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Review Article

The current developments in oncology nursing: A review

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ABSTRACT

Cancer has become one of the major causes of death in the growing world population, affecting people irrespective of their age, sex and culture. Cancer diagnosis and therapy is a distressing procedure and affects the physical, emotional and mental well-being of the patient. Many studies have reported that cancer has a long-term impact on patient's lives leading to mood dysfunction, heart problems and chemotherapy toxicity. Modern-day healthcare systems are moving towards a patient-oriented approach and are designed around the patient's well-being, needs and preferences. Oncology nurses form the fundamental part of this system and provide the patient with the much-needed care, support and hope for life. Oncology nursing has developed and evolved briefly in the recent few decades due to the advancement in treatment procedures. As cancer care continues to progress, nurses play a vital role in the field of oncology. Specialized oncology nurses are providing clinical care, or as nurse researchers leading revolutionary oncology research. The future of oncology nursing is optimistic. Nursing care for cancer patients not only requires guidance through medication and treatment, but also offers encouragement and motivation to the patients. The present review provides an insight into the nursing care of cancer patients, its brief history, advancements and the current practices of oncology nursing. Future prospects of oncology nursing have also been discussed in detail.

KEY WORDS: cancer, healthcare, nursing care, oncology, patients

INTRODUCTION

Diagnosis of cancer is a major life event in a person's life that disrupts the lives of the patient and his/her loved ones. As cancer is assumed to be a life-threatening and dreadful disease, fear is associated with the disease in the minds of people. However, the rising number of cancer cases worldwide is a growing cause of concern. Cancer not only affects the socio-economic structure of the society, but also hampers the mental and emotional well-being of the patient[1]. According to a survey, cancer affects around 18 million people around the world and causes a mortality rate of 9.6 million persons[2]. In the next ten years, the death rate due to cancer is assumed to reach 13 milion[2,3]. Cancer takes much time from diagnosis to treatment and causes detrimental effects on the body, also affecting the psychological and social status of the patient[4,5]. Most of the time, this period is shared between the patient, healthcare professionals and nurses. Nurses play a significant role in providing both care and support to patients[6]. Recently, modern healthcare systems have come up with a more patient-centric approach as compared to previous years[7,8]. The plan of care is prepared according to the patient's physiology, needs, values and preferences. In the patient-centered care approach, patients are actively taken care of by the caregivers[9].

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Oncology nursing has evolved enormously over the last decade as cancer has become one of the leading causes of death globally. Oncology nursing provides support to cancer patients in various forms like individualized/holistic care, family-centered care, self-determination, navigating the system, and coordinated continuous care[10-12]. Many studies have shown that relational nursing leadership is significantly related to improved outcomes for patient care and patients[13,14]. Many oncology nursing societies offer support to the nurses in their roles to provide the best care, education and support for those living with cancer and their families[12]. Oncology nursing is the fundamental need of cancer patients[15,16].

Patient-nurse partnership in nursing care is a vital part of patient-centered care, in which patients and nurses work together on decisions about daily life and care[17]. Although oncology nursing is still an essential part of cancer patients' lives, their presence is non-existent to the patient and its family members[18]. In many cases, the complexity of healthcare systems increases the distance between patients and nurses[19]. In nursing care, oncology nurses play an intricate role in enhancing the quality of life of their patients from cancer diagnosis to beyond treatment. Nurses play a distinctive role in influencing both the physiologic and psychological well-being of their patients, also helping cancer survivors to cope with the immensity of their experience and its resulting impact on their lives[20]. Oncology nurses care independently and collectively to attend to different patient needs such as pain, fatigue, depression, family coping, long-term treatment and numerous other areas of survivorship[21,22]. Majority of cancer patients are diagnosed with clinical depression. It is now imperative that health care professionals and oncology nurses develop a new perspective for caregiving to cancer patients. This review highlights the shreds of evidence of oncology nursing care for cancer patients, recent advancements, and current practices in oncology nursing.

LITERATURE REVIEW

Nursing as an occupation is dedicated to the care of patients and families during health and illness and across all settings of care. Nurses generally evaluate and plan to address the multidimensional spectrum of needs for those faced with cancer. Nurses have been innately involved in efforts concentrated on cancer prevention. They also are pivotal in the emerging area of clinical genetics for the prevention and early detection of cancer.

The foundation of oncology nursing is based on the core awareness of detection, diagnosis, care-giving and targeted therapy of cancer patients[23]. Around 60 years ago, oncology nurses who need to be specially trained rather than educated with basic nursing knowledge emerged as a necessity for cancer patients[24]. In the 1940's, oncology nurses worked as primary caregivers, assisting the doctors and serving the healthcare needs of the cancer patients[25]. Without proper training and knowledge about the treatment procedures, earlier oncology nurses worked only for symptom management of cancer patients. Nurses often had to use resourceful methods for assisting patients with chemotherapy burns and pain. Later, when chemotherapy was introduced as the standard treatment option for cancer patients in the early 20th century, oncology nursing was regarded as hazardous and undesirable due to the frequent exposure to radiation therapies and their harmful effects[26]. However, in the late 1950s, oncology nursing became validated and desirable when the impact of cancer was observed in society and many cases of cancer were reported[27].

Since the foundation of the Oncology Nursing Society in 1975, special priority has been given to the education and training of oncology nurses[25]. The Oncology Nursing Society is a professional organization majorly conducting awareness of survivorship concerns and providing extensive education to special practicing nurses[28]. The Oncology Certification Corporation was established in 1985 and it provided varying dimensions to oncology nursing beyond basic nursing practices[23]. With the advent of the 21st century, nursing roles advanced briefly due to the introduction of innovative treatment procedures and therapies[24]. The future work nature of oncology nurses will be based on the scientific advancements in the field of oncology. Molecular and gene therapies will form the major lead in the treatment process[29].

Oncology nursing- a perspective

Cancer is a dreadful disease, so early detection and treatment applications are of utmost importance[30]. Nurses are the primary caregivers and perform competently as patient navigators through the journey of cancer care to link the patient to local health systems and provide better caregiving. Oncology nurses are involved in many roles throughout a patients' cancer experience. Specialized oncology nursing is well versed with the knowledge of cancer and cancer risk factors, signs and symptoms[31]. They are well trained to work in different setups like cancer care centers, cancer rehabilitation centers, ambulatory services, and community health centers (Figure 1). Oncology nurses also execute the task to explain and raise awareness of patients for further diagnosis and treatment procedures[32]. The patient and health professional relationship and communication is the most important factor in supporting and facilitating the patients' ability

Fig 1: Different working areas for oncology nurses.

to cope with cancer in everyday life. Therefore, there is a need to do more research in this area, to study the interaction and intervention of oncology nurses for effectively supporting patients while undergoing treatment in an outpatient clinic[33].

Oncology nurses practice in various oncologic disciplines, including surgical oncology, radiation oncology, gynecologic oncology, pediatric oncology and medical oncology[15]. Oncology nurses can focus on patient assessment, patient education, coordination of care, direct patient care, symptom management and supportive care. Oncology nurses are expected to be experts in assessing a patient's physical and emotional status, past health history, health practices, and both the patient's and the family's knowledge of the disease and its treatment[34]. Nurses usually have the opportunity than any other member of the healthcare team to develop the required rapport for effective educational efforts with patients and their families. Every year more than one million people will be diagnosed with cancer, and nurses will care for these individuals. Nurses will be closely attached to their care and across all settings, and they will tremendously affect the quality of care of cancer survivors and their families[21].

Nakaguchi *et al*[35] assessed the accuracy of oncology nurses in determining the supportive care needs and symptoms of cancer patients. The participants of the study were selected from outpatient settings and those receiving chemotherapy in ambulatory settings. The patients were mostly suffering from breast, lung and colorectal cancer. The results of the assessment detailed that the oncology nurses could not accurately predict their patient's symptoms and needs for supportive cancer care; hence, routine checkup and follow-up were recommended to check the patient's symptoms and needs.

Komatsu and Yagasaki[10] performed a qualitative study to understand the experiences of oncology nurses in cancer patient counseling and support services. The study was conducted based on themes like connecting with the patient, personalized coordination and realizing the patient's potential. The conclusion of the study described the uniqueness and power of oncology nursing work. The oncology nurses prioritize personalized care for cancer patients; they also form the heart of the treatment process serving as a bridge between the patient and the medical professionals. Adam *et al*[36] explored the quality of oncology nursing through the perception of cancer patients in four European Countries (Cyprus, Finland, Greece and Sweden). Cancer patients from Finland and Sweden gave high scores for the quality of

nursing they received as in these countries, specialized nurses were appointed for cancer care. Meanwhile, as oncology nursing was just introduced in Greece and Cyprus, low scores were observed for nursing care. However, the responsiveness of the oncology nurses was observed to be very good.

Nurses are trained in structured and unstructured experiences to assist patients with coping with their diagnosis, long-term adjustments and symptoms; to gain information about prevention, diagnosis and care; and to develop skills, knowledge and attitudes to maintain or regain health status. This unique education uses an amalgamation of methods that best meet the needs, capabilities and learning style of the patient[37]. Nurses explanation of side effects that generally occur may allay patient anxiety and will assist nurses in selecting appropriate interventions. This may help to differentiate the side effects of chemotherapy from other possible causes of similar symptoms. Patient education is facilitated when side effects are classified as immediate, early, delayed and late.

Oncology nurses are staying in a challenging environment daily to deal with the numerous symptoms patients with cancer and their families encounter as a result of their cancer or its treatment[38]. Oncology nurses are involved with supportive care for cancer patients and their families, as well as pain management and survivorship (Figure 2)[39]. The concerted efforts of researchers worldwide will help to promote patient comfort, provide patients and their families with information related to pain control, provide information about and help with behavioral and physical interventions, prevent side effects of pharmacologic therapies, and promote patient compliance with therapy and follow up. The nurse should explain the rationale for interventions and provide time for patient and family questions. Oncology nurses educate patients on the names of the pharmacologic agents, dosage schedules, side effects, interventions to alleviate nausea and vomiting, and interventions to alleviate constipation. The oncology nurses observe the effectiveness and side effects of pharmacologic interventions, respiratory status and bowel functioning, as well as mental and cognitive functioning.

Kamisli *et al*[40] surveyed 70 oncology nurses working in Hacettepe University Oncology Hospital. The study was conducted to evaluate the facets of oncology nurses regarding their profession. The analysis of the data depicted that working with cancer patients increased work-related exhaustion, and stress that nurses also felt satisfaction and awareness about the quality of life. Maree and Mulonda[1] described the experiences of Zambian nurses working as oncology nurses for women with advanced breast cancer. The data obtained from the study revealed that caring for women with advanced cancer symptoms is challenging. Also, working without any formal training

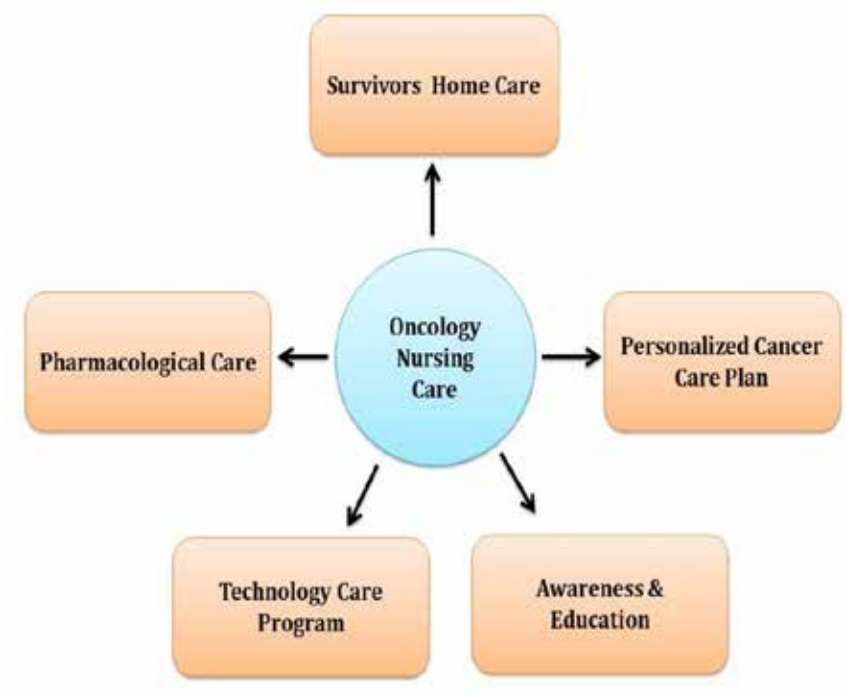

Fig 2: Oncology nursing care systems.

in oncology nursing is disempowering and stressful. However, developing a positive environment, learning opportunities and good nurse-patient relationship resulted in positive patient outcomes. The authors concluded that the education for oncology nursing should be necessarily taken care of and instituted effectively.

Kim *et al*[41] conducted a study about the awareness of oncology nurses related to cervical cancer and also the caring experiences of oncology nurses with cervical cancer patients. The authors conducted a qualitative study with descriptive work by interviewing 14 oncology nurses. The results of the study revealed that the nurses expressed fear and difficulty watching patients undergoing painful treatment. Also, they felt helpless while dealing with this life-threatening procedure along with the cancer patients. It was observed that the nurses were prejudiced about the cause of cervical cancer and sympathized with the cancer patients. Lacorossi *et al*[42] conducted an observational study for determining the competence of oncology nurses. Around 65 nurses and five head nurses who had been working in oncology care units for approximately 17 years were selected for the study. The nurse competence scale and Chi-Square test were done to obtain the required data. The results of the study showed that even if the oncology nurses lacked specific oncology competence, continuous work in oncology care units has helped them develop a good level of clinical competence.

Advancements in the fields

Cancer is a disorder described in cellular growth and refers to a range of diseases and not to a single entity. An oncology nurse is especially responsible for the care of cancer patients and patients at risk. They mainly monitor physical conditions, prescribe drugs, administer chemotherapy and other treatments. The upcoming oncology health care such as informatics have been identified, as well as opportunities for nursing professionals to be at the forefront of transforming cancer care. Advanced nursing practice mainly includes cancer screening, prevention, early detection, genetic risk, cancer diagnosis and progression, and cancer survival. Nurses have many responsibilities to deal with a cancer patient. Nursing care includes assessment, support for treatments (e.g., chemotherapy, radiation, etc.), pain control, nutrition enhancement and emotional support[43]. There are many recent advances in oncology-related to the organization of care, multidisciplinary cancer treatment team, supportive care for cancer patients, treatment goals, and the status of clinical trials[44].

