab Emirates*, Dubai
Email: info@academicsworld.org

International Virtual Conference on **COVID-19** and its Effect
Jan 01, 2024
*Malaysia*, Putrajaya
Email: info.conferenceonline@gmail.com

International Conference on **Healthcare and Clinical Gerontology**
Jan 02, 2024
*United Arab Emirates*, Dubai
Email: info.sciencefora@gmail.com

1649th International Conference on **Science, Health and Medicine**
Jan 02, 2024
*Germany*, Berlin
Email: info@iser.co

World **Disability & Rehabilitation** Conference
Jan 03, 2024
*China*, Shanghai
Email: papers.asar@gmail.com

International Conference on Recent Advances in **Medical, Medicine and Health Sciences**
Jan 03, 2024
*United States of America*, Houston
Email: contact.wrfer@gmail.com

International Conference on **Virology**
Jan 04, 2024
*Japan*, Tokyo
Email: papers.itrgroup@gmail.com

International Conference on **Medical and Health Sciences**
Jan 04, 2024
*United Kingdom*, London
Email: papers.scienceplus@gmail.com

World **Disability & Rehabilitation** Conference
Jan 05, 2024
*India*, Chennai, Tamil Nadu
Email: papers.asar@gmail.com

International Conference on **Medical and Health Sciences**
Jan 05, 2024
*United States of America*, Boston
Email: papers.scienceplus@gmail.com

1663rd International Conference on Recent Advances in **Medical and Health Sciences**
Jan 05, 2024
*New Zealand*, Auckland
Email: info@academicsworld.org

International Conference on **Healthcare and Clinical Gerontology**
Jan 06, 2024
*Australia*, Adelaide
Email: info.sciencefora@gmail.com

International Conference on **Medical Health Science, Pharmacology & Bio Technology**
Jan 06, 2024
*Singapore*, Singapore
Email: papers.issrd@gmail.com

International Conference on **Cell and Tissue Science**
Jan 07, 2024
*Germany*, Stuttgart
Email: info@conferencefora.org

Asian Symposium on Advancement in **Hematology and Oncology**
Jan 07, 2024
*Indonesia*, Bali
Email: info@biofora.org

International Conference on **Cardiology and Diabetes**
Jan 07, 2024
*Japan*, Tokyo
Email: info.iared.org@gmail.com

International Conference on **Healthcare and Clinical Gerontology**
Jan 08, 2024
*New Zealand*, Christchurch
Email: info.sciencefora@gmail.com

International Research Conference on **COVID-19** and its Impact on Mental Health
Jan 08, 2024
*India*, Goa
Email: info.researchconferences@gmail.com

World Conference on **Pharma Industry and Medical Devices**
Jan 10, 2024
*Egypt*, Luxor
Email: info.ifearpworld@gmail.com

1569th International Conference on **Food Microbiology and Food Safety**
Jan 10, 2024
*Spain*, Madrid
Email: info@theires.org

International Video Conference on **Healthcare**
Jan 10, 2024
*United Arab Emirates*, Abu Dhabi
Email: info.conferenceonline@gmail.com

World **Disability & Rehabilitation** Conference
Jan 11, 2024
*United Kingdom*, Georgetown
Email: papers.asar@gmail.com

International Conference on Recent Advances in **Medical, Medicine and Health Sciences**
Jan 12, 2024
*Doha*, Qatar
Email: contact.wrfer@gmail.com

1678th International Conference on **Medical, Biological and Pharmaceutical Sciences**
Jan 12, 2024
*Oman*, Muscat
Email: info@iastem.org

1656th International Conference on **Science, Health and Medicine**
Jan 13, 2024
*Belgium*, Brussels
Email: info@iser.co

International Conference on **Medical and Biological Engineering**
Jan 13, 2024
*United States of America*, Washington
Email: info.iared.org@gmail.com

1669th International Conference on Recent Advances in **Medical and Health Sciences**
Jan 14, 2024
*Brazil*, Sao Paulo
Email: info@academicsworld.org

International Conference on **Medical and Biological Engineering**
Jan 14, 2024
*Germany*, Berlin
Email: info.iared.org@gmail.com

International Conference on **Medical and Health Sciences**
Jan 15, 2024
*Japan*, Kawasaki
Email: papers.scienceplus@gmail.com

International Conference on **Medical, Medicine and Health Sciences**
Jan 15, 2024
*United States* of *America*, Boston
Email: contact.iierd@gmail.com

1530th International Conference on **Pharma and Food**
Jan 16, 2024
*United States of America*, Boston
Email: info@academicsera.com

International Conference on **Nursing Ethics and Medical Ethics**
Jan 17, 2024
*United States of America*, Kansas City
Email: info.sciencefora@gmail.com

1709th International Conference on Recent Advances in **Medical Science**
Jan 17, 2024
*United States of America*, Orlando
Email: info@theiier.org

International Conference on **Vaccine Research, Immunology and Clinical Trials**
Jan 18, 2024
*United Kingdom*, London
Email: info@meetingfora.com

World Conference on **Pharma Industry and Medical Devices**
Jan 18, 2024
*India*, Allahabad, Uttar Pradesh
Email: info.ifearpworld@gmail.com

1660th International Conference on **Science, Health and Medicine**
Jan 19, 2024
*Italy*, Florence
Email: info@iser.co

International Conference on **Cell and Tissue Science**
Jan 20, 2024
*Turkey*, Izmir
Email: info@conferencefora.org

International Conference on **Medical Health Science, Pharmacology & Bio Technology**
Jan 20, 2024
*Thailand*, Bangkok
Email: papers.issrd@gmail.com

International Conference on **Cell and Tissue Science**
Jan 20, 2024
*Egypt*, Giza
Email: info@conferencefora.org

International Conference on Recent Advancement in **Medical Education, Nursing, and Health Sciences**
Jan 20, 2024
*Australia*, Sydney
Email: info.irfconference@gmail.com

1534th International Conference on **Sports Nutrition and Supplements**
Jan 20, 2024
*Spain*, Madrid
Email: info@academicsera.com

1685th International Conference on **Medical and Health Sciences**
Jan 24, 2024
*South Africa*, Cape Town
Email: info@iserd.co

World Conference on **Pharma Industry and Medical Devices**
Jan 25, 2024
*United Arab Emirates*, Sharjah
Email: info.ifearpworld@gmail.com

1579th International Conference on **Food Microbiology and Food Safety**
Jan 25, 2024
*France*, Paris
Email: info@theires.org

International Conference on **Medical and Health Sciences**
Jan 26, 2024
*Greece*, Crete
Email: papers.academicsconference@gmail.com

16th Annual **Ottawa Conference**
Jan 26, 2024
*Canada*, Ottawa
Email: ottawaconference@ottawaheart.ca

International Conference on **Medicine, Nursing and Healthcare**
Jan 26, 2024
*Vietnam*, Hanoi
Email: info@yanjiuconference.com

International Conference on **Cardiology and Diabetes**
Jan 27, 2024
*Singapore*, Singapore
Email: info.iared.org@gmail.com

International Conference on **Nursing Ethics and Medical Ethics**
Jan 28, 2024
*United Arab Emirates*, Abu Dhabi
Email: info.wrfase@gmail.com

1678th International Conference on Recent Advances in **Medical and Health Sciences**
Jan 28, 2024
*Kuwait*, Kuwait City
Email: info@academicsworld.org

1678th International Conference on **Medical and Biosciences**
Jan 28, 2024
*Saudi Arabia*, Riyadh
Email: info@researchworld.org