Oncology research has benefited cancer patients in several ways. Research on oncology-specific Electronic Medical Record network has been discussed by Kanas *et al*[45]. For cancer patients, health professionals and oncology nurses, the most significant part of the treatment process is the improvement in health and the chances of survival of cancer patients, as well as prevention from future tumor recurrence. Electronic Medical Record systems are found to be very useful for cancer patients, medical professionals and policymakers. Kearney *et al*[46] investigated the use of a mobile phone-based remote monitoring system for advanced symptom management. The mobile phone-based system evaluated chemotherapy-based symptoms like nausea, vomiting, fatigue, mucositis, diarrhea, and hand-foot syndrome of patients suffering from lung, breast, and colorectal cancer. The authors of the study suggested that the mobile phone-based symptom management system supports the patients and the caregivers for the management of chemotherapy-related toxicity.

Wujcik[29] explained the advances in cancer care related to genomic testing. The study of the genetic makeup of the cancer patients will be helpful in designing precision medicines for cancer patients based on gene expression. Oncology nurses will have the further responsibility for collecting the patient's blood and tissue specimen, processing and transferring it for clinical use. The oncology nurses will have to be specially trained in genomics and advanced chemotherapy practices. Gustafson *et al*[47] discussed the role of the electronic health system for caregivers. The data obtained in the study revealed that the electronic health system-based system helped caregivers to perform online management of the patient's symptoms. The system alerts caregivers immediately and allows managing patient's distress.

Artificial intelligence and machine learning will be the next new technologies for dealing with cancer. Neuro-engineering could be used for conducting personal cancer treatment, the discovery of cancer drugs, and cancer control. Similarly, computational biology will be used to store large amounts of data and apply the gathered information for curing individual patient cases[44].

Digital symptom monitoring technology provides a variety of opportunities for oncology nurses. Advanced nursing practice helps symptom management in multiple settings and improves the quality of life for the patients. These digital monitoring systems employ in-house monitoring, clinic appointment monitoring and inpatient monitoring[48]. The in-house monitoring system includes automated self-management techniques and alarms the oncology nurses and patient's family members just before the patient's health deteriorates. The clinic appointment monitoring system maintains a digital account of

patient's medical records. Meanwhile, the inpatient monitoring system monitors the improvement in symptoms of bone marrow or stem cell transplant patients at the bedside[48]. Weis *et al*[49] conducted a qualitative study on the use of electronic health records by the caregivers of the cancer patients. With the advancement of information technology, patient-oriented health care systems have been designed. These electronic health care systems help not only the oncology nurses, but also the untrained caregivers like the family members of the cancer patient, to maintain a health record of the illness.

The future of oncology nursing care will be subjective to the aging population and the increase in the number of patients diagnosed with cancer. Much advancement has been reported in the field of molecular sequencing that will lead to more clinical trials, targeted therapies and treatment decisions based on the genetic makeup of both the patient and the tumor. Oncology nurses should be aware of the current research scenario with an ever-changing array of targeted therapies and emerging scientific inventions[29]. The oncology nurse plays a vital role in coordinating the multiple and complex technologies now commonly used in cancer diagnosis and treatment. In the modern era, cancer care is performed at multiple sites by a variety of personnel at a pace that is accelerated by cost-conscious staff. Thus, the important responsibility of nurses involved in the delivery of chemotherapy is to ensure that the correct dose and drug are administered by the correct route to the right patient. Complex regimens of potentially lethal drugs are being employed in a variety of settings[50].

Oncology nursing in COVID-19

The world observed the global outbreak of SARS-CoV-2 in December 2019 that originated from Wuhan, China, and spread rapidly through continents[51,52]. The World Health Organization (WHO) regarded the attack of SARS coronavirus as a global pandemic and named it as Novel Coronavirus Disease (COVID-19)[53]. The disease severely affected the upper and lower respiratory tract of individuals causing symptoms like cough, cold, sneezing, difficulty in breathing, fever and pneumonia[51,54,55]. WHO released an advisory for children below 10 years of age, cancer patients, diabetics and other immuno-suppressed persons to strictly stay at home and quarantine themselves to get secured from the COVID infection[54,56].

Studies conducted at Wuhan, China, and several other countries found that cancer patients are more prone to coronavirus attack; also, mortality rate of COVID positive cancer patients was very high compared to other COVID positive individuals[54,57]. Cancer patients due to their weak immunity and harmful effects of radiation therapy and strong medication suffer multiple organ failure and acute respiratory dysfunction[53,58]. In this period of global emergency, nurses were the largest groups of healthcare professionals providing frontline care to the patients[52,55]. Oncology nurses had to face unique challenges while overcoming the pandemic situation. Oncology nurses had the tough responsibility of providing life-surviving cancer care while protecting the patients against the risks associated with COVID infections[52,58].

The healthcare providers were advised for frequent use of personal protective equipment along with performing standard sanitization procedures[59]. The non-essential surgeries were postponed due to lockdown conditions throughout the world[57]. Many cases were reported where oncology nurses were the only person who stayed with the cancer patients and served as a navigator between the patient and its family members[54]. Thus, the responsibility of the oncology nurses in caregiving increased many folds during COVID situation. Also, in the corona situation, the treatment methods for cancer patients shifted to telemedicine due to the quarantine rules[57]. Oncology nurses also had the task of dealing with patients' stress and anxiety due to pandemic conditions, while also providing details regarding medication and health care procedures to be followed at home[54,60]. The heroic work of the oncology nurses fighting the battle with corona at the frontline has been highly recognized and the year 2020 has been declared as the "International year of the Nurses and Midwife"[54].

One of the major concerns of healthcare professionals during this time of distress was the transmission of COVID infection from corona positive individuals. There was an atmosphere of anxiety and fear of bringing the virus to the home[55,59]. Oncology nurses also faced a shortage of personal protective equipment kits and other protective types of equipment[57,59]. Also, the physical strain due to long working hours and the psychosocial impact of the pandemic situation reflected in the form of anxiety and depression in caregivers. WHO had to release an advisory on ways to cope up with the mental stress caused due to COVID-19[54].

Efficient management and handling of this global crisis revealed the leadership abilities of the oncology nurses. In times of this global threat, oncology nurses provided unprecedented support to the cancer patients and worked tirelessly in hospitals and outpatient locations to cope up with the pandemic situation.

Limitations of oncology nursing

The primary objective of nursing is providing noble care to the patients while establishing a healthy

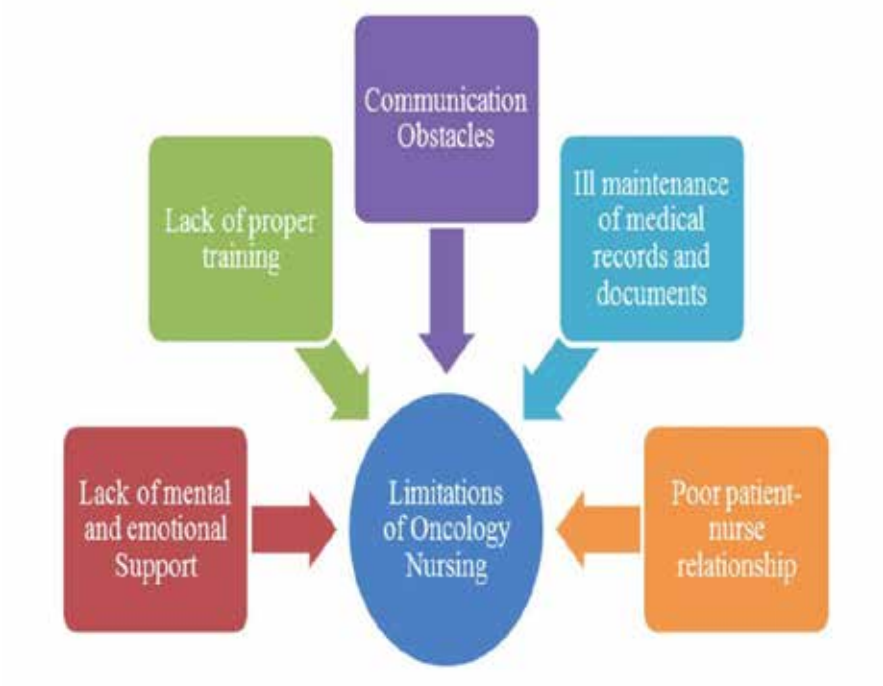

Fig 3: Limitations of oncology nursing.

atmosphere for the patients and it's loved ones[36,61]. Oncology nurses are in proximal contact with the patients' pain, physical and mental health, and also the anxiety and fear of uncertainty of life due to cancer[62]. Although oncology nurses efficiently manage all the facets of cancer illness, still there are some gaps in caregiving procedures that need to be fulfilled. Lack of proper communication is one of the most important factors that affect the patient-nurse relationship (Figure 3)[62-64]. Lack of considerable interaction between the patient and nurse leads to the anonymity of several treatment procedures to the patient. Molina-Mula and Gallo-Estrada[64] investigated the effect of the nurse-patient relationship and its role in decision making during the treatment process. The authors concluded that the use of effective language and communication skills will form a bond of affection between the nurse and the patient. Also, the nurses need to employ new strategies to amplify the role of patients regarding decision making, and rather a mutual decision should be taken with the consent of the healthcare professional, caregiver and the patient.

Also, the incompetence of nurses while dealing with radiation therapies and advanced treatment procedures may lead to a major hindrance in providing cancer care[65]. Sharour[66] conducted a study on the awareness of oncology nurses regarding chemotherapy complications, its management and preventive measures. The author observed that the oncology nurses had satisfactory knowledge about radiation therapy protocols, but incompetence regarding the risk factors and specific treatment procedures was observed[66]. Specialized and trained oncology nurses will ensure better care-giving for cancer patients[41]. Oncology nurses are not trained sufficiently for providing emotional support to the patients in times of pain and suffering[1]. Lack of proper psychosocial coaching results in the patient feeling distressed and abandoned. Li *et al*[67] performed a meta-analysis regarding the role of oncology nurses to increase hope and positivity in cancer patients. The results of the study depicted that the intervention of oncology nurses to inculcate optimism in cancer patients proved very valuable in the treatment process. The absence of proper documentation and irregular maintenance of medical records also forms an obstacle in the treatment of cancer patients. With the increasing number of new cancer cases, it is forming a burden on the global healthcare system[63]. It is becoming imperative to develop patient-related advancements in the field of oncology nursing[68]. With the coming era and the recent pandemic situations, oncology nursing needs to be enriched with advancements and a skilled patient-centric approach.

Future prospects

Oncology nurses are playing a pivotal role in delivering evidence-based care and support to cancer patients. Despite the complex working scenario, oncology nurses have a significant role in the

treatment and recovery of cancer patients. However, certain breakthroughs are needed to be considered for the future establishment of oncology nursing practices. The future developments for oncology nursing should include knowledgeable assessment of the care and the guidance needed by the patients for the foundation of patient-centered care services. Management studies should be designed to develop the abilities of the caregivers to fulfill patients' demands. There are few studies available based on the patient's perception of the quality of the care that is needed. Thus, a detailed follow-up of the patient's perception of the quality of care that is needed should be implemented. With the frequent advancements in the field of medicine, continued education and training is a basic requirement for oncology nurses to ensure enhanced caregiving. Review and revision of the nursing curriculum and development of specialization courses will improve the quality of treatment and care patients receive. Research-based studies should be encouraged for oncology nurses. Psychosocial training of nurses to deal with the stress and anxiety of patients also needs to be considered. Much research is needed for the preparation and analysis of documentation of patients related to the nature of cancer, clinical outputs received involving length of treatment, recovery time, and satisfaction with the care provided. Effective communication practices should also be encouraged for the oncology nurses to form a strong patient-caregiver foundation. Oncology nurses form the central link between the patients, their family members and the doctors, and these future implications will play a directive role in strengthening the patient-caregiver relationship and also help the patient to effectively deal with this traumatizing situation.

CONCLUSION

As the global burden of cancer continues to rise, the role of oncology nurses has also risen. Nurses are expected to pursue a patient-centered approach with multidisciplinary communication as a key filament to it. Co-ordination with care and navigating through cancer illness plays a central role in overcoming health barriers. At the preliminary stage of cancer, patients and family members do not understand the essential role of oncology nurses in caregiving. However, with the progression of the disease, oncology nurses form the heart of the treatment and recovery process. Cancer patients need a comprehensive approach involving physical and psychosocial support, and oncology nurses can efficiently fulfill the support and care needed by the patients. However, certain advancements like the development of better communication skills, overcoming language barriers and understanding the psychological needs of the patient can go a long way. Also, the maintenance of proper documentation and medical records of cancer patients will provide an insight into the symptom management and survival of cancer patients. The present review provides an overview of oncology nursing, its different perspectives, advancements, and the management of cancer patients in times of pandemic.

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Original Article

Single center experience with laparoscopic adrenalectomy on a large clinical series: Lessons learned from 273 cases: A retrospective cohort study

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ABSTRACT

Objectives: We aim to evaluate the risk of laparoscopic adrenalectomy (LA) for large adrenal tumors and the risk of learning curve.
Design: Single centre, retrospective study
Setting: Uludag University, Bursa, Turkey
Subjects: A study in a large patient population (N=273) who underwent LA between 2006 and 2017.
Interventions: The patients were divided into two study groups according to tumour size as estimated by pathologic specimen maximum diameter, Group A (less than 5cm) and group B (larger than 5cm). In addition, to evaluate learning curve of LA, the patients were divided into two groups according to time interval: the first period was 2006 to 2011, and the second period 2012-2017.
Main outcome measures: To evaluate the risk of learning curve and tumour size
Results: There was no statistical difference between the two groups for per-operative and postoperative complications according to tumour size <5 or ≥5 cm, and there was statistical difference between the two groups for operation time, length of hospital stay; but no statistical difference for postoperative complications according to time interval.
Conclusion: LA in large adrenal masses (5 cm or larger) is not associated with longer operative time, increased blood loss and longer hospital stay, without affecting perioperative morbidity, Hence, the size of an adrenal mass should not be the only factor in determining whether LA or not. Besides, learning curve may affect outcomes of LA.