World **Disability & Rehabilitation** Conference
Jan 29, 2024
*Canada*, Montreal
Email: papers.asar@gmail.com

International Conference on **Medical, Medicine and Health Sciences**
Jan 29, 2024
*Egypt*, Cairo
Email: contact.iierd@gmail.com

Practical AI for **Drug Discovery and Preclinical Development** Summit
Jan 30, 2024
*United States of America*, San Diego, California
Email: info@hansonwade.com

International Conference on **Medical and Biological Engineering**
Jan 31, 2024
*France*, Paris
Email: info.iared.org@gmail.com

International Conference on Advances in **Health and Medical Science**
Jan 31, 2024
*United Kingdom*, London
Email: info.saard.org@gmail.com

The **Pan Arab Spine Society** – Kuwait Conference
Feb 01-03, 2024
*Kuwait*, Kuwait city
Website: https://www.passkw2024.com

International Conference on **Medical and Biological Engineering**
Feb 02, 2024
*India*, Ooty, Tamil Nadu
Email: papers.techno@gmail.com

1501st International Conference on **Medical & Health Science**
Feb 03, 2024
*Germany*, Munich
Email: info@researchfora.com

International Conference on Advances in **Health and Medical Science**
Feb 04, 2024
*Scotland*, Glasgow
Email: info.saard.org@gmail.com

Global **Cardiology** and Healthcare Summit
Feb 04, 2024
*Singapore*, Singapore
Email: info@biofora.org

International Conference on **Medical, Pharmaceutical and Health Sciences**
Feb 06, 2024
*Japan*, Yokohama
Email: info.gsrd@gmail.com

1721st International Conference on Recent Advances in **Medical Science**
Feb 07, 2024
*Turkey*, Antalya
Email: info@theiier.org

International Virtual Conference on **COVID-19** and its Effect
Feb 07, 2024
*United Arab Emirates*, Abu Dhabi
Email: info.conferenceonline@gmail.com

1685th International Conference on **Medical and Biosciences**
Feb 08, 2024
*Australia*, Perth
Email: info@researchworld.org

26th Kuwait **OBGYN** Annual Conference
Feb 08-10, 2024
*Kuwait*, Kuwait City
Website: www.26obgynkw.com

International Conference on **Medical and Health Sciences**
Feb 10, 2024
*Egypt*, Cairo
Email: papers.academicsconference@gmail.com

1673rd International Conference on **Science, Health and Medicine**
Feb 10, 2024
*Bahrain*, Manama
Email: info@iser.co

International Conference on **Medical, Medicine and Health Sciences**
Feb 12, 2024
*France*, Paris
Email: contact.iierd@gmail.com

International Conference on Recent Advances in **Medical and Health Sciences**
Feb 13, 2024
*Saudi Arabia*, Al Khobar
Email: info@academicsworld.org

10th Annual Conference of **SWAAC ELSO** 2024
Feb 15-17, 2024
*Kuwait*, Kuwait City
Website: www.swaacelso2024.com

International Conference on Recent Advancement in **Medical Education, Nursing, and Health Sciences**
Feb 16, 2024
*Australia*, Melbourne
Email: info.irfconference@gmail.com

International Conference on **Medical, Pharmaceutical and Health Sciences**
Feb 17, 2024
*Switzerland*, Bern
Email: info.gsrd@gmail.com

International Conference on **Obesity, Weight Management and Nutrition Research**
Feb 17, 2024
*Japan*, Tokyo
Email: info.irfsr@gmail.com

International Conference on **Virology**
Feb 18, 2024
*France*, Paris
Email: papers.itrgroup@gmail.com

1716th International Conferences on **Medical and Health Science**
Feb 19, 2024
*United States of America*, Cambridge
Email: info@theires.org

International Conference on **Medical and Biological Engineering**
Feb 20, 2024
*United States of America*, Edinburg
Email: papers.techno@gmail.com

1680th International Conference on **Science, Health and Medicine**
Feb 21, 2024
*Czech Republic*, Prague
Email: info@iser.co

International Conference on **Medical and Health Sciences**
Feb 23, 2024
*United States of America*, Chicago
Email: papers.academicsconference@gmail.com

1554th International Conference on **Sports Nutrition and Supplements**
Feb 23, 2024
*Romania*, Bucharest
Email: info@academicsera.com

1705th International Conference on **Medical, Biological and Pharmaceutical Sciences**
Feb 24, 2024
*South Africa*, Cape Town
Email: info@iastem.org

International Conference on **Cardiology and Diabetes**
Feb 25, 2024
*Indonesia*, Bali
Email: info.iared.org@gmail.com

1684th International Conference on **Science, Health and Medicine**
Feb 27, 2024
*Canada*, Ottawa
Email: info@iser.co

1707th International Conference on **Medical, Biological and Pharmaceutical Sciences**
Feb 28, 2024
*Kuwait*, Kuwait City
Email: info@iastem.org

International Conference on Recent Advances in **Medical, Medicine and Health Sciences**
Feb 29, 2024
*Turkey*, Istanbul
Email: contact.wrfer@gmail.com

International Conference on **Cell and Tissue Science**
Mar 01, 2024
*Oman*, Salalah
Email: info@conferencefora.org

International Conference on Recent Advances in **Medical and Health Sciences**
Mar 02, 2024
*United Arab Emirates*, Al-Khaimah
Email: info@academicsworld.org

International Conference on **Medical, Pharmaceutical and Health Sciences**
Mar 03, 2024
*Germany*, Berlin
Email: info.gsrd@gmail.com

International Conference on Advances in **Health and Medical Science**
Mar 04, 2024
*Scotland*, Glasgow
Email: info.saard.org@gmail.com

International Conference on Recent Advances in **Medical, Medicine and Health Sciences**
Mar 04, 2024
*Switzerland*, Geneva
Email: contact.wrfer@gmail.com

International Conference on **Nursing Ethics and Medical Ethics**
Mar 06, 2024
*Australia*, Adelaide
Email: info.sciencefora@gmail.com

International Conference on Recent Advances in **Medical and Health Sciences**
Mar 06, 2024
*Lebanon*, Byblos
Email: info@academicsworld.org

1710th International Conference on **Medical, Biological and Pharmaceutical Sciences**
Mar 06, 2024
*Australia*, Melbourne
Email: info@iastem.org

International Virtual Conference on **Medical, Biological and Pharmaceutical Science**
Mar 07, 2024
*United Arab Emirates*, Abu Dhabi
Email: info.conferenceonline@gmail.com

1742nd International Conference on Recent Advances in **Medical Science**
Mar 09, 2024
*Netherlands*, Amsterdam
Email: info@theiier.org

International Conference on **Cardiology and Diabetes**
Mar 10, 2024
*United States of America*, Washington D.C
Email: info.iared.org@gmail.com

Global **Cardiology and Healthcare** Summit
Mar 10, 2024
*Canada*, Toronto
Email: info@biofora.org

International Conference on **Climate Change and Human Health** Impacts
Mar 11, 2024
*United Kingdom*, London
Email: info.isfecc@gmail.com

1744th International Conference on Recent Advances in **Medical Science**
Mar 12, 2024
*Egypt*, Cairo
Email: info@theiier.org

International Conference on **Medical Ethics and Professionalism**
Mar 15, 2024
*Switzerland*, Bern
Email: info.sciencefora@gmail.com

1567th International Conference on **Sports Nutrition and Supplements**
Mar 16, 2024
*United States of America*, New York
Email: info@academicsera.com

International Conference on Recent Advances in **Medical, Medicine and Health Sciences**
Mar 16, 2024
*United Arab Emirates*, Abu Dhabi
Email: contact.wrfer@gmail.com

International Conference on **Medical, Biological and Pharmaceutical Sciences**
Mar 17, 2024
*United Kingdom*, London
Email: info.ipharmaconferences@gmail.com

1612th International Conference on **Food Microbiology and Food Safety**
Mar 17, 2024
*United States of America*, Denver
Email: info@theires.org

Global **Cardiology and Healthcare** Summit
Mar 17, 2024
*Thailand*, Phuket
Email: info@biofora.org

International Conference on **Obesity and Chronic Diseases**
Mar 18, 2024
*United Kingdom*, London
Email: info.iared.org@gmail.com

International Conference on Recent Advances in **Medical, Medicine and Health Sciences**
Mar 19, 2024
*Ireland*, Dublin
Email: contact.wrfer@gmail.com

1569th International Conference on **Pharma and Food**
Mar 19, 2024
*United States of America*, Cambridge
Email: info@academicsera.com

European **Breast Cancer** Conference
Mar 20, 2024
*Italy*, Milan
Email: ebcc@eortc.org

1712th International Conference on **Medical and Biosciences**
Mar 20, 2024
*Italy*, Rome
Email: info@researchworld.org

International Conference on **Medical and Biological Engineering**
Mar 20, 2024
*United Arab Emirates*, Dubai
Email: papers.techno@gmail.com

1720th International Conference on **Medical, Biological and Pharmaceutical Sciences**
Mar 21, 2024
*Turkey*, Antalya
Email: info@iastem.org

International Conference on **Sports Nutrition and Supplements**
Mar 22, 2024
*Argentina*, Buenos Aires
Email: info.wrfase@gmail.com

International Conference on Recent Advances in **Medical, Medicine and Health Sciences**
Mar 23, 2024
*Spain*, Barcelona
Email: contact.wrfer@gmail.com

International Conference on **Medical Health Science, Pharmacology & Bio Technology**
Mar 24, 2024
*Italy*, Rome
Email: papers.issrd@gmail.com

1722nd International Conference on **Medical and Health Sciences**
Mar 25, 2024
*Italy*, Rome
Email: info@iserd.co

International Conference on **Medical, Pharmaceutical and Health Sciences**
Mar 28, 2024
*Canada*, Ottawa
Email: info.gsrd@gmail.com

1701st International Conference on **Science, Health and Medicine**
Mar 28, 2024
*Kuwait*, Kuwait City
Email: info@iser.co

International Conference on **Nursing Science and Healthcare**
Mar 28, 2024
*France*, Paris
Email: info.iared.org@gmail.com

International **Cancer** Conference
Mar 30, 2024
*Malaysia*, Kuala Lumpur
Email: info@biofora.org

1579th International Conference on **Pharma and Food**
Apr 05, 2024
*Sweden*, Stockholm
Email: info@academicsera.com

International **Cancer** Conference
Apr 05, 2024
*Canada*, Ottawa
Email: info@biofora.org

International Conference on **Medical and Health Sciences**
Apr 07, 2024
*New Zealand*, Wellington
Email: papers.academicsconference@gmail.com

1722nd International Conference on **Medical and Biosciences**
Apr 07, 2024
*United Kingdom*, London
Email: info@researchworld.org

International Conference on **Healthcare and Clinical Gerontology**
Apr 09, 2024
*Japan*, Kitakyushu
Email: info.sciencefora@gmail.com

1732nd International Conference on **Medical, Biological and Pharmaceutical Sciences**
Apr 10, 2024
*Spain*, Madrid
Email: info@iastem.org

Global **Cardiology and Healthcare** Summit
12th Apr 2024
*Japan*, Kyoto
Email: info@biofora.org

1711th International Conference on **Science, Health and Medicine**
Apr 13, 2024
*Saudi Arabia*, Riyadh
Email: info@iser.co

1766th International Conference on Recent Advances in **Medical Science**
Apr 15, 2024
*India*, New Delhi
Email: info@theiier.org

1726th International Conference on Recent Advances in **Medical and Health Sciences**
Apr 16, 2024
*United States of America*, New York
Email: info@academicsworld.org

.

International Conference on **Healthcare and Clinical Gerontology**
Apr 17, 2024
*United States of America*, Kansas City
Email: info.sciencefora@gmail.com

1729th International Conference on **Medical and Biosciences**
Apr 18, 2024
*United States of America*, New Orleans
Email: info@researchworld.org

1589th International Conference on **Pharma and Food**
Apr 19, 2024
*United Kingdom*, Oxford
Email: info@academicsera.com

International Conference on Research in **Life-sciences & Healthcare**
Apr 19, 2024
*Netherlands*, Amsterdam
Email: info@biofora.org

International Conference on **Medical and Biosciences**
Apr 20, 2024
*Malaysia*, Malacca
Email: info@researchworld.org

1769th International Conference on Recent Advances in **Medical Science**
Apr 20, 2024
*Italy*, Rome
Email: info@theiier.org

1549th International Conference on **Medical & Health Science**
Apr 22, 2024
*United States of America*, Chicago
Email: info@researchfora.com

International Conference on Recent Advancement in **Medical Education, Nursing, and Health Sciences**
Apr 26, 2024
*United Arab Emirates*, Dubai
Email: info.irfconference@gmail.com

1762nd International Conferences on **Medical and Health Science**
Apr 28, 2024
*United States of America*, Philadelphia
Email: info@theires.org

1742nd International Conference on **Medical and Health Sciences**
Apr 28, 2024
*Kuwait*, Kuwait City
Email: info@iserd.co

2nd CME **Cardiologists** Conference
Apr 29, 2024
*United Arab Emirates*, Dubai
Email: eaccm@plenareno.net

International Conference on **Medical and Health Sciences**
Apr 30, 2024
*Canada*, Montreal
Email: papers.academicsconference@gmail.com

# WHO-Facts Sheet

**1. Colorectal cancer**
**2. Depression**
**3. Lung cancer**
**4. Nipah virus**
**5. Rheumatoid arthritis**

Compiled and edited by
**Vineetha E Mammen**

Kuwait Medical Journal 2023; 55 (4): 381 - 391

## 1. Colorectal cancer

### KEY FACTS

- Colorectal cancer is the third most common cancer worldwide, accounting for approximately 10% of all cancer cases and is the second leading cause of cancer-related deaths worldwide.
- It predominantly affects older individuals, with the majority of cases occurring in people aged 50 and above.
- Several lifestyle factors contribute to the development of colorectal cancer such as a high intake of processed meats and low intake of fruits and vegetables, sedentary lifestyle, obesity, smoking, and excessive alcohol consumption.
- Colorectal cancer is often diagnosed at advanced stages when treatment options are limited.
- The incidence and impact of colorectal cancer can be significantly reduced by implementing primary prevention strategies such as adopting a healthy lifestyle, avoiding risk factors, and practicing early detection through screening.

### Overview

Colorectal cancer is a type of cancer that affects the colon (large intestine) or rectum. It is one of the most common types of cancer worldwide. It can cause severe harm and death. The risk of colorectal cancer increases with age. Most cases affect people over 50 years old. Common symptoms include diarrhoea, constipation, blood in the stool, abdominal pain, unexplained weight loss, fatigue, and low iron levels. Many people will not have symptoms in the early stages of the disease.