KEY WORDS: adrenal, adrenalectomy, laparoscopy, learning curve, oncology

INTRODUCTION

Since its introduction in 1992, laparoscopic adrenalectomy (LA) has been preferred more owing to shorter hospital stay, less morbidity, quick recovery, less pain and better cosmesis it provides[1]. Over time and with increasing experience, LA has become the procedure of choice for large adrenal tumors. The Society of American Gastrointestinal and Endoscopic Surgeons guidelines have shown that LA can be safely performed for adrenal masses up to 6 cm, except for adrenocortical carcinoma (ACC) or the tumors that show infiltration to surrounding structures on computerized tomography (CT)[2]. Some publications have stated that laparoscopic approaches for ACC can be considered if there are minimal invasive findings[3,4]. This study aimed to evaluate the safety and efficacy of LA for tumors larger than 5 cm by comparing the outcomes. In contrast, performing laparoscopic procedures such as adrenalectomy requires a high level of dexterity and technical skills. Apart from the surgeon's experience, reducing the rate of complications, the rate of conversion, and the operating

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time also depend on several other factors, such as patient characteristics. Therefore, other purposes of this study also aimed to evaluate the learning curve for LA of experienced laparoscopic urologists.

MATERIALS AND METHODS

This study was a single-center retrospective cohort study comprising a large patient population (273 patients) that underwent LA between June 2006 and June 2017 at the Department of Urology, Uludag University Hospital. Data were obtained from the electronic medical records and patient data files. All the patients were preoperatively assessed using a CT or magnetic resonance and by an endocrinologist. In addition, if presence of pheochromocytoma was suspected, a total body metaiodobenzylguanidine scintigraphy was performed on all the patients. Indications of LA in our clinic were: (1) functional adenoma; (2) macronodular hyperplasia (primary hyperaldosteronism, Cushing syndrome, pheochromocytoma); and (3) unconfined masses larger than 4 cm, which were identified as masses with rapid size increase and malignancy during the follow-up. All the patients were closely followed up by an endocrinologist after surgery until they regained normal functioning. All the patients were operated using a standard transperitoneal laparoscopic technique by three surgeons (urologists) who had five years of surgical training. Six patients were excluded from the study because they underwent bilateral adrenalectomies, while the remaining 273 patients were included in the study. The patients were divided into two study groups based on the tumor size, using the postoperative pathological reports. Group A comprised patients with adrenal tumors smaller than 5 cm and group B comprised those with tumors larger than 5 cm, which was considered as the definition of large adrenal tumors. Although radiological reports were available in our records, the evaluation was based on pathological reports because the imaging modalities were applied by different radiologists, which could have resulted in inaccurate tumor size classification and misinterpretation of study data. Operating time was calculated based on the skin-to-skin time. The hospital stay was defined as the duration from the day of surgery until discharge. Long-term complications were assessed by reviewing the outpatient charts. In addition, the study period was divided into two to analyze the learning curve of this procedure for a large volume set: group A/first period (between 2006 and 2011) and group B/second period (between 2012 and 2017). Age, gender, American Society of Anaesthesiology (ASA) score, preoperative

Table 1: Patient and tumour characteristics

Patient and tumour characteristics	Control group (<5 cm)	Large mass group (≥5 cm)	*P*
Gender [n(%)]	182	91	*P*= 0.431
Male	69 (37.9)	39 (42.9)	*P*>0.05
Female	113 (62.1)	52 (57.1)	
Age (years, Mean±S.D)	52.13±11.56(24-82)	48.35±12.68(21-88)	*P*=0.067
Body mass index (BMI) (kg/m^2)[1]	31.03±6.74(182)	30.03±6.75(91)	*P*>0.05
BMI group			
<18.49	3 (42.9)	4 (57.1)	*P*=0.12
18.5 - 24.99	40 (70.3)	17 (29.8)	*P*>0.05
>25	139 (66.5)	91 (33.3)	
American Society of Anaesthesiology score (%)[2]			
1	10 (5.5)	20 (22.0)	
2	165 (90.7)	69 (75.8)	*P*=0.000
3	7 (3.8)	2 (2.2)	*P*<0.05
Tumour size (cm)	28.04±8.92 (Min:10.00-45.00)	59.40±17.39 (Min.32.0-130)	
Tumour side [n (%)]			
Right	89 (48.9)	47 (51.6)	*P*=0.69
Left	93 (51.1)	44 (48.4)	*P*>0.05
Final pathology [n (%)]			
Adrenocortical adenoma	112 (61.5)	29 (31.9)	
Adrenal hyperplasia	2 (1.1)	1 (1.1)	*P*=0.000
Benign pheochromocytoma	17 (9.3)	24 (26.4)	*P*<0.05
Malignant pheochromocytoma	0 (0)	1 (1.1)	
Adrenal metastasis	24 (13.1)	10 (11.0)	
Adrenocortical carcinoma	3 (1.6)	4 (4.39)	
Other [3]	24 (13.1)	22 (24.17)	

[1]The data were not available in 12 patients in the control group, and in 13 patients in the large mass group
[2]The data were not available in 11 patients in the control group and in 7 patients in the large mass group
[3]It includes nodular hyperplasia, para-adrenal, paraganglioma, ganglioneuroma, myelolipoma, oncocytoma and cysts

Table 2: Intraoperative and postoperative outcomes between groups

Intraoperative and postoperative outcomes	Control group (<5 cm) n=182	Large mass group (≥5 cm) n=91	*P*
Operation time (min)	98.35 (30-180)	103.46 (40-210)	*P*>0.05
Convertion to open (n (%))	0 (0)	1 (1.09)	*P*>0.05
Bleeding due to vascular injury	0 (0)	1 (1.09)	
Bleeding due to organ injury	0 (0)	0 (0)	
Adhesions	0 (0)	0 (0)	
Suspected cancer	0 (0)	0 (0)	
Intra-operative complications (n (%))	6 (3.29)	4 (4.39)	*P*>0.05
Bleeding due to vascular injury	4 (2.19)	2 (2.19)	
Bleeding due to organ injury	2 (1.09)	2 (2.19)	
Bowel perforation	0	0	
Post-operative complications (Clavien-Dindo) (n (%)			*P*>0.05
No complications	175 (96.1)	82 (90.1)	
Minor (1-2)	7 (3.84)	6 (6.59)	
Major (3-4)	1 (0.005)	3 (3.29)	
Death (5)	0	0	
Hospital length of stay (days)	2.92 (1-9)	2.98 (1-26)	*P*>0.05
Blood loss (cc)	47.6 (10-300)	51.59 (10-350)	*P*>0.05

diagnosis, tumor size, operating time, conversion to open surgery, morbidity and mortality were assessed for all the study groups. Complications were classified based on the Clavien-Dindo score[5]. The college research review committee revised the paper according to the rule and regulation. Accordingly, the study was approved by the Ethics Committees of Pamukkale University.

Table 3: Association between baseline characteristics and prolonged operative time according to tumour size cut-off point of ≥5 cm

Baseline characteristics	T	DF	Sig2 tailed	*P*
Age	2.257	14 /38/52	0.023	*P*<0.05
Body mass index	1.477	14 /38/52	0.157	*P*>0.05
Study period	0.740	14 /38/52	0.722	*P*>0.05
Gender (male)	1.381	14 /38/52	0.220	*P*>0.05

DF: degrees of freedom; T: T-distribution

Statistical analysis

Demographic and clinical characteristics were analyzed in relation to the tumor size. Quantitative variables were summarized as percentiles, median, mean and compared using the Kruskal-Wallis test. Absolute and percentage frequencies were used to summarize qualitative variables, and Chi-square, ANOVA, Mann-Whitney, and Shapiro-Wilk tests to evaluate differences between variable categories and the different surgical approaches.

Cox regression analysis was performed to evaluate the effect of clinical and demographic characteristics on the median values of operating time, study period and hospital stay (dependent variable). Statistical significance was assessed at a level of probability of 0.05. All statistical analyses were performed using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp. Released 2011. Armonk, NY: IBM Corp.).

RESULTS

This study included 273 patients who underwent LA between the years 2006 and 2017 at the University of Uludag Hospital. Patient and tumor characteristics such as gender, age, body mass index (BMI), ASA score, tumor size, and final pathology features are shown in Table 1, and no significant intergroup differences were observed regarding these characteristics, except for BMI (BMI, *P*=0.12, *P* >0.05). The smallest tumor size was 10 mm, while the largest tumor size was measured as 150 mm. Overall, 113 patients were operated in the first period (group A) and 160 patients in the second period (group B). Intraoperative and postoperative outcomes of the groups are shown in Table 2. Logistic regression analysis could not be performed on these variables because of the low number of postoperative complications. ANOVA *t*-test was performed to evaluate the association between the baseline characteristics and prolonged operative time for large tumors, and only age was found to be a statistically significant factor and not the study period (Table 3). In addition, ANOVA *t*-test was performed to evaluate

Table 4: Association between baseline characteristics and hospital stay according to tumour size cut-off point of ≥5 cm

Characteristics	T	DF	Sig2 tailed	*P*
Age	1.248	6 /48/52	0.30	*P*>0.05
Body mass index	0.483	6 /48/52	0.817	*P*>0.05
Study period	2.715	6 /48/52	0.024	*P*<0.05
Gender (male)	0.435	6 /48/52	0.852	*P*>0.05

DF: degrees of freedom; T: T-distribution

Table 5: Association between peroperative and postoperative changes according to study period

Peroperative and Postoperative changes	First period (2006-2011)	Second period (2012-2017)	*P*
Operation time (min)	110.39 (45-210)	92.75 (30-205)	*P*<0.001
Post-operative complications (Clavien-Dindo) (n (%)			*P*>0.05
No complications	105 (92.9)	151 (94.3)	
Minor (1-2)	8 (7.07)	6 (3.7)	
Major (3-4)	0 (0.005)	3 (1.87)	
Death (5)	0	0	
Hospital length of stay (days)	3.54 (1-9)	2.52 (1-26)	*P*<0.001

the association between baseline characteristics and hospital stay for large tumors, and hospital stay was found to be shorter in the second period of the learning curve (Table 4). We compared the first and second periods, group A (between 2006 and 2011) and group B (between 2012 and 2017), respectively. Operation time and hospital stay were found to be significantly shorter in group B, but no statistically significant difference was observed in terms of complications, such as blood loss (Table 5). No significant intergroup differences were observed regarding patient and tumor characteristics.

DISCUSSION

Are large adrenal tumors an obstacle to laparoscopy?

Although LA has increasingly become widespread, its negative results owing to the increase in the size of the tumor make the limit of laparoscopy a controversial topic. As the size of adrenal masses increases, the study area becomes more limited and anatomy becomes more complex, which may lead to increased risk of blood loss, vascular injury, organ damage and prolonged hospital stay. In addition, there is the risk of invasion and spread owing to the risk of cancer that cannot be diagnosed through radiological imaging. Several previous studies have defined the size of the large mass between 3.5 cm and 8 cm, and we identified the size of the largest mass as 5 cm in our study[6]. The literature reported that the large adrenal masses (> 6 cm) were associated with duration of surgery and with an increased risk of intraoperative incident. Many authors reported lesion diameter over 5-6 cm as independent predictive factors for conversion[7,8]. The literature reveals that the rate of complications, conversion rate and hospital stay increase with the increase in tumor size. Besides, the mean operative time can also get hampered with increase in the tumor size[9]. However, contrary to the literature, our data revealed no significant difference regarding the outcomes of LA, such as hospital stay, operation time, preoperative and postoperative complications, for patients with large tumors compared with those with smaller tumors[10]. Possibly, as the surgeons gained experience, especially in the second period of the learning curve, they began to effortlessly operate on larger adrenal tumors. ANOVA *t*-test was used to evaluate the association between the baseline characteristics and prolonged operative time for larger tumors, and only age was statistically significant, but not the study period. As a result, the tumor size alone is not an absolute contraindication to LA alone. Correct preoperative patients selection and surgical technique could minimize this risk.

Should tumor size affect the surgical approach because of the risk of malignancy?

Despite advances in radiological imaging, the risk of malignancy in adrenal masses cannot be determined before surgery. However, some of the radiological imaging techniques have been allowed to underestimate benign tumors, that is, poor lipid nonfunctioning adenomas with atypical features on CT scan. Therefore, the main challenge in the management of adrenal incidentalomas is the selection of appropriate cases by distinguishing between malignant lesions and non-malignant lesions. The risk of adrenocortical carcinoma increases with tumour size and becomes significant for lesions over 4 cm in diameter, as previously reported. This is why adrenalectomy is recommended for all adrenal lesions larger than 4 cm with atypical biochemical or imaging features[11,12]. Suspected primary malignant adrenal tumors are considered as contraindication to laparoscopic approach because of the poor oncological outcome and the high risk of peritoneal dissemination of primary adrenal cancer[13-15]. The National Institute of Health consensus statement reported that the ACC risk was 2% in adrenal masses below 40 mm, 6% between 41 and 60 mm, and 25% above 60 mm[16]. Notably, there are several reasons to avoid a laparoscopic approach in case of suspected cancer, such as peritoneal tumor dissemination and local recurrence because of incomplete removal of the primary malignant lesion[1]. In our study, ACC was observed in seven patients, three of them were in group A and four in group B. Contrary to the literature, we believe that open surgery should not be preferred depending on the tumor size because even though the tumor size is a useful index,

it is insufficient for decision making and should not be the only predictor of malignancy[7].

How important is the learning curve?

Laparoscopic surgery was also more difficult to learn than open surgery because it required different psychomotor skills. This study comprised 273 patients who underwent LA over a period of 12 years. This study is one of the largest cohorts in which the learning curve of LA was evaluated. Operating times of LA significantly decreased in the second period, which is comparable to the results reported in the literature[17,18]. With respect to the operating times and hospital stay, the learning curve in this study shows a similar pattern to that reported in the literature. Barczynski *et al* showed that operating times which were described for the first period were much longer (110 min after the introduction, 75 min after 20 patients, and 65 min after 40 patients)[19]. Cabalag *et al* showed that a learning curve of 10 patients in posterior retroperitoneoscopic adrenalectomy was shorter (110-60 min) after an intensive training course with an expert[17]. ANOVA *t*-test was used to evaluate the association between baseline characteristics and hospital stay for larger tumors, and hospital stay was shorter in the second period of the learning curve. However, because of the small number of complications, advanced analysis techniques could not be applied to determine which factors were effective.

Strengths and limitations of the study

Nonetheless, this study has some limitations. It is limited by its retrospective nature, and three surgeons having a similar level of skill performed the surgery in a high-volume center. Moreover, all the baseline characteristics were comparable, except for the parameter of ASA, which did not seem to influence the outcomes in univariate analysis.

CONCLUSION

The size of an adrenal mass should not be the only factor used to determine malignancy. Therefore, the laparoscopic technique is safe and feasible for large adrenal tumors regardless of the suspicion of malignancy. Moreover, LA can be performed by general surgeons with experience in laparoscopic techniques after an intensive training course with an expert.

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Original Article

Could Mean Platelet Volume and Red Cell Distribution Width be related with the progression and severity of gestational hypertensive disorders?

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ABSTRACT

Objective: To evaluate the correlation between thrombocyte indices, red cell distribution width and the progression of gestational hypertensive disorders
Design: Retrospective and cross-sectional study
Setting: Abant İzzet Baysal University Hospital and Bolu State Hospital, Bolu, Turkey
Subjects: Five hundred and one pregnant women were included in this study, which included 115 severe-preeclampsia (PE), 155 mild-PE, 105 gestational hypertension (GHT) and 126 healthy pregnant women (control group).
Intervention: 2 ml blood samples were taken by using 19-G needles. Hematological parameters values were studied using a blood count analyzer.
Main outcome measure(s): Comparison of hematological parameters before and after diagnosis of GHT, mild-PE and severe-PE.
Results: Mean platelet volume (MPV) was found significantly higher in the severe-PE group than GHT, mild-PE and control groups (P=0.005). MPV was higher in the severe-PE group concerning mild-PE and GHT groups (P=0.043, P=0.014 respectively), and it was unchanged between mild-PE, GHT and control groups. Platelet distribution width, red cell distribution width (RDW), plateletcrit, neutrophil/lymphocyte ratio and platelet/lymphocyte ratio were found unchanged among four groups. Platelet count (PC) was significantly lower in the severe-PE group than mild-PE, GHT and control groups (P=0.021). PC was not found to be significantly different among GHT, mild-PE and control groups. Hematological parameters before and after diagnosis of GHT, mild-PE and severe-PE were compared and RDW was significantly higher after progression of the disease (P=0.009, P=0.006, P=0.0002 respectively).
Conclusions: Elevation in RDW levels is associated with a progression of GHT, mild PE and severe PE. MPV levels are found higher and PC levels are found lower in severe-PE. However, there was no significant change observed according to the severity of gestational hypertensive disorders.

KEY WORDS: hypertension, mean platelet volume, platelet count, platelet distribution width, preeclampsia

INTRODUCTION

Hypertension is the most common medical problem seen during pregnancy, complicating 2-4% of pregnancies. Hypertensive disorders during pregnancy are classified into four categories, as recommended by the National High Blood Pressure Education Program Working Group on high blood pressure in pregnancy: 1) chronic hypertension; 2) preeclampsia-eclampsia; 3) preeclampsia superimposed on chronic hypertension; and 4) gestational hypertension[1]. Gestational hypertension is the new onset of hypertension after 20 weeks of gestation. Approximately 50% of women diagnosed with gestational hypertension between 24 and 35 weeks develop preeclampsia (PE). PE is characterized by hypertension and proteinuria that begins after the

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20th week of pregnancy. It is classified as mild- PE and severe-PE forms[2]. Severe-PE may complicate with eclampsia, hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome, abruptio placentae, and may lead to maternal morbidity and mortality[3]. The etiology and pathogenesis of PE are still not fully understood and is considered multifactorial. It is thought that the most important factor is vascular endothelial damage and consequently a systemical inflammatory reaction and multiorgan response[4]. Activation of thrombocytes in preeclamptic women was shown as elevated plasma levels and augmented thrombocyte surface activity of thrombocyte activating markers (β-thromboglobulin and platelet factor-4)[5,6]. There are some studies involving the relations among hematological parameters with hypertension and PE. It is shown that platelet indices may be useful in determining the severity of preeclampsia and predicting its progression[7-14]. Red cell distribution width (RDW) is a hematological index that shows the erythrocyte volume differentiation. Elevated RDW values are usually related to inflammatory response, and for some studies, emphasized in conditions such as increased cardiac disease risks, hypertension and PE[15-17].

This study aimed to investigate whether there is a relationship between the progression and severity of gestational hypertensive disorders and hematological parameters.

MATERIALS AND METHODS

This research is a retrospective and cross-sectional study. After the approval of the local institutional board was obtained, the research was conducted by evaluation of medical records of inpatient and outpatient obstetrical patients in Abant Izzet Baysal University Hospital Bolu, between January 2009 and November 2018.

Criteria in recruitment to the study

The patients were identified as with gestational hypertension (GHT), mild-PE and severe-PE, according to the criteria of the American College of Obstetrics and Gynecology Practice Bulletin[18].

GHT is identified as the progression of hypertension that is defined as blood pressure at a level of ≥140/90 mmHg on two occasions which are measured at least six hours apart beyond the 20th week of pregnancy with no known history of the hypertensive disorder.

Pregnant women at 20th week or later with blood pressure ≥140/90 mmHg and who additionally have a 24-hour proteinuria value of ≥0.3gr are defined as mild-PE. The preeclamptic patients complicated with blood pressure 160/110 mmHg or higher, proteinuria with 2gr/24 hours or more, presence of severe headache and upper abdominal pain, pulmonary edema, oliguria, and intrauterine growth restriction were diagnosed as severe-PE. The control group included healthy pregnant women in the third trimester. Patients meeting these criteria were selected, and their medical records were sampled from the first identification of their pregnancy and live birth. Patients complicated with diabetes mellitus, chronic hypertension, chronic renal failure, hepatitis, HELLP syndrome, hematological co-morbidities, anti-coagulant drug use, smoking, anemia and intrauterine fetal demise were excluded from the study.

Patients enrolled in the study were classified into four groups as GHT, mild-PE, severe-PE and control. Hematological parameters of 2-4 weeks before the diagnosis and at the time of the diagnosis were compared in these four groups. All of these parameters were sampled within the third trimester of pregnancies.

Blood sampling and laboratory process

Blood samples of 2 ml were taken into pink sampling tubes containing 2.0 mg/ml EDTA-2K (ethylenediaminetetraacetic acid, dipotassium salt, dihydrate) by using 19-G needles. After ten minutes of centrifuging; hemoglobin (Hb), platelet count (PC), lymphocytes, neutrophils, mean platelet volume (MPV), RDW, platelet distribution width (PDW) and plateletcrit (PCT) studied by using Cell Dyn 3700 (Abbott, IL, USA) blood count analyzer. Neutrophil lymphocyte ratio (NLR) is calculated by division of neutrophils to lymphocytes, and platelet lymphocyte ratio (PLR) is calculated by division of platelet count to lymphocytes.

Assessment of data and statistical analysis

Statistical Package for Social Sciences (SPSS) version 15.0 (SPSS Inc., USA) is used for statistical analysis. Kolmogorov-Smirnov test is performed for the distribution of compliance before the assessment. When comparing the groups, the analysis of variance test was performed in normally distributed data, and the Kruskal-Wallis test was chosen for the remaining. The homogeneity of variants is tested by Levene's test (homogeneity of variances). In non-homogenous variants, the Scheffe test (post-hoc test) is performed to disclose the different features of the groups. For the data of the features of early and late results of the patients before and after the disorder, in uniform Distribution Paired Samples test is used and for the remaining results, the Wilcoxon test was performed. Test results were assessed within a 95% confidence

Table 1: Maternal demographical and clinical features of the patients among the groups.

Features	GHT (n=105)	Mild-PE (n=155)	Severe-PE (n=115)	Control (n=126)	*P*
Age (year)	28.51±5.52	28.8±5.9	29.9±6.0	27.68±5.93	0.520
Weeks at delivery	37.62±1.53	37.5±1.3	32.6±2.5	36.96±2.95	<0.001
No. of pregnancies	1.83±0.82	1.8±0.8	1.7±0.7	2.34±1.29	0.510
Systolic BP (mmHg)	145.81±8.72	164.83±13.8	164.7±8.1	112.76±9.76	< 0.001
Diastolic BP(mmHg)	91.0±3.83	93.2±4.8	112.8±4.9	72.87±7.56	<0.001
24 hours Urinary protein(g)	0.0±0.0	1.0±0.6	3.8±1.5	0.0±0.0	<0.001

Data are given as mean ± standard deviation. *P* <0.05 was considered significant.
BP: blood pressure; GHT: gestational hypertension; mild-PE: mild preeclampsia; severe-PE: severe preeclampsia

interval, and *P* <0.05 was considered statistically significant.

RESULTS

Five hundred and one pregnant women were recruited into this study. This study was conducted with 115 severe-PE, 155 with mild-PE, 105 with GHT and 126 healthy pregnant women.

Demographical features of the patients

The demographical and clinical parameters of the patients are shown in Table 1. There were no significant differences in age, number of pregnancies and systolic blood pressure measurements among the first three groups (respectively *P*=0.52, *P*=0.51, *P*=0.40). Systolic blood pressure was significantly lower in the control group than in GHT, mild-PE and severe-PE groups (*P* <0.001). Diastolic blood pressure and 24 hour urinary protein levels were found to be significantly higher, and weeks of delivery were found significantly lower in the severe-PE group than mild-PE, GHT and control groups (respectively *P* <0.001, *P* <0.001, *P* <0.001).

A comparison of the hematological parameters after the diagnosis of severe-PE, mild-PE, GHT and the control groups, are shown in Table 2. MPV was found significantly higher in the severe-PE group than GHT, mild-PE and control groups (*P*=0.005). MPV was higher in the severe-PE subgroup concerning mild-PE and GHT subgroups (*P*=0.043, *P*=0.014 respectively), and it was unchanged between mild-PE, GHT and control groups (*P*=0.651). PDW, RDW, PCT, NLR, Hb and PLR were found unchanged among four groups (*P*=0.66, *P*=0.153, *P*=0.908, *P*=0.137, *P*=0.350, *P*=0.528 respectively). PC was significantly lower in the severe-PE group than mild-PE, GHT and control groups (*P*=0.021). PC was not found to have a significant difference among GHT, mild-PE and control groups (*P*=0.651).

A comparison of the hematological parameters before the diagnosis of severe-PE, mild-PE, GHT and the control groups are shown in Table 3. MPV, RDW, PDW, PCT, NLR, PC, PLR and Hb parameters were not found to be significantly different among four groups prior to diagnoses of severe-PE, mild-PE, GHT and control groups (*P*=0.60, *P*=0.153, *P*=0.388, *P*=0.908, *P*=0.443, *P*=0.154, *P*=0.103, *P*=0.350 respectively).

Changes in hematological parameters before and after the onset of the disorder

Severe-PE group

In this group, the mean age was 29.9±6.0 years, the mean number of pregnancies was 1.7±0.7, and the mean number of weeks at delivery was 32.6±2.5 weeks. Hematological parameters are shown before and after

Table 2: Comparison of hematological parameters in severe-PE, mild-PE, GHT and control groups

Hematologic parameters	Severe-PE (n=115)	Mild-PE (n=155)	GHT (n=105)	Control (n=126)	*P*
MPV	9.42±1.57	8.90± 1.56	8.57±1.26	8.87±2.19	0.005
RDW	16.63±1.81	16.16±1.89	16.13±1.65	16.17±1.88	0.153
PDW	17.76±2.15	17.17±1.90	17.60±1.66	17.39±1.45	0.66
PCT	0.203±0.10	0.203±0.057	0.208±0.05	0.204±0.07	0.108
NLR	8.19±12.04	5.61±7.03	5.48±3.29	5.17±3.65	0.137
Hb	12.16±1.60	12.11±1.48	12.38±1.52	12.01±1.33	0.350
PC	216.88±88.49	236.95±70.86	238.55±58.51	247.56±65.74	0.021
PLR	129.45±75.27	143.19± 62.58	151.87±134.71	153.34±105.54	0.528

Data are given as mean ± standard deviation. *P* <0.05 was considered significant.
GHT: gestational hypertension; mild-PE: mild preeclampsia; severe-PE: severe preeclampsia; MPV: mean platelet volume; RDW: red cell distribution width; PDW: platelet distribution width; PCT: plateletcrit; NLR: neutrophile lymphocytes ratio; Hb: hemoglobin; PC: platelet count; PLR: platelet lymphocytes ratio

Table 3: Hematological parameters of groups before the diagnoses of severe-PE, mild-PE, GHT and control groups.

Hematologic parameters	Severe-PE (n=115)	Mild-PE (n=155)	GHT (n=105)	Control (n=126)	*P*
MPV	9.12±1.49	8.92±1.56	8.51±1.40	8.87±2.19	0.060
RDW	16.20±1.82	16.05±1.86	15.61±1.59	16.17±1.88	0.153
PDW	17.44±2.07	17.21±2.17	17.66±1.58	17.39±1.45	0.388
PCT	0.208±0.07	0.204±0.05	0.206±0.05	0.204±0.07	0.908
NLR	9.68±48.87	4.59±3.31	5.28±4.97	5.17±3.65	0.443
Hb	12.36±1.38	12.10±1.40	12.13±1.40	12.01±1.33	0.350
PC	234.36±66.36	231.71±64.50	251.57±58.36	247.56±65.74	0.154
PLR	129.24±49.60	131.03±74.81	136.67±59.81	153.34±105.54	0.103

Data are given as mean ± standard deviation. *P* <0.05 was considered significant.
GHT: gestational hypertension; mild-PE: mild preeclampsia; severe-PE: severe preeclampsia; MPV: mean platelet volume; RDW: red cell distribution width; PDW: platelet distribution width; PCT: plateletcrit; NLR: neutrophile lymphocytes ratio; Hb: hemoglobin; PC: platelet count; PLR: platelet lymphocytes ratio

the progression to severe-PE, respectively, in Table 4. After the progression to severe-PE, MPV, RDW and PDW were found to be significantly higher (*P*=0.005, *P*=0.0002, *P*=0.032 respectively). NLR, PC and PCT were significantly lower after progression to severe-PE (*P*=0.007, *P*=0.000, *P*=0.018 respectively). The change in PLR and Hb values were found to be insignificant before and after severe-PE (P=0.136, P=0.550 respectively).