The risk of colorectal cancer can be reduced by eating a healthy diet, staying physically active, not smoking tobacco and limiting alcohol. Regular screenings are crucial for early detection.

Colon cancer is the second leading cause of cancer-related deaths worldwide. In 2020, more than 1.9 million new cases of colorectal cancer and more than 930 000 deaths due to colorectal cancer were estimated to have occurred worldwide. Large geographical variations in incidence and mortality rates were observed. The incidence rates were highest in Europe and Australia and New Zealand, and the mortality rates were highest in Eastern Europe. By 2040 the burden of colorectal cancer will increase to 3.2 million new cases per year (an increase of 63%) and 1.6 million deaths per year (an increase of 73%).

Incidence rates of colorectal cancer have been decreasing in high-income countries, largely as a result of effective screening programmes. The prognosis for colorectal cancer varies depending on the stage at diagnosis. Early-stage cancers have higher survival rates than advanced-stage cancers. Timely diagnosis, appropriate treatment, and regular follow-up care are important for improving survival rates and quality of life.

### Risk Factors

Factors that may increase the risk of developing colorectal cancer include:

- age: the risk of developing colorectal cancer increases with age, with most cases occurring in individuals over 50 years old;
- family history: a family history of colorectal cancer or certain genetic conditions, such as Lynch syndrome and familial adenomatous polyposis (FAP), can increase the risk;
- personal history: individuals who have had colorectal cancer before or certain types of polyps are at a higher risk; and
- lifestyle factors: unhealthy lifestyle choices, such as

***Address correspondence to:***
*Office of the Spokesperson, WHO, Geneva. Tel.: (+41 22) 791 2599; Fax (+41 22) 791 4858; Email: inf@who.int; Web site: http://www.who.int/*

a diet high in processed meats and low in fruits and vegetables, sedentary behaviour, obesity, smoking and excessive alcohol consumption, can increase the risk.

**Symptoms**

Colorectal cancer often has no symptoms in the early stages. Regular screenings are important to catch the disease early and begin treatment.

Common symptoms include:

- changes in bowel habits such as diarrhoea, constipation, or narrowing of the stool
- blood in the stool (rectal bleeding), either bright red or dark and tar-like
- abdominal cramps, pain or bloating that won't go away
- unexplained weight loss that is sudden and losing weight without trying
- feeling constantly tired and lacking energy, even with enough rest
- iron deficiency anaemia due to chronic bleeding, causing fatigue, weakness and paleness.

**Prevention**

Lifestyle changes and regular screening can help prevent colorectal cancer.

Lifestyle changes to help prevent colorectal cancer include:

- eating a healthy diet rich in fruits and vegetables
- not smoking tobacco
- keeping an active lifestyle
- limiting alcohol consumption
- avoiding exposure to environmental risk factors.

People who suspect they may have colorectal cancer should speak to their healthcare provider right away.

Regular screening for colorectal cancer (secondary prevention) is the best way to catch the disease early.

Treatments are more likely to cure the disease in the early stages. Studies have shown that screening can reduce both the incidence and mortality of colorectal cancer through early detection and removal of precancerous growths.

Stool-based tests are non-invasive screening methods used to detect the presence of colorectal cancer or precancerous polyps in the stool. The common type of stool-based tests is the fecal occult blood test (FOBT). FOBT detects hidden blood in the stool, which can be an indicator of colorectal cancer or polyps. It involves collecting a small sample of stool and sending it to a laboratory for analysis. If blood or abnormal findings are detected in the stool, further diagnostic procedures, such as colonoscopy, are usually recommended to confirm the presence of colorectal cancer or polyps.

Stool-based tests are convenient, non-invasive, and can be effective in detecting colorectal cancer at early stages or identifying precancerous polyps. Individuals with a family history of colorectal cancer or certain genetic conditions may benefit from genetic counselling and genetic testing to assess their risk and determine appropriate screening measures.

**Diagnosis**

Diagnostic methods for colorectal cancer include physical examination, imaging (such as abdominal ultrasound, computed tomography scans, and magnetic resonance imaging), examination of the inside of the colon using colonoscopy or sigmoidoscopy, taking a sample of tissue (biopsy) for histopathology examination, and molecular testing to identify specific genetic mutations or biomarkers to guide the best treatment option.

**Treatment and care**

Treatments for colorectal cancer are based on the type and progression of the cancer and the person's medical history. Early detection of colorectal cancer can lead to better treatments and outcomes.

Treatments include:

- surgery
- radiotherapy (radiation)
- chemotherapy
- targeted therapy
- immunotherapy.

Surgery is often used in the early stages of cancer if the tumour has not spread to other areas of the body. Chemotherapy and radiation therapy can help shrink the tumour. Doctors from several disciplines often work together to provide treatment and care of people with colorectal cancer.

Supportive care is important for people with colorectal cancer. It aims to manage symptoms, provide pain relief, and give emotional support. It can help to increase quality of life for people with colorectal cancer and their families.

**Stages of care**

**a) Early stage disease**. The primary treatment for early stage colorectal cancer (i.e. tumour limited to the bowel or local lymph nodes, with no metastatic dissemination to distant organs) is surgical removal of the tumour and nearby lymph nodes. The specific surgical procedure depends on the location of the tumour. It may involve a colectomy (removal of a portion of the colon) or a proctectomy (removal of the rectum). In some cases, a temporary or permanent colostomy or ileostomy may be needed to create an opening for waste elimination. Adjuvant therapy refers to additional treatment given after surgery to lower

the risk of cancer recurrence. In early-stage colorectal cancer, adjuvant chemotherapy may be recommended to kill any remaining cancer cells that cannot be seen or removed during surgery. Adjuvant chemotherapy is typically recommended for patients with a higher risk of recurrence, such as those with lymph node involvement or certain tumour characteristics. Sometimes chemotherapy may be given before surgery (neoadjuvant chemotherapy) to shrink the tumour. Radiation therapy can be associated in tumours of the last segment of the intestine (rectum) to increase the chance of reduce the size of the tumour.

After treatment, regular follow-up visits and surveillance are essential to monitor for any signs of recurrence or new cancer. Surveillance may include physical examinations, blood tests, and imaging studies (such as CT scans) to detect any potential recurrence at an early stage.

**a) Advanced disease.** Systemic therapy is the primary treatment approach for metastatic colorectal cancer, as it aims to treat cancer cells throughout the body. Chemotherapy is often used as the first-line treatment for metastatic colorectal cancer. Combination chemotherapy regimens are commonly used to kill cancer cells or slow down their growth. Targeted therapy may be used in combination with chemotherapy for patients with specific genetic mutations, such as KRAS or BRAF mutations. Immunotherapy drugs may be considered for patients with tumours that exhibit specific genetic markers, such as microsatellite instability-high (MSI-H) or mismatch repair deficiency (dMMR).

In some cases, surgery may be recommended for metastatic colorectal cancer to remove tumours that are causing symptoms or blocking the intestine. Localized treatments, such as radiofrequency ablation, cryoablation, or radiation therapy, may be used to treat specific areas of metastasis, such as liver metastases. Radiation therapy may be used to help control the disease and manage symptoms, such as pain or bleeding.

**Clinical Trials**

Clinical trials offer opportunities to access novel treatments or experimental therapies for patients. Participation in clinical trials helps advance medical knowledge and potentially offers new treatment options.