Table 4: Hematological parameters before and after progression to severe-PE

Hematologic parameters	Before severe-PE	After severe-PE	*P*
MPV	9.12±1.49	9.42±1.57	0.005
RDW	16.20±1.82	16.63±1.81	0.0002
PDW	17.44±2.07	17.76±2.15	0.032
PCT	0.208±0.07	0.203±0.10	0.018
NLR	9.68±48.87	8.19±12.04	0.007
PC	234.36±66.36	216.88±88.49	<0.001
PLR	129.24±49.60	129.45±75.27	0.136
Hb	12.36±1.38	12.16±1.60	0.550

Data are given as mean ± standard deviation. *P* <0.05 was considered significant.
GHT: gestational hypertension; mild-PE: mild preeclampsia; severe-PE: severe preeclampsia; MPV: mean platelet volume; RDW: red cell distribution width; PDW: platelet distribution width; PCT: plateletcrit; NLR: neutrophile lymphocytes ratio; Hb: hemoglobin; PC: platelet count; PLR: platelet lymphocytes ratio

Mild-PE group

In this group, the mean age was 28.51±5.52 years, the mean number of pregnancies was 1.8±0.8, and the mean number of weeks at delivery was 37.5±1.3 weeks. Hematological parameters before and after the diagnosis of mild-PE are shown in Table 5. Before and after the mild-PE threshold, MPV, PDW, PCT, NLR, PLR, PC and Hb findings were found to be unchanged significantly (*P*=0.879, *P*=0.086, *P*=0.566, *P*=0.305, *P*=0.772, *P*=0.245, *P*=0.550 respectively). RDW levels were observed as significantly elevated after the diagnosis of mild-PE (*P*=0.006).

Gestational hypertension group

In this group, the mean age was 29.9±6.0 years, the mean number of pregnancies was 1.83±0.82, and the mean number of weeks at delivery was 37.62±1.53 weeks. A comparison of hematological parameters before and after the diagnosis of GHT is shown in Table 6. MPV, PDW, PCT, NLR, Hb and PLR were found to be unchanged significantly (*P*=0.269, *P*=0.410, *P*=0.089, *P*=0.197, *P*=0.350, *P*=0.694 respectively). RDW and PC were found significantly changed before and after the diagnosis of GHT (*P*=0.009, *P*=0.003 respectively). After the GHT diagnosis, the mean RDW was significantly elevated, and PC significantly decreased.

DISCUSSION

In this study, MPV was significantly higher in the severe-PE group than mild-PE, GHT and control groups. There was no significant difference found concerning MPV among GHT, mild-PE and control groups. PC was significantly lower in the

Table 5: Hematological parameters before and after the diagnosis of mild-PE

Hematologic parameters	Before mild-PE	After mild-PE	*P*
MPV	8.92±1.56	8.91±1.51	0.879
RDW	16.05±1.86	16.19±1.99	0.006
PDW	17.21±2.17	17.17±1.91	0.0866
PCT	0.204±0.05	0.202±0.058	0.566
N/L	4.59±3.31	5.55±7.03	0.305
PLT	236.71±64.64	230.95±70.86	0.245
PLT/L	131.03±74.81	145.19±162.58	0.772
Hb	12.01±1.29	12.10±1.40	0.550

Data are given as mean ± standard deviation. *P* <0.05 was considered significant.
mild-PE: mild preeclampsia; severe-PE: severe preeclampsia; MPV: mean platelet volume; RDW: red cell distribution width; PDW: platelet distribution width; PCT: plateletcrit; NLR: neutrophile lymphocytes ratio; Hb: hemoglobin; PC: platelet count; PLR: platelet lymphocytes ratio

Table 6: Comparison of hematological parameters before and after GHT

Hematologic parameters	Before GHT	After GHT	*P*
MPV	8.51±1.40	8.67±1.23	0.269
RDW	15.61±1.59	16.10±1.69	0.009
PDW	17.66±1.58	17.70±1.56	0.410
PCT	0.206±0.05	0.218±0.06	0.089
NLR	5.28±4.97	5.38±3.24	0.197
PC	251.57±58.36	239.55±55.52	0.003
PLR	152.87±133.78	136.67±59.81	0.694
Hb	12.13±1.40	12.18±1.42	0.350

Data are given as mean ± standard deviation. $P < 0.05$ was considered significant.
mild-PE: mild preeclampsia; severe-PE: severe preeclampsia; MPV: mean platelet volume; RDW: red cell distribution width; PDW: platelet distribution width; PCT: plateletcrit; NLR: neutrophile lymphocytes ratio; Hb: hemoglobin; PC: platelet count; PLR: platelet lymphocytes ratio

severe-PE group than mild-PE, GHT and control groups. However, there is no significant difference concerning PC among GHT, mild-PE and control groups. When hematological parameters were evaluated before and after the disease, RDW elevation was found to accompany the progression of GHT, mild PE and severe PE.

In some studies, MPV and NLR were found to be higher in preeclamptic women compared to the control group. Bellos *et al*[8] examined the data of 50 studies in their meta-analysis and reported that MPV was higher in preeclamptic women than healthy pregnant women. Monteith *et al*[9] reviewed 9000 deliveries and found that at the time of diagnosis and late in the third trimester, MPV levels significantly increased than normotensive control patients. Yucel *et al*[16] studied 219 patients with groups of non-hypertensive pregnants, mild-PE and severe-PE. They found insignificant NLR, higher RDW and MPV in severe-PE with contrast to the non-hypertensive group and reported that MPV and PCT may be markers for progression to severe-PE. In their study, compared to the difference at MPV, PCT and RDW levels between non-hypertensive patients and severe-PE, their findings were lacking the correlation with the severity and progression of the disorder. Serin *et al*[17] has shown a relation between NLR and the severity of hypertensive disorders. Kirbas *et al*[19] reported that NLR was predictive at PE progression and found a correlation between first trimester parameters and PE severity. Akil *et al*[20] mentioned the severity of hypertension in preeclampsia is related to decreased platelet count and elevated MPV and NLR, and these may be independent indicators in establishing the severity of the disorder. In these studies, because of the comparison of the severe preeclampsia group and the healthy patient group, there are deficiencies in predicting preeclampsia and showing its relationship with the severity of preeclampsia.

Kirbas *et al* found PLR was slightly lower but not significantly lower in mild-PE patients than the control group[19], and was higher in severe-PE than in mild-PE and the control group. However, their findings are those detected in the first trimester and there could be changes in hematological parameters according to the trimesters of pregnancy. Yucel *et al* found lower PLR and PCT in severe-PE patients[16]. In our study, we found no correlation between PLR, PCT and severity of the disorder.

RDW is a hematological index thought to be an indicator of inflammatory response due to systemic vascular dysfunction in PE patients. Kurt *et al*[15] found higher RDW in severe-PE than in mild-PE and healthy pregnant women and elevated RDW in the existence and severity of PE. Abdullahi *et al*[21] found no correlation between PE and RDW value in Sudanese pregnant women. Sen-Yu *et al*[22] studied RDW in the second trimester and found a relation between higher RDW with the progression of PE in the third trimester. Similarly, we found that RDW elevation accompanied the progress of GHT, mild PE and severe PE.

MPV and PCT are indicators of thrombocyte volumes. It is not well-known what induces thrombocytes in preeclampsia, but that larger platelet volumes are seen with the level of hypertension[23]. However, this value is not a good predictor for PE progression. Han *et al*[12] studied MPV in the first and the third trimesters and speculated progression to severe-PE with the first trimester MPV values. Karateke *et al*[14] found lower PCT in severe-PE patients. Yang *et al*[24] found elevated PDW in severe-PE patients, and that may be a marker at determining the severity of PE. In our study, PDW is slightly but insignificantly elevated among the groups. AlSheeha *et al* found a relation between PE progression and lower PC and higher PC/MPV ratio[25]. We also found a lower platelet count in severe-PE patients.

In summary, the use of hematological parameters to determine the existence and severity of PE is controversial in the literature. This study is more comprehensive than other studies because it includes hematologic parameters before and after the onset of the diagnosis and making comparisons within and among the GHT, mild-PE, severe-PE and control groups. The fact that RDW is associated with the progression of the disease shows us that it could be used in the prediction and follow-up of the progress of gestational hypertensive disorders.

CONCLUSION

MPV levels are found to be higher and PC levels are found to be lower in severe preeclampsia among patients with gestational hypertensive diseases. However, there was no significant change observed according to the severity of gestational hypertensive disorders. Elevation in RDW levels was found to be associated with GHT, mild PE and severe PE progression. Further studies are needed to confirm these results.

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Original Article

Correlation of immunohistochemistry-equivocal (2+) human epidermal growth factor receptor 2 (HER2) with fluorescence in situ hybridization (FISH) gene status in invasive breast cancer: Is FISH necessary for all HER2 equivocal breast cancer cases?

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ABSTRACT

Objectives: Identifying human epidermal growth factor receptor 2 (HER2) gene amplification status is mandatory in patients with breast cancer for predictive and prognostic purposes. It can be determined by different techniques including fluorescence in situ hybridization (FISH). This study aimed to identify the final gene amplification status by FISH for HER2 equivocal cases using immunohistochemistry (IHC).
Design: Retrospective study
Setting: Faculty of Pathology, King Saud University Medical Center, King Saud University, Riyadh, Saudi Arabia
Subjects: All patients with suspected breast cancer and HER2 equivocal (2+) status examined using IHC between May 2017 and August 2019 were selected and reviewed.
Interventions: FISH was performed to determine the amplification status of the HER2 gene.
Main outcome measure: Amplification of the HER2 gene using FISH
Results: The study identified 300 patients with invasive breast cancer, of whom 57 had HER2 equivocal (2+) status. FISH revealed that multiple copies of the HER2 gene were not detected in 52 patients (91.2%), while the remaining five (8.8%) had an amplified gene status.
Conclusions: Even though nine of ten patients with breast cancer of equivocal HER2 identified with IHC had non-amplification of the HER2 gene, FISH must be performed on all the equivocal HER2 IHC cases despite the difficulties and cost associated with conducting the technique. The need to determine HER2 by FISH in HER2–IHC cases with a score of 2 is well recognized by pathologists and oncologists who diagnose and treat patients with breast cancer.

KEY WORDS: adjuvant therapy, breast cancer, gene amplification, risk factors

INTRODUCTION

Currently, breast cancer is considered one of the major causes of death globally. The increasing incidence of breast cancer and its associated poor prognosis demand urgent and effective therapy, particularly targeted therapy[1]. The prognostic factors of breast cancer include tumor size, mitotic activity, lymph node status, level of lymphatic and vascular invasion, histological form, tumor classification, and estrogen receptor (ER) and progesterone receptor (PR) status[2].

The overexpression and development of multiple copies of the human epidermal growth factor receptor 2 (HER2) gene are correlated with the rapid and exponential increase in the incidence of the disease, increased metastatic potential, and aversion to selective ER modulation. Effective treatment modalities for patients with breast cancer are increasing, particularly

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after the exploration and identification of therapies directed at the HER2 gene[3].

Specific tests must be performed on the tumor cells before being qualified for anti-HER2 therapy. Immunohistochemistry (IHC) analysis is a reliable and cost-effective preliminary test to identify HER2 protein expression[4]. Four different score ratings (range: 0 to +3), based on the cumulative overall score of positive tumor cells and bleaching intensity, form the basis of analyzing the results of HER2-IHC. The United States Food and Drug Administration suggests that the ratings of HER2-IHC that range between 0 and +1 be considered as HER2 negative, while those with HER2 ratings of +3 be considered as HER2 positive[5].

Nevertheless, HER2 equivocal invasive breast cancers are those with a ranking HER2 score of +2. Unfortunately, patients with this status need further evaluation to ascertain their HER2 gene status. This evaluation can be performed with different techniques including fluorescence in situ hybridization (FISH), silver deoxyribonucleic acid in situ hybridization, and chromogenic in situ hybridization (CISH). FISH is a verified standard technique to determine HER2 gene status. Despite the need for a qualified operator, lengthy techniques, unique tools, and difficulty in preserving slides for subsequent critiques, FISH is more precise and reliable than IHC. These extensive requisites for conducting the test are also the known disadvantages of FISH[4]. However, this study was conducted to determine and correlate the HER2 gene status of invasive cases of breast cancer associated with a rating of (2+) on IHC. To examine this correlation, FISH was performed using several clinicopathological factors such as age of the patient and type of breast cancer.

SUBJECTS AND METHODS

This retrospective research was carried out by examining the medicals profiles of all patients who had invasive breast cancer and a HER2 equivocal (2+) status determined using IHC in Riyadh, Saudi Arabia, at the King Saud University Medical Centre between May 2017 and August 2019. Ethical approval was received from the Institutional Review Board (E-19-4510). This meant that all details from medical reports were handled anonymously and for experimental purposes alone. Owing to the retrospective nature of this study, informed consent was not sought from the patients. A total of 300 cases of breast cancer were identified. The data collected were reviewed by a breast pathologist to determine the IHC status of HER2 (negative, equivocal or positive). The HER2 IHC status of the cases was as follows: 34 HER2 positive, 57 equivocal and 209 HER2 negative. Immunoreactivity for all cases was analyzed using the Ventana Benchmark XT, which was an automated computerized system (Ventana Media System. Inc., F. Hoffmann-la Roche Ltd, Basel, Switzerland) while utilizing the Ultra View Universal DAB Detection Kit (Ventana Medical System, Inc., F. Hoffmann-la Roche Ltd, Basel, Switzerland). Four-micrometer-thick tissue sections and HER2 rabbit monoclonal primary antibodies (clove 4B5) were used.

The staining protocols adopted for HER2 conformed to the generic bleaching guidelines of the VENTANA-BenchMark-XT computer-controlled integrated framework. The immunoreactivity requirement for incorporation of all instances in the sample (HER2 level 2+, inaccurate) was poor-to-average full radial membranous staining in greater than 10% of intrusive cancer cells. All equivocal cases were sent to an accredited private laboratory, wherein they were analyzed with a PathVysion HER-2 DNA Probe Kit from Abbott Molecular Inc. to determine the HER2 gene amplification status by FISH studies: amplified or non-amplified.

Data were recorded and computed using IBM SPSS software version 23. Categorical data were calculated as descriptive statistics, while continuous data were calculated as mean and standard deviation. Independent Student t-tests were performed to assess the discrepancies in mean age among patients with an amplified and non-amplified HER2 gene status. For the results of this study to be significant, we considered a *P*-value of less than or equal to 0.05 to indicate statistical significance.

RESULTS

Of the 300 patients with invasive breast cancer, 57 (19.0%) were HER2 equivocal (+2). The mean patient age was 53.4±11.8 years (range: 30-80 years), with 27 (48%) younger than 50 years and 30 patients (52%) older than 50 years of age. The majority of patients (55 out of 57, 96.5%) had invasive ductal carcinoma not otherwise specified, and the remaining two patients (3.5%) had invasive lobular carcinoma (Table 1).

The HER2 gene was not amplified in 52 patients (91.2%) tested with FISH. Five patients (8.8%) had an amplified gene status. All amplified cases were invasive ductal carcinoma, not otherwise specified. There was no significant difference in mean age between patients with and without an amplified gene status (46.0±11.0 years vs. 54.15±11.7 years, *P*=0.141). There were no other substantial differences among patients with and without an amplified gene status. All amplified cases had a Ki67 proliferation index of 20% or more. All patients showed positive ER status, and four out of five (80%) patients showed positive PR status (ER: 6.60±2.07 vs. 6.62±2.58, *P*=0.990; PR: 4.00±3.39 vs. 4.98±3.07, *P*=0.501; Ki67: 35.00±15.81 vs. 33.62±27.78, *P*=0.913). There were no significant gene

Table 1: Demographic characteristics of the 57 patients with HER2 equivocal invasive breast cancer

Parameters	Mean and SD	n (%)	*P*-value
Age in years	53.4±11.8		
Type of breast cancer			
Invasive ductal not otherwise specified		55 (96.5)	
Invasive lobular carcinoma		2 (3.5)	
Receptors			
ER			*P*=0.990
ER (with amplified HER2 gene)	6.60±2.07		
ER (with non-amplified HER2 gene)	6.62±2.58		
PR			*P*=0.501
PR (with amplified HER2 gene)	4.00±3.39		
PR (with non-amplified HER2 gene)	4.98±3.07		
Proliferation index			
Ki67			*P*=0.913
Ki67 (with amplified HER2 gene)	35.00±15.81		
Ki67 (with non-amplified HER2 gene)	33.62±27.78		
FISH			
Amplified HER2 gene		5 (8.8)	
Non-amplified HER2 gene		52 (91.2)	

FISH: fluorescence in situ hybridization; HER2: human epidermal growth factor receptor 2; ER: estrogen receptor; PR: progesterone receptor; SD: Standard deviation

amplification associations with ER (r=-0.002, *P*=0.990), PR (r=-0.091, *P*=0.501), Ki67 (r=0.015, *P*=0.913), or tumor type (*P*=0.724).

DISCUSSION

Accurate assessment of the HER2 status is crucial for developing a strategic treatment plan to achieve the best outcome in patients with breast carcinoma[6]. Findings from a study conducted in Saudi Arabia showed that HER2-positive patients accounted for 12.3% of all patients with breast cancer, with subtype luminal A in 58.5% cases, luminal B in 14.5%, and triple-negative status in 14.8% cases[7]. This value was comparable with the percentage of triple-negative breast cancer cases (12.2%) from a study conducted in Kuwait[8]. Generally, IHC is adequate for the assessment of HER2. However, patients with 2+ (equivocal) tumors would gain from FISH, as it can appropriately evaluate HER2 status and circumvent incorrect prognosis and inappropriate management[9].

FISH is a practical, reliable, and measurable approach used to detect HER2 amplification in the nucleus of cancer cells. The limitations of this technique are the expense (10 times that of IHC), the technological complexity, the need for a fluorescence microscope, and the failure to determine tumor cell morphology[10]. Other options for HER2 testing include CISH and in situ silver hybridization[11]. Previous studies have investigated patients with HER2 amplification and described an association with an increasing number of cancerous cell grades, loss of ER and PR expression, deoxyribonucleic acid aneuploidy, and an increase in proliferation indices[12-14].

This study focused on those with invasive breast cancer identified as equivocal HER2 by IHC (rating of 2+), which was further examined using FISH. The connection between HER2 amplification status and several clinical and pathological components including the type of tumor, patient's age, ER status, PR status and Ki67 proliferation index was examined. With regard to the 57 patients with a HER2 rating of 2+ determined using IHC, 52 (91.2%) exhibited non-amplification and 5 (8.8%) had an amplified HER2 gene status. The amplified gene status showed no significant correlations with the Ki67 proliferation index, ER status or PR status. The results indicated that there was no significant age variation among patients with HER2 gene amplification and those with non-amplification.

Currently, there are limited published reports on patients with equivocal IHC findings of HER2[4,15-17]. In one study that investigated patients with invasive breast cancer, 419 respondents among the overall 1735 respondents had a rating of 2+ HER2, which was determined using IHC[15]. Their result demonstrated that only 14% of these cases (57 out of 413) showed HER2 amplification based on the United States Food and Drug Administration criteria (the ratio of HER2 signals to chromosome 17 signals greater or equal to 2.0). In addition, HER2 amplification was interconnected with the overall membrane staining cumulative total. According to a study conducted by Chibon *et al* on 108 respondents who had breast cancer with a HER2 rating of 2+ assessed by IHC, the score for HER2 amplification by FISH was 33%, which was significantly higher than that found in our

results[16]. Tumor differentiation and cell percentage indicating membrane staining were signs of HER2 status. According to a study conducted by Dieci *et al* on 480 patients with breast cancer with a score of 2+ HER2, the findings indicated that a high tumor score and a high Ki67 proliferation index were significantly correlated with HER2 FISH gene multiplication[17]. Consequently, the results reported by Payandeh *et al* indicated that HER2 was amplified in 12 of 37 (32.4%) of the IHC equivocal cases using FISH test results[18]. Ji Y *et al* suggested that HER2 gene multiplication was observed in 34.6% of cases using FISH-based on FDA criteria, and cancer cells with HER2 gene multiplication were observed to harbor ER-negative or PR-negative findings[4]. According to a report published by Wang *et al*, the interpretation of ER and PR status and HER2 was determined by IHC, whereas FISH was utilized to examine HER2 status in instances that recorded 2+ IHC. They recommended that only females older than 40 years of age might have an association between ER and PR expression and HER2 status[19]. A negative association was observed between ER, PR and HER2, although they did not indicate a significant difference in age.

There were also debatable relationships between the ER and PR expression and HER2 amplification in both preclinical and clinical studies[20-23]. The ER and HER2 signals have an inverse correlation through the transcriptional repression of HER2 by binding of estradiol to ER[24]. Assessment of hormone receptors can forecast the efficacy of hormone treatment in breast carcinoma conditions[25]. HER2 amplified tumor cells have an increased correlation with negative ER and PR staining results[1,26,27]. It has been observed that patients with positive ER are occasionally seen together with HER2 amplification. This group of patients has a poor survival rate compared to that of individuals with more common positive ER and HER2 non-amplified tumors, indicating HER2 status is a crucial indicator of hormone therapy response[28]. The negative PR status impacts the likelihood of HER2 amplification in instances with positive ER[22]. One study reported that HER2 amplification was observed more in patients with negative ER or PR results[20], which was not observed in this study.

Surrogate techniques have been used[29]. CISH is an easy, adequate approach to identify the HER2 gene amplification using steps like those of IHC, ordinary light microscopes and everlasting signal intensities[30,31]. The small sample size and the retrospective nature of this study were limitations because we were not able to deduce further any conclusive statements based on the limited available data.

CONCLUSION

The findings of this study are relevant and should be employed or recognized by pathologists and oncologists when administering treatment to patients with breast cancer. Herein, we discovered that nine out of ten patients with breast cancer and equivocal HER2 IHC indicated non-amplification of the HER2 gene when tested with FISH. We must perform FISH on all equivocal HER2 cases identified with IHC despite the difficulties and high cost of the technique. Further prospective research is needed to verify the findings that we have observed in this study.

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Original Article

Are you aware "asthmatic nephropathy"? Metabolic and renal parameters in newly diagnosed untreated asthmatic patients without diabetes

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ABSTRACT

Objective(s): To compare the metabolic and renal parameters with the control group in newly diagnosed untreated asthmatic patients
Design: Cross-sectional study
Setting: Kayseri City Hospital, Turkey
Subjects: A total of 84 patients (42 asthmatic and 42 control), 18-75 years old
Intervention(s): None
Main outcome measure(s): Participants' pulmonary function tests, body mass index (BMI), insulin resistance, glycemic index (including HbA1c), proteinuria (urine protein/urine creatine ratio) and other laboratory findings
Results: Age, gender, BMI and the presence of obesity, homeostasis model assessment of insulin resistance and the presence of insulin resistance were similar in both groups. Glycemic index, lipid profile and other metabolic parameters were statistically similar between the two groups. In the renal parameters of the subjects under these similar conditions, proteinuria was higher in asthmatic group (P <0.001), whereas the values of serum blood urea nitrogen, serum creatine and Chronic Kidney Disease Epidemiology Collaboration were similar in both groups (P=0.641, P=0.701, P=0.865 respectively).
Conclusion: In this study, the renal functions tests in asthmatic patients was compared with the control group which has similar age, gender and metabolic parameters. To the best of our knowledge, proteinuria in newly diagnosed untreated asthmatic patients were determined firstly in the literature. Our study shows that even at the time of new diagnosis, asthma causes nephropathy through proteinuria. This study, which we first gained in order to raise awareness in the literature of "asthmatic nephropathy", should be elaborated with further studies.

KEY WORDS: asthma, kidney diseases, nephropathy, proteinuria

INTRODUCTION

Chronic kidney disease (CKD) is a growing public health problem. The course of CKD is variable. To date, several risk factors have been identified for the development and progression of CKD, such as older age, obesity, cigarette smoking, diabetes and hypertension. Patients who progress to end-stage renal disease need dialysis or transplantation, which cause heavy medicoeconomic burden. Recent studies have found that predictors of CKD include metabolic syndrome, obesity, vascular diseases, hyperlipidemia and cardiovascular diseases, hypertension, diabetes mellitus and heart disease[1-4].

Bronchial asthma, which is a common condition due to chronic inflammation of the lower respiratory tract, influences some chronic diseases such as coronary heart disease, diabetes mellitus and hypertension[5,6]. Although asthma patients have also higher risk of developing CKD, there are few studies and limited data investigating the interactions between asthma and CKD[4,7]. In our study, we aimed to compare the metabolic index, renal functions and the other laboratory findings with the control group in newly diagnosed untreated asthmatic patients.

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SUBJECTS AND METHODS

Ethical issues

The protocol, protocol amendments, consent form and subject information sheet were reviewed and approved by health authorities according to local regulations and by the local independent ethics committees Erciyes University Ethical Committee (Date and Decision number: 2018/471) prior to trial initiation. This trial was performed in accordance with the Declaration of Helsinki and Good Clinical Practice. All study participants gave written consent prior to any trial-related activities, and the investigator retained the consent forms.

Participants

A cross-sectional study was conducted from June 2018 to April 2019. Participants in this study are from a tertiary care hospital. Patients admitted to outpatient clinic with recurrent attacks of breathlessness and/or wheezing were included in the study. Fasting plasma glucose (FPG), 2-h plasma glucose (PG) and glycated hemoglobin (HbA1c) levels was conducted for all participants without diagnosed diabetes. A total of 84 patients (42 asthmatic and 42 control), ranging in age from 18-75 years old, were included in the study. Exclusion criteria were as follows: renal disorders (nephrotic syndrome, lupus, vasculitis, recent urinary tract infection, urinary calculus, renal failure), endocrinological disorders (diabetes mellitus, clinically significant thyroid dysfunctions, cushing disease, acromegaly), pulmonary disorders (chronic obstructive pulmonary disease, vasculitis, pneumonia), cardiovascular diseases, malignancies, treatment with corticosteroids, and previous history of asthma.

Pulmonary functions

The pulmonary function of patients was performed using a spirometry analyser (Cosmed microquark PC based USB spirometer, Rome, Italy). The percentage of forced vital capacity (%FVC), the forced expiratory volume in 1st second (FEV1), the ratio of FEV1 to observed forced vital capacity (FEV1/FVC), peak expiratory flow, the average forced expiratory flow rate between 25% and 75% of FVC were calculated. Bronchodilator responsiveness was defined as change in FEV1 (ΔFEV1) over pre-bronchodilator baseline levels 30 minutes after inhalation of 400 g of salbutamol. If the FEV1 increases >12% and >200 ml over baseline, the bronchodilator test is positive[8]. Suspect diagnoses were excluded via spirometry and other clinical findings. Asthmatic patients, who are diagnosed for the first time by the specialist medicine doctor of chest diseases, were included in the study.

Health indicators

Height and weight were measured and used to calculate body mass index (BMI), weight in kilograms divided by height in meters squared. BMI was then categorized as normal (<30 kg/m^2), and obese (30 kg/m^2 and above)[9]. In order to exclude the effect of obesity, the control group consisted of subjects with similar BMI to the asthmatic group.

Measurement of laboratory parameters

A fasting venous blood sample was collected after an overnight fast of at least 8-hour for biochemical investigations and samples were processed at the hospital laboratory on the same day. FPG, 2h-PG, fasting plasma insulin (FPI), serum blood urea nitrogen, serum creatine (SCre), plasma and urine protein, total cholesterol, low-density lipoprotein-cholesterol, high-density lipoprotein-cholesterol, triglyserides, calcium, phosphor, uric acid, thyroid stimulating hormone, insulin-like growth factor-1 were estimated using a Roche Cobas 8000 immunoassay analyzer (Roche Diagnostics, USA). HbA1c were estimated using an Adams A1c HA-8180V automatic analyzer (Arkray Diagnostics, USA). All assays were performed with specific kits and calibrators supplied by the manufacturers.

Insulin resistance

Fasting blood samples were obtained for FPI and FPG determinations in order to calculate the homeostasis model assessment of insulin resistance (HOMA-IR). It was determined by the formula[10]:

HOMA-IR = FPI (mU/L) x FPG (mmol/L) / 22.5. If the result is ≥2.5, it indicates the presence of insulin resistance. The higher the score, the greater the insulin resistance is measured.