**WHO response**

The WHO is actively involved in addressing the global burden of colorectal cancer and implementing strategies to reduce its impact. WHO's approach involves raising awareness, cancer prevention and control, early detection and screening, strengthening health systems, capacity building, research and surveillance, as well as collaboration and partnerships. These comprehensive efforts contribute to reducing the burden of colorectal cancer by promoting prevention, early detection, equitable access to quality care, and improving overall cancer control globally.

## 2. Depression

**KEY FACTS**

- Depression is a common mental disorder.
- Globally, an estimated 5% of adults suffer from depression.
- More women are affected by depression than men.
- Depression can lead to suicide.
- There is effective treatment for mild, moderate and severe depression.

**Overview**

Depressive disorder (also known as depression) is a common mental disorder. It involves a depressed mood or loss of pleasure or interest in activities for long periods of time. Depression is different from regular mood changes and feelings about everyday life. It can affect all aspects of life, including relationships with family, friends and community. It can result from or lead to problems at school and at work.

Depression can happen to anyone. People who have lived through abuse, severe losses or other stressful events are more likely to develop depression. Women are more likely to have depression than men.

An estimated 3.8% of the population experience depression, including 5% of adults (4% among men and 6% among women), and 5.7% of adults older than 60 years. Approximately 280 million people in the world have depression *(1)*. Depression is about 50% more common among women than among men. Worldwide, more than 10% of pregnant women and women who have just given birth experience depression *(2)*. More than 700 000 people die due to suicide every year. Suicide is the fourth leading cause of death in 15–29-year-olds.

Although there are known, effective treatments for mental disorders, more than 75% of people in low- and middle-income countries receive no treatment *(3)*. Barriers to effective care include a lack of investment in mental health care, lack of trained health-care providers and social stigma associated with mental disorders.

**Symptoms and patterns**

During a depressive episode, a person experiences a depressed mood (feeling sad, irritable, empty). They may feel a loss of pleasure or interest in activities.

A depressive episode is different from regular mood fluctuations. They last most of the day, nearly every day, for at least two weeks.

Other symptoms are also present, which may include:

- poor concentration
- feelings of excessive guilt or low self-worth
- hopelessness about the future
- thoughts about dying or suicide
- disrupted sleep
- changes in appetite or weight
- feeling very tired or low in energy.

Depression can cause difficulties in all aspects of life, including in the community and at home, work and school.

A depressive episode can be categorized as mild, moderate, or severe depending on the number and severity of symptoms, as well as the impact on the individual's functioning.

There are different patterns of depressive episodes including:

- single episode depressive disorder, meaning the person's first and only episode;
- recurrent depressive disorder, meaning the person has a history of at least two depressive episodes; and
- bipolar disorder, meaning that depressive episodes alternate with periods of manic symptoms, which include euphoria or irritability, increased activity or energy, and other symptoms such as increased talkativeness, racing thoughts, increased self-esteem, decreased need for sleep, distractibility, and impulsive reckless behaviour.

**Contributing factors and prevention**

Depression results from a complex interaction of social, psychological, and biological factors. People who have gone through adverse life events (unemployment, bereavement, traumatic events) are more likely to develop depression. Depression can, in turn, lead to more stress and dysfunction and worsen the affected person's life situation and the depression itself.

Depression is closely related to and affected by physical health. Many of the factors that influence depression (such as physical inactivity or harmful use of alcohol) are also known risk factors for diseases such as cardiovascular disease, cancer, diabetes and respiratory diseases. In turn, people with these diseases may also find themselves experiencing depression due to the difficulties associated with managing their condition.

Prevention programmes have been shown to reduce depression. Effective community approaches to prevent depression include school-based programmes to enhance a pattern of positive coping in children and adolescents. Interventions for parents of children with behavioural problems may reduce parental depressive symptoms and improve outcomes for their children. Exercise programmes for older persons can also be effective in depression prevention.

**Diagnosis and treatment**

There are effective treatments for depression. These include psychological treatment and medications. Seek care if you have symptoms of depression.

Psychological treatments are the first treatments for depression. They can be combined with antidepressant medications in moderate and severe depression. Antidepressant medications are not needed for mild depression.

Psychological treatments can teach new ways of thinking, coping or relating to others. They may include talk therapy with professionals and supervised lay therapists. Talk therapy can happen in person or online. Psychological treatments may be accessed through self-help manuals, websites and apps.

Effective psychological treatments for depression include:

- behavioural activation
- cognitive behavioural therapy
- interpersonal psychotherapy
- problem-solving therapy.

Antidepressant medications include selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine.

Health-care providers should keep in mind the possible adverse effects associated with antidepressant medication, the ability to deliver either intervention (in terms of expertise, and/or treatment availability), and individual preferences.

Antidepressants should not be used for treating depression in children and are not the first line of treatment in adolescents, among whom they should be used with extra caution.

Different medications and treatments are used for bipolar disorder.

**Self-care**

Self-care can play an important role in managing symptoms of depression and promoting overall well-being.

What you can do:

- try to keep doing activities you used to enjoy
- stay connected to friends and family
- exercise regularly, even if it's just a short walk
- stick to regular eating and sleeping habits as much as possible
- avoid or cut down on alcohol and don't use illicit

drugs, which can make depression worse
- talk to someone you trust about your feelings
- seek help from a healthcare provider.

If you have thoughts of suicide:
- remember you are not alone, and that many people have gone through what you're experiencing and found help
- talk to someone you trust about how you feel
- talk to a health worker, such as a doctor or counsellor
- join a support group.

If you think you are in immediate danger of harming yourself, contact any available emergency services or a crisis line.

**WHO response**

WHO's Mental health action plan 2013–2030 highlights the steps required to provide appropriate interventions for people with mental disorders including depression.

Depression and self-harm/suicide are among the priority conditions covered by WHO's Mental Health Gap Action Programme (mhGAP). The Programme aims to help countries increase services for people with mental, neurological and substance use disorders through care provided by health workers who are not specialists in mental health.

WHO has developed brief psychological intervention manuals for depression that may be delivered by lay therapists to individuals and groups. An example is the Problem management plus (PM+) manual, which describes the use of behavioural activation, stress management, problem solving treatment and strengthening social support. Moreover, the Group interpersonal therapy for depression manual describes group treatment of depression. Finally, the Thinking healthy manual covers the use of cognitive-behavioural therapy for perinatal depression.

**REFERENCES**

1. Institute of Health Metrics and Evaluation. Global Health Data Exchange (GHDx). https://vizhub.healthdata.org/gbd-results/ (Accessed 4 March 2023).
2. Woody CA, Ferrari AJ, Siskind DJ, Whiteford HA, Harris MG. A systematic review and meta-regression of the prevalence and incidence of perinatal depression. J Affect Disord. 2017;219:86–92.
3. Evans-Lacko S, Aguilar-Gaxiola S, Al-Hamzawi A, et al. Socio-economic variations in the mental health treatment gap for people with anxiety, mood, and substance use disorders: results from the WHO World Mental Health (WMH) surveys. Psychol Med. 2018;48(9):1560-1571.

## 3. Lung cancer

**KEY FACTS**

- Lung cancer is the leading cause of cancer-related deaths worldwide, accounting for the highest mortality rates among both men and women.
- Smoking is the leading cause of lung cancer, responsible for approximately 85% of all cases.
- Lung cancer is often diagnosed at advanced stages when treatment options are limited.
- Screening high risk individuals has the potential to allow early detection and to dramatically improve survival rates.
- Primary prevention (such as tobacco control measures and reducing exposure to environmental risk factors) can reduce the incidence of lung cancer and save lives.