Nephropathy assessment

A random spot urine sample was collected as part of each routine clinical assessment. Proteinuria is measured by urine protein/urine creatine ratio. Creatinine clearance was evaluated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation[11]:

$$\text{CKD-EPI} = 186 \times \text{Scre}^{-1.154} \times \text{age}^{-0.203} \times (1.212 \text{ if Black}) \times (0.742 \text{ if female})$$

Statistical analysis

For statistical analyses, SPSS 22.0 (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.) program was used. Frequencies were expressed in percentage (%). For comparison of categorical data, Chi-square test was used. Whether numeric (digital) data is

Table 1: Clinical status and laboratory parameters of patients with asthma and control group

Clinical parameters	Asthma (n=42)	Control (n=42)	*P*-value
Gender (F/M), n(%)	30/12 (71.4/28.6)	30/12 (71.4/28.6)	0.533
Age (year), mean±SD	50.55 ± 13.09	48.52 ± 13.46	1.000
BMI (kg/m^2), mean±SD	32.5 ± 9.6	31.9 ± 6.9	0.751
Obesity (+)ve, n(%)	22 (52.4)	24 (57.1)	0.827
HOMA-IR; median (IQR)	2.28 (3.63)	2.04 (1.71)	0.649
Insulin-resistant patients, n(%)	20 (47.6)	17 (40.5)	0.661
FPG (mg/dL), mean±SD	99.02 ± 8.92	97.69 ± 9.78	0.516
2-h PG (mg/dL), mean±SD	123.82 ± 31.23	119.37 ± 28.05	0.566
HbA1c (%), median (IQR)	5.7 (0,33)	5.6 (0.7)	0.379
Total cholesterol (mg/dL), mean±SD	200 ± 39	204 ± 34	0.657
LDL-c (mg/dL), mean±SD	122 ± 32	127 ± 32	0.542
HDL-c (mg/dL), mean±SD	48 ± 11	48 ± 15	0.878
Triglycerides, median (IQR)	128 (107)	121 (72)	0.552
TSH (mU/L), median (IQR)	1.97 (1.43)	1.67 (1.65)	0.136
IGF-1 (ng/mL), mean±SD	126.1 ± 50.3	127.9 ± 49.4	0.866
Calcium (mg/dL), mean±SD	9.42 ± 0.34	9.48 ± 0.42	0.535
Phosphor (mg/dL), median (IQR)	3.35 (0.70)	3.44 (0.72)	0.401
Uric acid (mg/dL), mean±SD	5.13 ± 1.12	5.14 ± 1.35	0.971
BUN (mg/dL), mean±SD	12.42 ± 3.97	12.82 ± 3.61	0.641
Creatin (mg/dL), mean±SD	0.73 ± 0.12	0.74 ± 0.14	0.701
CKD-EPI (mL/m/1.73m^2), mean±SD	100.9 ± 14.2	100.4 ± 13.8	0.865
Proteinuria (mg/mg), median (IQR)	88.7 (51.5)	64.1 (24.7)	<0.001

F/M: female/male; BMI: body mass index; HOMA-IR: homeostasis model assessment of insulin resistance; FPG: fasting plasma glucose; HbA1c: glycated hemoglobin; LDL-c: low-density lipoprotein-cholesterol; HDL-c: high-density lipoprotein-cholesterol; TSH: thyroid stimulating hormone; IGF-1: insulin-like growth factor-1; BUN: blood urea nitrogen; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration. (*P* <0.05 considered statistically significant)

distributed normally or not was determined by Kolmogorov-Smirnov test and Histogram graphs. Numeric (digital) data relating to independent groups demonstrating a normal distribution were compared by Student t test. Variables which were demonstrating normal distribution were expressed in mean (standard deviation). If it was abnormal distribution, Mann Whitney U test was used. Variables which were demonstrating abnormal distribution were expressed in median (minimum-maximum; standard deviation). *P* <0.05 was accepted and considered as significant.

RESULTS

A total of 42 asthmatic and 42 control group participants, aged 18-75 years, were recruited to the study consecutively. Age, gender, BMI and the presence of obesity, HOMA-IR and the presence of insulin resistance were similar in both groups.

Glycemic index (FPG, 2-h PG, HbA1c), lipid profile (total cholesterol, low-density lipoprotein-cholesterol, high-density lipoprotein-cholesterol, triglycerides) and other metabolic parameters (calcium, phosphor, uric acid, thyroid stimulating hormone, insulin-like growth factor-1) were statistically similar between the two groups. A comparison of asthmatic and control groups' data was summarized in Table 1.

In the renal parameters of the subjects under these similar conditions, proteinuria was higher in asthmatic group (*P* <0.001) whereas the values of serum blood urea nitrogen, SCre and CKD-EPI were similar in both groups (*P*=0.641, *P*=0.701, *P*=0.865 respectively).

DISCUSSION

In this study, the renal functions tests in asthmatic patients was compared with the control group with similar age, gender and metabolic parameters. To the best of our knowledge (Pubmed, google academic), proteinuria in newly diagnosed untreated asthmatic patients were determined firstly in the literature.

There are a limited number of studies demonstrating the effects of asthma on the kidney. After adjusting for gender, age and co-morbidities (such as obesity, hyperlipidemia, hypertension, diabetes mellitus), subjects with asthma still have significant and independent high risk of CKD[12]. The possible mechanism underlying these processes could be an effect on renal capillary permeability due to inflammatory mediators such as TNF-α and interleukins, and induction of endothelial dysfunction such as rheumatoid arthritis[13-15]. Asthma can produce right ventricular volume overload by increasing pulmonary vascular resistance leading to reduced cardiac output and kidney perfusion with resulting reductions in Glomerular Filtration Rate (GFR)[16].

Recently, one study of 2,354 asthma patients from a retrospective cohort in China indicates that there is 9.6% incidence of CKD in a period of six-year follow-up, in which the group of persistent asthma has independent,

higher risk of CKD than the nonpersistent group[12]. In another study, an association between asthma and later CKD using a large cohort comprising asthma subjects (n=35,086) and non-asthma controls (n=105,258) in a three-year period of follow-up was reported by Huang *et al*[7]. In a study by Adawy *et al*, the renal functions of patients with asthma was measured via eGFR (CKD-EPI). While eGFR was significantly lower in the asthmatic group compared with healthy individuals (92.6±19.6 versus 100.8±12.5 respectively; P <0.001), BMI was significantly lower in the asthmatic group than in the healthy group (26.4±4.3 versus 28.6±5.8 respectively; P=0.001). Adawy's study has been conducted on patients with a history of asthma and emphasizes that GFR was higher in the well-controlled group than in the uncontrolled group[4]. Our study was performed with newly diagnosed asthmatics and healthy group with similar BMI values (32.5±9.6 versus 31.9±6.9), and there was no difference between groups in terms of GFR (P = 751).

Proteinuria is a well-established marker of disease progression in CKD patients. Higher levels of proteinuria are associated with a more rapid decline in GFR, as well as with a higher incidence of fatal and nonfatal cardiovascular events[1]. Therefore, proteinuria and diseases leading to proteinuria should be taken under control as soon as possible. Hypertension and diabetes are among the leading ones. Proteinuria is associated with the presence of hypertension and hyperglisemia, which are significant risk factors for proteinuria compared with completely normal glucose level[17,18]. While there were seven patients (16.7%) with hypertension in asthmatic patients, control group had eleven subjects (26.2%) with hypertension in our study. There was no statistically significant difference between the two groups (P=0.426). Diabetic patients were not included in the study. There were twenty-seven patients (64.3%) with prediabetic (neither diabetic, nor normoglycemic) range (FPG: 100-125 mg/dL, 2-h PG:140-199 mg/dL) in asthmatic patients, and control group had twenty-one subjects (50%) with prediabetic in our study. There was no statistically significant difference between the two groups (P=0.270). Thus, direct effect of asthma on proteinuria was observed. Consequently, the median urine protein/urine creatine ratio was higher in asthmatic group (88.7 mg/mg) than the control one (64.1 mg/mg). This was statistically significant (P <0.001).

One of the limitations of our study is that we did not compare smoking and alcohol intake of patients. Although the number of patients included in the study is more than the number of studies in the literature, our another limitation is the small number of patients. Since asthma is a common condition in the community, there is a need for longitudinal studies with a very large population to obtain clear data.

CONCLUSION

In conclusion, our study shows that even at the time of new diagnosis, asthma causes nephropathy through proteinuria. This study, which we first gained to raise awareness in the literature of "asthmatic nephropathy", should be elaborated with further studies.

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Author contribution: Ulas Serkan Topaloglu conceived the idea, planned the methodology, provided participants and collected the data. Burcu Baran Ketencioglu was responsible for critical review, providing participants, analysis and interpretation. Both authors read and approved the final manuscript.
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Original Article

Children with effusion in the middle ear: A prevalent infection of secretory otitis media and its associated risk factor in China

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ABSTRACT

Objectives: To investigate the prevalence and demographic, environmental risk and their associated risk factors of secretory otitis media (SOM) infection in Chinese school children
Design: Cross-sectional study
Setting: Dazhou Central Hospital, Dazhou, Sichuan, China
Subjects: The number of participants were 1000, aged 5-13 years, randomly selected from different primary schools in China region.
Intervention: Medical records of all the patients were reviewed and data were collected.
Main outcome measures: Medical experts were appointed to look after the participating children and made the examined report. Patients with SOM infection were assessed through the otoscope and tympanometry.
Results: Among the 1000 patients who participated in this study, only 210 (21%) children suffered from SOM infection. The prevalence rate of SOM infection was 10.4% among those Chinese children, associated with risk factors such as lower class family ($P<0.05$), breast feeding duration ($P>0.001$), younger aged children ($P<0.05$), the ear wax factor ($P<0.05$) and exposure of cigarette smoking ($P<0.05$). No significant differences were found for upper respiratory tract infection (URTI), premature-birth, gender and previous ear, nose and throat (ENT) surgery with SOM ear infection. Children with SOM infection had less developed speech and language, adversely affecting its academic field also.
Conclusions: The finding in this study was the high prevalence of SOM in the Chinese children. Living standard of parents, frequent exposure to cigarette smoke, younger aged children and ear wax factor were actual detrimental risk factors of the SOM prevalence instead of other factors like URTI, premature-birth, gender and previous ENT surgery.

KEYWORDS: Chinese school children, prevalence, risk factors, secretory otitis media

INTRODUCTION

Secretory otitis media (SOM) is a prevalent kind of incidence relevant to ear infection, its occurrence possibly due to biofilm formation[1,2] and eustachian tube dysfunctions[3]. SOM is mostly prevalent in younger age groups. Two research studies were conducted in Hong Kong to discuss the prevalence rate of SOM, and it was noted to be 9.5% and 5.3% among the studied Caucasian children[3] and Chinese children[4] respectively during the first year of primary school. SOM disease, if it remains untreated or inadequately treated, can cause ear deafness because of tympanic membrane disruption, adversely affecting child behavior like improper speech and language development. This would affect academic achievements, and other complications such as retraction pockets, adhesive otitis media and tympanosclerosis may arise. Physicians need to recognize these important clinical signs while treating patients with otitis media infection. Some risk factors associated with otitis media infection include: younger children[4,5] with low feeding[6-8], mother's lack of education[8,9], low socioeconomic value[10,11], day care[12,9], parental smoking behavior[9,13], respiratory tract infections[8,9,14], allergic[8-10,15,16] and snoring[8,9] conditions. In extreme cases of SOM, it may also affect

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the academic education and their quality of life. It had been reported that SOM long term effects adversely affect speech and language development, even recovering from this disease[17]. Hence, it would be necessary to identify those children with otitis media infection. Sometimes, these children were also affected with cleft plate or Down's syndrome[18]. Cases mostly arise in public day care centers compared to children who stay at home[12]. Only some risk factors have been reported till date concerning SOM infection in Chinese children. The aim of this study was to investigate the association between long-term SOM infections, and their external factors connected to environmental and internal risk factors and prevalence of the disease in Chinese children.

SUBJECTS AND METHODS

This study was conducted in the Department of Otolaryngology, The 2nd Affiliated Hospital of Kunming Medical University, Kunming, Yunnan-650101, China.

One thousand participants aged 5-13 years were randomly selected from different primary schools in China region. The current study was conducted from January 2019 to the end of April 2019. Considered factors included in this study were patient's ages, gender and grade, number of family members, breast feeding in first two years of life span, exposure to cigarette smoke at home, attendance of daycare centers, preschool acute otitis media history, hearing loss as reported by parents, sneezing, snoring, nasal discharge, ENT clinic visit with ENT operations (adenoidectomy, tonsillectomy, myringotomy and ventilation tube insertion), parents income and living standard. Medical experts were appointed to look after the participating patients and made the examination based on these factors and provide the report to parents through school administration. School teachers evaluate the children's performance to classify them into very good, good, acceptable or poor, except those who are affected by immune deficiencies disorder or with perforated tympanic membrane, tympanostomy tube insertion at the time of study or having chronic disease like cholesteatoma, and children affected by craniofacial anomalies were excluded from the study. Patients with secretory otitis media infection were assessed through the highly sophisticated instrument otoscope and a portable tympanometry machine of model number (Amplaid 766), with a probe frequency of 226Hz and air pressure range of -400 to +100 mm H_2O with automatic reading setup. Different pattern of peak *i.e.*, tympanogram was obtained to categorize further into following types: Type A (with air pressure range of -90 to +99 mm H_2O), Type B with flat curve with no peaks, and Type C (with air pressure >100 mmH_2O). Before using tympanometry, patients undergo cleanup of ear wax in the hospital clinic. Children with otoscopic appearance of Otitis media infection had abnormal tympanogram including the type-B or type-C peaks were considered as positive results and prescribed to follow up regular checkup within three months after initial screening.

Statistical analysis

Statistical data analysis was done by SPSS version 25. Regression analysis was done to establish the correlation between the associations of SOM with studied risk factors. Risk factors were studied at *P* >0.05 level, using multivariate logistic regression analysis for further investigations of SOM occurrence and their associated factors calculated through the partial logistic regression coefficient b, logistic odds ratio and its 95% confidence interval (CI).

Ethics approval and consent to participate

The above study was approved by the Human Ethical Committee (Ethics Committee approval number: KMUK/TM/11/19 dated 24 June 2019) of the The 2nd Affiliated Hospital of Kunming Medical University, Kunming Yunnan-650101, China and informed consent was obtained from the patients before the study.