**Overview**

Lung cancer is a type of cancer that starts when abnormal cells grow in an uncontrolled way in the lungs. It is a serious health issue that can cause severe harm and death.

Symptoms of lung cancer include a cough that does not go away, chest pain and shortness of breath.

It is important to seek medical care early to avoid serious health effects. Treatments depend on the person's medical history and the stage of the disease.

The most common types of lung cancer are non-small cell carcinoma (NSCLC) and small cell carcinoma (SCLC). NSCLC is more common and grows slowly, while SCLC is less common but often grows quickly.

Lung cancer is a significant public health concern, causing a considerable number of deaths globally. GLOBOCAN 2020 estimates of cancer incidence and mortality produced by the International Agency for Research on Cancer (IARC) show as lung cancer remains the leading cause of cancer death, with an estimated 1.8 million deaths (18%) in 2020.

Smoking tobacco (including cigarettes, cigars, and pipes) is the primary risk factor for lung cancer but it can also affect non-smokers. Other risk factors include exposure to secondhand smoke, occupational hazards (such as asbestos, radon and certain chemicals), air pollution, hereditary cancer syndromes, and previous chronic lung diseases.

**Symptoms**

Lung cancer can cause several symptoms that may indicate a problem in the lungs.

The most common symptoms include:
- cough that does not go away
- chest pain
- shortness of breath
- coughing up blood (haemoptysis)

- fatigue
- weight loss with no known cause
- lung infections that keep coming back.

Early symptoms may be mild or dismissed as common respiratory issues, leading to delayed diagnosis.

**Prevention**

Not smoking tobacco is the best way to prevent lung cancer.

Other risk factors to avoid include:

- secondhand smoke
- air pollution
- workplace hazards like chemicals and asbestos.

Early treatment can prevent lung cancer from becoming worse and spreading to other parts of the body.

Prevention of lung cancer include primary and secondary prevention measures. Primary prevention aims to prevent the initial occurrence of a disease through risk reduction and promoting healthy behaviour. In public health, these preventive measures include smoking cessation, promoting smoke-free environments, implementing tobacco control policies, addressing occupational hazards, and reducing air pollution levels.

Secondary prevention for lung cancer involves screening methods that aim to detect the disease in its early stages, before symptoms become apparent and can be indicated for high-risk individuals. In this population, early detection can significantly increase the chances of successful treatment and improve outcomes. The primary screening method for lung cancer is low-dose computed tomography (LDCT).

**Diagnosis**

Diagnostic methods for lung cancer include physical examination, imaging (such as chest X-rays, computed tomography scans, and magnetic resonance imaging), examination of the inside of the lung using a bronchoscopy, taking a sample of tissue (biopsy) for histopathology examination and definition of the specific subtype (NSCLC versus SCLC), and molecular testing to identify specific genetic mutations or biomarkers to guide the best treatment option.

**Treatment and care**

Treatments for lung cancer are based on the type of cancer, how much it has spread, and the person's medical history. Early detection of lung cancer can lead to better treatments and outcomes.

Treatments include:

- surgery
- radiotherapy (radiation)
- chemotherapy
- targeted therapy
- immunotherapy.

Surgery is often used in the early stages of lung cancer if the tumour has not spread to other areas of the body. Chemotherapy and radiation therapy can help shrink the tumour.

Doctors from several disciplines often work together to provide treatment and care of people with lung cancer.

Supportive care is important for people with lung cancer. It aims to manage symptoms, provide pain relief, and give emotional support. It can help to increase quality of life for people with lung cancer and their families.

**Stages of care**

**a) Early stage disease**: The primary treatment for early stage lung cancer (i.e. tumour limited to the lung, with no metastatic dissemination to distant organs or lymph nodes) is surgical removal of the tumour through procedures such as lobectomy, segmentectomy, or wedge resection. Neoadjuvant therapy (chemotherapy and/or radiation therapy before surgery) can help reduce tumour size, making it more manageable for surgical removal. Adjuvant treatment (chemotherapy and/or radiation therapy) is very often recommended after surgery to reduce the risk of cancer recurrence. In cases where surgery is not feasible, radiation therapy or stereotactic body radiation therapy (SBRT) may be used as the primary treatment. Targeted therapy and immunotherapy may also be considered based on specific tumour characteristics. Individualized treatment plans should be discussed with healthcare professionals.

**b) Advanced disease:** The treatment for metastatic stage lung cancer, where the cancer has spread to distant organs or lymph nodes, is based on various factors, including the patient's overall health, the extent and location of metastases, histology, genetic profile, and individual preferences. The primary goal is to prolong survival, alleviate symptoms, and improve quality of life. Systemic therapies, such as chemotherapy, targeted therapy, and immunotherapy, play a crucial role in the treatment of metastatic lung cancer.

Chemotherapy is often the first-line treatment for the majority of patients around the world and involves the use of drugs that circulate throughout the body to kill cancer cells. Combination chemotherapy regimens are commonly used, and the choice of drugs depends on factors such as the histological type of the cancer and the patient's general health conditions. Targeted therapy, designed to block the signalling pathways that drive the growth of cancer cells, is an important

option for patients with specific genetic mutations or biomarkers identified in their tumour. Immunotherapy, specifically immune checkpoint inhibitors, has revolutionized the treatment of metastatic lung cancer. These drugs help to stimulate the immune system to recognize and attack cancer cells. Local treatments, such as radiation therapy and surgery, may be used to manage specific metastatic sites or alleviate symptoms caused by tumour growth.

**Clinical Trials**

Clinical trials offer opportunities to access novel treatments or experimental therapies for patients. Participation in clinical trials helps advance medical knowledge and potentially offers new treatment options.

**WHO response**

WHO recognizes the significant impact of lung cancer on global health and has implemented several initiatives to address the disease comprehensively. The WHO's response focuses on tobacco control, cancer prevention, early detection, and improving access to quality treatment and care. WHO supports countries in implementing evidence-based tobacco control policies, including increasing tobacco taxes, enforcing comprehensive bans on tobacco advertising, promotion, and sponsorship, and implementing strong graphic health warnings on tobacco products.

The Organization also promotes cancer prevention strategies by advocating for healthy lifestyles, including regular physical activity, a healthy diet, and minimizing exposure to environmental risk factors. Additionally, WHO supports early detection programs and encourages countries to implement screening measures for high-risk populations to detect lung cancer at earlier stages when treatment options are more effective. Last, WHO works towards ensuring access to quality treatment and care for lung cancer patients by providing technical guidance to member states, promoting equitable access to essential cancer medicines, and fostering international collaboration to share best practices and improve cancer care outcomes.

## 4. Nipah virus

**KEY FACTS**

- Nipah virus infection in humans causes a range of clinical presentations, from asymptomatic infection (subclinical) to acute respiratory infection and fatal encephalitis.
- The case fatality rate is estimated at 40% to 75%. This rate can vary by outbreak depending on local capabilities for epidemiological surveillance and clinical management.
- Nipah virus can be transmitted to humans from animals (such as bats or pigs), or contaminated foods and can also be transmitted directly from human-to-human.
- Fruit bats of the Pteropodidae family are the natural host of Nipah virus.
- There is no treatment or vaccine available for either people or animals. The primary treatment for humans is supportive care.
- The 2018 annual review of the WHO R&D Blueprint list of priority diseases indicates that there is an urgent need for accelerated research and development for the Nipah virus.

**Overview**

Nipah virus (NiV) is a zoonotic virus (it is transmitted from animals to humans) and can also be transmitted through contaminated food or directly between people. In infected people, it causes a range of illnesses from asymptomatic (subclinical) infection to acute respiratory illness and fatal encephalitis. The virus can also cause severe disease in animals such as pigs, resulting in significant economic losses for farmers.

Although Nipah virus has caused only a few known outbreaks in Asia, it infects a wide range of animals and causes severe disease and death in people, making it a public health concern.

**Past Outbreaks**

Nipah virus was first recognized in 1999 during an outbreak among pig farmers in, Malaysia. No new outbreaks have been reported in Malaysia since 1999.

It was also recognized in Bangladesh in 2001, and nearly annual outbreaks have occurred in that country since. The disease has also been identified periodically in eastern India.

Other regions may be at risk for infection, as evidence of the virus has been found in the known natural reservoir (*Pteropus* bat species) and several other bat species in a number of countries, including Cambodia, Ghana, Indonesia, Madagascar, the Philippines, and Thailand.

**Transmission**

During the first recognized outbreak in Malaysia, which also affected Singapore, most human infections resulted from direct contact with sick pigs or their contaminated tissues. Transmission is thought to have occurred via unprotected exposure to secretions from the pigs, or unprotected contact with the tissue of a sick animal.

In subsequent outbreaks in Bangladesh and India, consumption of fruits or fruit products (such as raw date palm juice) contaminated with urine or saliva

from infected fruit bats was the most likely source of infection.

There are currently no studies on viral persistence in bodily fluids or the environment including fruits.

Human-to-human transmission of Nipah virus has also been reported among family and care givers of infected patients. During the later outbreaks in Bangladesh and India, Nipah virus spread directly from human-to-human through close contact with people's secretions and excretions. In Siliguri, India in 2001, transmission of the virus was also reported within a health-care setting, where 75% of cases occurred among hospital staff or visitors. From 2001 to 2008, around half of reported cases in Bangladesh were due to human-to-human transmission through providing care to infected patients.

**Signs and symptoms**

Human infections range from asymptomatic infection to acute respiratory infection (mild, severe), and fatal encephalitis.

Infected people initially develop symptoms including fever, headaches, myalgia (muscle pain), vomiting and sore throat. This can be followed by dizziness, drowsiness, altered consciousness, and neurological signs that indicate acute encephalitis. Some people can also experience atypical pneumonia and severe respiratory problems, including acute respiratory distress. Encephalitis and seizures occur in severe cases, progressing to coma within 24 to 48 hours.

The incubation period (interval from infection to the onset of symptoms) is believed to range from 4 to 14 days. However, an incubation period as long as 45 days has been reported.

Most people who survive acute encephalitis make a full recovery, but long term neurologic conditions have been reported in survivors. Approximately 20% of patients are left with residual neurological consequences such as seizure disorder and personality changes. A small number of people who recover subsequently relapse or develop delayed onset encephalitis.

The case fatality rate is estimated at 40% to 75%. This rate can vary by outbreak depending on local capabilities for epidemiological surveillance and clinical management.

**Diagnosis**

Initial signs and symptoms of Nipah virus infection are nonspecific, and the diagnosis is often not suspected at the time of presentation. This can hinder accurate diagnosis and creates challenges in outbreak detection, effective and timely infection control measures, and outbreak response activities.

In addition, the quality, quantity, type, timing of clinical sample collection and the time needed to transfer samples to the laboratory can affect the accuracy of laboratory results.

Nipah virus infection can be diagnosed with clinical history during the acute and convalescent phase of the disease. The main tests used are real time polymerase chain reaction (RT-PCR) from bodily fluids and antibody detection via enzyme-linked immunosorbent assay (ELISA).

Other tests used include polymerase chain reaction (PCR) assay, and virus isolation by cell culture.

**Treatment**

There are currently no drugs or vaccines specific for Nipah virus infection although WHO has identified Nipah as a priority disease for the WHO Research and Development Blueprint. Intensive supportive care is recommended to treat severe respiratory and neurologic complications.

**Natural host: fruit bats**

Fruit bats of the family *Pteropodidae* – particularly species belonging to the *Pteropus* genus – are the natural hosts for Nipah virus. There is no apparent disease in fruit bats.

It is assumed that the geographic distribution of *Henipaviruses* overlaps with that of *Pteropus* category. This hypothesis was reinforced with the evidence of *Henipavirus* infection in *Pteropus* bats from Australia, Bangladesh, Cambodia, China, India, Indonesia, Madagascar, Malaysia, Papua New Guinea, Thailand and Timor-Leste.

African fruit bats of the genus *Eidolon*, family *Pteropodidae,* were found positive for antibodies against Nipah and Hendra viruses, indicating that these viruses might be present within the geographic distribution of *Pteropodidae* bats in Africa.

**Nipah virus in domestic animals**

Outbreaks of the Nipah virus in pigs and other domestic animals such as horses, goats, sheep, cats and dogs were first reported during the initial Malaysian outbreak in 1999.

The virus is highly contagious in pigs. Pigs are infectious during the incubation period, which lasts from 4 to 14 days.

An infected pig can exhibit no symptoms, but some develop acute feverish illness, labored breathing, and neurological symptoms such as trembling, twitching and muscle spasms. Generally, mortality is low except in young piglets. These symptoms are not dramatically different from other respiratory and neurological illnesses of pigs. Nipah virus should be suspected if pigs also have an unusual barking cough or if human

cases of encephalitis are present. For more information of Nipah in animals, see the Food and Agriculture Organization of the United Nations webpage on Nipah and the World Organization for Animal Health (OIE) webpage on Nipah.

**Prevention**

**Controlling Nipah virus in pigs**

Currently, there are no vaccines available against Nipah virus. Based on the experience gained during the outbreak of Nipah involving pig farms in 1999, routine and thorough cleaning and disinfection of pig farms with appropriate detergents may be effective in preventing infection. If an outbreak is suspected, the animal premises should be quarantined immediately. Culling of infected animals – with close supervision of burial or incineration of carcasses – may be necessary to reduce the risk of transmission to people. Restricting or banning the movement of animals from infected farms to other areas can reduce the spread of the disease. As Nipah virus outbreaks have involved pigs and/or fruit bats, establishing an animal health/wildlife surveillance system, using a One Health approach, to detect Nipah cases is essential in providing early warning for veterinary and human public health authorities.

**Reducing the risk of infection in people**

In the absence of a vaccine, the only way to reduce or prevent infection in people is by raising awareness of the risk factors and educating people about the measures they can take to reduce exposure to the Nipah virus. Public health educational messages should focus on:

- **Reducing the risk of bat-to-human transmission.**

Efforts to prevent transmission should first focus on decreasing bat access to date palm sap and other fresh food products. Keeping bats away from sap collection sites with protective coverings (such as bamboo sap skirts) may be helpful. Freshly collected date palm juice should be boiled, and fruits should be thoroughly washed and peeled before consumption. Fruits with sign of bat bites should be discarded.

- **Reducing the risk of animal-to-human transmission**.

Gloves and other protective clothing should be worn while handling sick animals or their tissues, and during slaughtering and culling procedures. As much as possible, people should avoid being in contact with infected pigs. In endemic areas, when establishing new pig farms, considerations should be given to presence of fruit bats in the area and in general, pig feed and pig shed should be protected against bats when feasible.

- **Reducing the risk of human-to-human transmission**.

Close unprotected physical contact with Nipah virus-infected people should be avoided. Regular hand washing should be carried out after caring for or visiting sick people.

**Controlling infection in health-care settings**

Health-care workers caring for patients with suspected or confirmed infection, or handling specimens from them, should implement standard infection control precautions at all times

As human-to-human transmission has been reported, in particular in health-care settings, contact and droplet precautions should be used in addition to standard precautions. Airborne precautions may be required in certain circumstances.

Samples taken from people and animals with suspected Nipah virus infection should be handled by trained staff working in suitably equipped laboratories.

**WHO response**

WHO is supporting affected and at risk countries with technical guidance on how to manage outbreaks of Nipah virus and on how to prevent their occurrence.

The risk of international transmission via fruits or fruit products (such as raw date palm juice) contaminated with urine or saliva from infected fruit bats can be prevented by washing them thoroughly and peeling them before consumption. Fruit with signs of bat bites should be discarded.

## 5. Rheumatoid arthritis

**Key facts**

- In 2019, 18 million people worldwide were living with rheumatoid arthritis (1).
- About 70% of people living with rheumatoid arthritis are women, and 55% are older than 55 years (1).
- 13 million people with rheumatoid arthritis experience severity levels (moderate or severe) that could benefit from rehabilitation (2).
- While rheumatoid arthritis is a systemic autoimmune disease that affects multiple body systems, the joints of hands, wrists, feet, ankles, knees, shoulders and elbows are most often affected (3).

**Overview**

Rheumatoid arthritis (RA) is a chronic disease that causes inflammation around the body and commonly presents with pain in the joints.

Untreated, RA can cause severe damage to the joints and their surrounding tissue. It can lead to heart, lung or nervous system problems.

Common symptoms include chronic pain, stiffness, tenderness, heat and swelling in the joints. RA can make it hard to move and perform daily activities.

The causes of rheumatoid arthritis are unknown. Risk factors include smoking, obesity and exposure to air pollution. Women and older people have a higher risk of developing RA.

If diagnosed timely, symptoms and disease progression can be controlled with pharmacological treatment, and optimal functioning can be maintained through rehabilitation (including the use of assistive products). In cases with severe joint damage, surgical procedures, including joint replacement, may help to restore movement or manage pain, and maintain physical function.

**Scope of the problem**

The typical onset of the disease occurs in adults in their sixties. Women are two-to-three times more often affected than men. The prevalence of rheumatoid arthritis is higher in industrialized countries, which may be explained by demographics (higher average age), exposures to environmental toxins and lifestyle risk factors, and under-diagnosis in low-and-middle-income countries.

**Signs and symptoms**

Rheumatoid arthritis causes inflammation and pain in one or more joints. It can happen in most joints, but it's most common in the small joints of the hands, wrists and feet.

RA is chronic and may worsen over time without treatment. It can lead to severe damage to the joint and surrounding tissue. It can also affect the heart, lung and nervous systems.

Early signs and symptoms:

- pain
- stiffness
- tenderness
- swelling or redness in one or more joints, usually in a symmetrical pattern (e.g., both hands or both feet).

The symptoms can worsen over time and spread to more joints including the knees, elbows or shoulders. RA can make it hard to perform daily activities like writing, holding objects with the hands, walking and climbing stairs.

People with RA often feel fatigue and general malaise (e.g., fever, poor sleep quality, loss of appetite) and may experience depressive symptoms.

Pain and difficulty moving can lead to problems with sexual function and intimate relationships. Trouble moving easily can cause lower physical fitness and lead to loss of independence, inability to work, reduced well-being and mental health problems.

**Causes and risk factors**

The specific causes for the disease are still unknown, but several modifiable lifestyle-associated (smoking, obesity) and non-modifiable (genetics, female gender, age) risk factors have been identified.

**Prevention and control**

Several key prevention strategies have been proposed to prevent rheumatoid arthritis and control the disease progression. In particular, reducing exposure to inhaled silica, dusts and occupational risks, and lifestyle related behaviours (e.g., prevention of/stop smoking, healthy nutrition, physical activity, maintaining a normal body weight, maintaining good dental hygiene) play an important role. Some evidence also suggests breastfeeding may be protective to the mother *(4)*.

**Treatment and management**

Rheumatoid arthritis is not curable. Management of rheumatoid arthritis often involves different health workers, who contribute to a rehabilitative strategy tailored to a person's needs and preferences.

Early diagnosis and management can reduce symptoms, slow the disease and prevent disability. In some cases, the disease can go into remission.

Therapeutic approaches help to improve and maintain joint mobility and muscle strength, to reduce and cope with pain, and to increase exercise capacity and the ability to perform daily activities.

Assistive technologies (e.g., orthosis, assistive products for self-care) help people to protect their joints and to perform meaningful activities independently.

Medicines to reduce inflammation, pain and swelling may include:

- non-steroidal anti-inflammatory drugs (NSAIDs)
- glucocorticoids
- disease-modifying antirheumatic drugs (DMARDs)
- biological agents.

In severe cases, orthopaedic surgery can reduce pain and restore movement. Rehabilitation is essential to achieve the best outcomes following surgery.

It is important to keep a healthy lifestyle. Education and counselling are important to help people manage their symptoms and work-related tasks.

**Self-care**

Rheumatoid arthritis is a chronic condition that impacts many aspects of life. Lifestyle changes are often needed for individuals and their families. Education and support help people with rheumatoid

arthritis to develop strategies to cope with the disease. It is important to maintain a healthy lifestyle with regular physical activity and a nutritious diet.

**WHO response**

WHO is taking action to extend access to care in rheumatoid arthritis in different ways:

**WHO Rehabilitation 2030 Initiative**

The Package of Interventions for Rehabilitation provides information on essential interventions for rehabilitation (including assistive products), and human and material resources for 20 health conditions, including rheumatoid arthritis.

**UN Decade of Healthy Ageing**

WHO recommends a reorientation of health and care systems to promote healthy ageing and address the diverse needs of older persons.

The Integrated Care for Older People (ICOPE) approach promotes the person-centred assessment of the older person to guide the design of personalized, health and social care, including long-term care interventions. Specific recommendations are provided to prevent the loss of locomotor and psychological capacity because of pain.

**REFERENCES**

1. GBD 2019: Global burden of 368 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. https://vizhub.healthdata.org/gbd-results/.
2. Cieza A, Causey K, Kamenow K, Wulf Hansen S, Chatterji S, Vos T. Global estimates of the need for rehabilitation based on the Global Burden of Disease study 2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet. 2020 Dec 19; 396(10267): 2006–17.
3. Long H, Liu Q, Yin H, Diao N, Zhang Y, Lin J et al. Prevalence trends of site-specific osteoarthritis from 1990 to 2019: Findings from the global burden of disease study 2019. Arthritis Rheumatol 2022; 74(7): 1172-83.
4. Koller-Smith L, Mehdi AM, March L, Tooth L, Mishra GD, Thomas R. Rheumatoid arthritis is a preventable disease: 11 ways to reduce your patients' risk. Internal Medicine Journal 2022;52:711–6.

# Yearly Author Index
# Kuwait Medical Journal
# 2023; Volume 55

Kuwait Medical Journal 2023, 55 (4) : 392 - 393

# Yearly Title Index
# Kuwait Medical Journal
# 2023; Volume 55

Kuwait Medical Journal 2023, 55 (4) : 394 - 395