RESULTS

Among the 1000 children who participated in this study, only 210 (21%) children suffered from SOM infection. Out of the 210 children, the remaining 149 (70.96%) were diagnosed with Type A SOM infection directly. Children who had type B tympanogram underwent physical examination, result obtained after examination indicate the children with SOM infection. The remaining 61 patients were further categorized as 21 (8.67%) who underwent type B tympanogram without physical examination observation of SOM infection, 10 (4.76%) patients underwent type B tympanogram with tympanic membrane retraction and only 30 (14.29%) children underwent type C2 tympanogram with or without physical examination findings. While SOM was bilateral in 90 cases (42.85%), it was unilateral in 120 cases (57.15%). Out of 1000

Table 1: Number of children with/without SOM affected by aged risk factor

Risk factors (age)	Number of children with SOM		Number of children without SOM		*P*-value
	Boys	Girls	Boys	Girls	
5-7 years	62	37	122	98	<0.05
8-10 years	48	29	185	83	<0.05
11-13 years	20	14	196	106	<0.05

SOM: secretory otitis media

patients, 80 girls (8% of a total of 367 girls) and 130 boys (11.47% of a total of 633 boys) were infected with SOM, and no significant differences were observed between the two participating groups at P <0.05 level as depicted in Table 1.

Data related to age group showed SOM disease prevalence between the ages of 5-13 years of age, and was most commonly found in the age group of 5-7 years in boys (47.69%, 62 cases) and 32 cases of girls with SOM infection. Negative significant relation was noted among SOM and age because SOM occurrence tended to decrease in aged children observed at P <0.05 level, already summarized in Table 2.

Table 2: Number of children with/without SOM affected by socio-economic status

Risk-factors (socio-economics status)	Number of children with SOM		Number of children without SOM		*P*-value
	Boys	Girls	Boys	Girls	
Higher class	11	8	240	138	<0.05
Middle class	19	17	124	115	>0.05
Lower class	92	63	85	88	>0.05

SOM: secretory otitis media

Another risk factor of SOM prominence in those patients was belonging to lower class family, mostly boys (51.98%, 92 cases) were affected with SOM infection compared to girls (23.96%, 63 cases), but reverse situation was observed in higher class, *i.e.* 2.35% (8 cases) of girls and 2.033% (11 cases) of boys at P <0.05 level. Current study reveals that no significant differences were observed in between premature birth and SOM disease, but SOM had a significant relation with breast feeding duration adversely affecting 22.4% of boys (80 cases) and 22.8% of girls (88 cases) with less than 6 months of breast feeding. Children who were breast fed for >12 month duration were least affected, observed at P >0.001 as shown in Table 3.

There was no significant difference found between the groups in terms of premature-birth (SOM prevalence of 30.24% in both groups) and previous ENT surgery (4.68% with a previous operation versus 95.32% without an operation, at P >0.001 level). No significant results were obtained between the groups if comparing the upper respiratory tract infection with SOM infection in both the case of boys and girls as shown in Table 4.

Table 3: Number of children with/without SOM affected by breast-feeding duration/ pre-mature birth

Risk factors (breast-feeding duration)	Number of children with SOM		Number of children without SOM		*P*-value
	Boys	Girls	Boys	Girls	
<6 months	80	88	177	198	>0.001
6-12 months	15	22	174	116	>0.05
>12 months	4	1	49	76	>0.001
Pre-mature birth					<0.001
Yes	13	7	30	100	
No	110	80	460	200	

SOM: secretory otitis media

Table 4: Number of children with/without SOM affected by previous ENT surgery

Risk factors (previous ENT Surgery)	Number of children with SOM		Number of children without SOM		*P*-value
	Boys	Girls	Boys	Girls	
Yes	9	2	183	201	>0.0001
No	43	156	299	107	>0.0001
Presence of upper respiratory tract infection					<0.005
Yes	37	32	46	23	
No	68	73	523	198	

SOM: secretory otitis media; ENT: ear, nose, throat

Table 5: Number of children with/without SOM affected by exposure of smoking

Risk factors (smoking exposure)	Number of children with SOM		Number of children without SOM		*P*-value
	Boys	Girls	Boys	Girls	
5-7 years	82	75	249	211	>0.05
8-10 years	30	23	198	132	>0.05

SOM: secretory otitis media

This study also considers the ear wax factor to reveal the status of SOM dominancy. It was noted that SOM infection was prevalent in children with ear wax (18.98%) compared to those without ear wax (10.43%), and the obtained results showed the statistically significant differences (P <0.05). Among children of different age groups ranging from 5-10 years, significant relation was shown between the exposure to cigarette smoking and prevalence of SOM infection. The obtained results showed in Table 5 depicts the children aged 5-7 years were more prone to be affected with SOM infection compared to children aged 8-10 years and reverse situation was found in children without SOM infection and the difference was statistically significant (at P >0.05) with prevalence rate of 10.4% of SOM infection.

DISCUSSION

Most common health issue in a younger aged child is SOM infection. SOM infection depends on the health treatment[19], if it remains untreated, it could approach a chronic state, ultimately resulting

in hearing loss, chronic ear problems and imbalance in speech and language[8] development in children. Proper treatment and early diagnosis are helpful to eliminate the morbidity complication and significantly reduces the SOM occurrence rate. However, in mostly cases, its early diagnosis is not possible since the SOM infection spread in a subtle way, as is usual in a newborn child. Hence, it is important to investigate the causing risk factors responsible for the prevalence of SOM infection. In addition, involved risk factors are helpful to make up the proper treatment plan and precautions to be taken against SOM infection. SOM prevalence rate across the world would be 1.3-61%, depending on the method followed for treatment among race and population[20]. Similar studies were also conducted in the Mediterranean area, including China suggesting a prevalence rate of 6.45-18%[9,12]. Instead of the method followed for treatment, all the reports discuss about age as another important risk factor related to SOM infection[21]. The current study clearly reveals a 23.93% prevalence rate of SOM infection with 12.99% reported in boys and 10.94% in girls at the age of 5-7 years that coincides with previously reported studies. SOM prevalence rate of infection[22,23] was significantly higher in younger children aged 5-7 years at P <0.001 level, that declines with increasing age. No significant differences were observed between the older aged groups at P >0.05 level. Observed results showed that age is one of the most important risk factors determining the SOM prevalence. The higher incidence of SOM in a younger aged child may be related to predisposition of infections usually seen in primary school children. This study also demonstrates the risk factors of SOM occurrence in those children who are continuously exposed to the cigarette smoke. Previously studied reports suggest that there was no association between parental smoking with SOM[24-26], while other reports demonstrate there was a relationship[27-29] between them. Blakley and Blakley's[30] report discussed cigarette smoking with SOM infection of ear, but they found no data related showing the negative impact of smoking on SOM disease[31,32] and significantly correlated to SOM in this study at P >0.05 level. Breast feeding effect on SOM infection is still controversial according to previously reported studies because some reports were in favor of breast-feeding's effect on SOM disease, while there are some studies revealing that there was no relation between breast feeding and SOM infection of ear[6,33]. Present study results follow the positive correlation between SOM incidence in children and breast-feeding duration at P >0.001 level. The low incidence of SOM in children who are properly breast fed compared to those less fed, and a significant relation was found between the breast-feeding duration with SOM infection at P >0.001 level, which favors the observation of Martines *et al*[8]. Similar studies also report the incidence of SOM among children who were breast fed for a shorter duration of time compared to those who are breast fed for a duration >9 months of time[34,10], but their results were not support of this study.

CONCLUSIONS

The current study concluded that the SOM infection prevalence depends on the existing risk factors. Parents living standard, frequent exposure to cigarette smoke, younger aged children and ear wax factor were actual detrimental risk factors of SOM prevalence instead of other factors like upper respiratory tract infection, premature-birth, gender and previous ENT surgery. Infection of SOM severity form arises when the sequential complications like tympanosclerosis, retraction pocket in tympanic membrane, acute otitis media and speech language impairment make the disease an important health issue. Detecting risk factors associated with SOM infection development and their alteration results, if the precaution taken is avoided while disease is at initial stage and status of disease is changed to chronic condition. Caretakers must know about these crucial risk factors, SOM development can be prevented at initial stage and serious consequences are also avoided.

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Original Article

The relationship of serum lipid levels and antimicrobial resistance states in ventilator associated pneumonia patients

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ABSTRACT

Objective: We have aimed to evaluate the relation of lipid metabolism alterations with the type of ventilator associated pneumonia (VAP) and the link between inflammatory responses and the antimicrobial resistance patterns.
Design: Prospective observational study
Setting: Konya Numune Hospital, Turkey
Subjects: The research was conducted on 111 VAP and 50 control group patients. Based on the disease onset, patients were divided into early and late-onset VAP groups.
Intervention: None
Main outcome measure: The patient specific lipid profiles and inflammatory responses were analyzed according to the pneumonia types and the antimicrobial resistance states, then the clinical results were recorded. The identification of respiratory isolates with significant growth [$>10^4$ colony forming units/mL] and the antimicrobial susceptibility were evaluated by VITEK 2 compact system.
Results: In early and late-onset VAP groups, total cholesterol, high-density lipoprotein (HDL) and low-density lipoprotein levels decreased, but white blood cell, C-reactive protein and procalcitonin (PCT) levels increased (P <0.05). In 75 of all VAP patients (68%), the causative agent was found to be a multi-drug resistant pathogen (MDR-P). There was a significant difference between MDR-P and non-MDR-P infected patients as regards HDL (P=0.002) and PCT (P=0.001) levels. A serum HDL best cut-off value was 36.2 mg/dL and a serum PCT best cut-off value was 19.8 μg/L for identifying the MDR organisms.
Conclusion: Serum cholesterol levels decrease in VAP patients but do not change according to early and late-onset pneumonia types. MDR infection was related with amplified acute phase response and prominent alterations in lipid metabolism.

KEY WORDS: inflammation, lipid metabolism, multi-drug resistance, ventilator associated pneumonia

INTRODUCTION

Ventilator-associated pneumonia (VAP) arises at least 48 hours after endotracheal intubation and invasive mechanical ventilation (MV)[1]. VAP is the most common nosocomial infection encountered in patients undergoing invasive MV. Approximately half of all antibiotics consumed in intensive care unit (ICU) are reserved for treatment of VAP[2]. Early-onset VAP usually has less severity and better prognosis and the agent is often an antibiotic sensitive pathogen. On the other hand, late-onset VAP is associated with increased morbidity and mortality and the agent is often a multi-drug resistant pathogen (MDR-P)[1,3].

Cholesterol molecules collected from peripheral tissues are conveyed back to the liver by high-density lipoproteins (HDLs), which is why they provide cardiovascular protective effects[4]. Also, they play a role in innate and adaptive immunities[5]. HDL levels are

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significantly reduced in infectious and inflammatory diseases[6,7]. Therefore, decrease in serum HDL levels is expected in patients with pneumonia[8]. According to several recent studies, levels of the inflammatory markers like acute phase proteins, cytokines and HDLs are interrelated[9,10]. However, it is still a conundrum whether the changes in lipid metabolism are affected by the type of pneumonia, including early-onset VAP and late-onset VAP, and help to distinguish MDR-Ps from antibiotic-susceptible agents. Hence, we have made our investigation on clinical characteristics, serum lipids and systemic inflammatory markers of early and late onset VAP patients and exhibited their value in prediction of antibiotic susceptibility or MDR patterns of isolates.

SUBJECTS AND METHODS

Study population

This prospective observational single-centered study was performed in adolescent and adult patients. They were intubated endotracheally and received MV treatment for at least 48 hours in Konya Numune Hospital ICU, which had 42 surgery and medicine beds. The study was conducted in between September 2018 and July 2019 and approved by the Ethics Committee of Selçuk University Medical School. Informed consents were obtained from patients who participated in the study or from their relatives.

Inclusion and exclusion criteria

Patients aged 16 years or older, having no symptoms and signs of infection at admission were included in the study. They met the VAP criteria specified in the American Thoracic Society guidelines[1], and had the simplified version of Clinical Pulmonary Infection Score (CPIS) above 6[11].

Patients having one or more of the conditions such as chronic inflammation, hepatic dysfunction, active tuberculosis, malignancy, malnutrition and immunosuppression (neutropenia, HIV positivity, transplantation, prednisone treatment of ≥20 mg/day, etc.) were excluded out the study. Patients diagnosed with any extra-pulmonary infection within 72 hours of inclusion in the study were excluded as well. Lastly, isolation of a fungal agent, a normal flora bacterium, an organism with uncertain pathogenity, or no isolation of a microbial organism at all were counted in the exclusion criteria.

Definitions

VAP was defined as the lung infection of which diagnosis was established at least 48 hours after endotracheal intubation and initiation of MV therapy. VAP developing in first four days of MV was defined as "early", whereas VAP developing after this period was defined as "late"[1]. Control group included patients who were intubated endotracheally and received MV therapy for more than 48 hours but had no suspicion of VAP or other nosocomial infections.

The severity of the disease was assessed by the Acute Physiology and Chronic Health Evaluation (APACHE) II score at the onset of infection. MDR definition was established based on the study of Magiorakos *et al*[12]. MDR state was defined when organisms were non-susceptible to at least one agent in three or more antimicrobial categories whereas extensive-drug resistance (XDR) state was defined when the organisms were non-susceptible to at least one agent in all except two or fewer antimicrobial categories. Pan-drug resistance state was defined when non-susceptibility to all agents in all antimicrobial categories existed. Polymicrobial pneumonia was diagnosed when more than one potentially pathogenic microorganism was isolated[13]. For MDR infection to be defined, isolation of at least one MDR-P in a polymicrobial VAP patient was essential. XDR and pan-drug resistant pan-drug resistance organisms were assumed as MDR-Ps[12]. Empirical antibiotherapy was defined as "appropriate" if the organism isolated was susceptible against the antibiotics initiated immediately following VAP diagnosis and continued until the resistance tests were resulted.

Hepatic dysfunction was considered when ≥2 of the following criteria were present: total bilirubin concentration being ≥2.5 mg/dL, aspartate transaminase or alanine transaminase level being more than twice the upper limit of normal range, and documented diagnosis of cirrhosis.

Death from any cause occurring in 28 days after VAP onset was defined as 28-day ICU mortality.

Study protocol

One hundred and eleven VAP and 50 control group patients without any nosocomial infection were prospectively and consecutively included in the study. VAP was clinically and microbiologically diagnosed, that is, the diagnosis was established if clinical suspicion of pneumonia existed, CPIS of patient was >6, and a growth of at least one potentially pathogenic microorganism in the conventional culture of patient's respiratory samples was $>10^4$ CFU/mL.

Routine microscopic gram stain was performed before each culture. If squamous epithelial cells were displayed <10 cells/low-power field and polymorphonuclear leucocytes were displayed >25 cells/low-power field, the specimen was regarded as adequate. An organism was considered to be the potential etiological agent of VAP if its colonies produced from endotracheal suction specimens were reported as moderate or numerous in quantity.

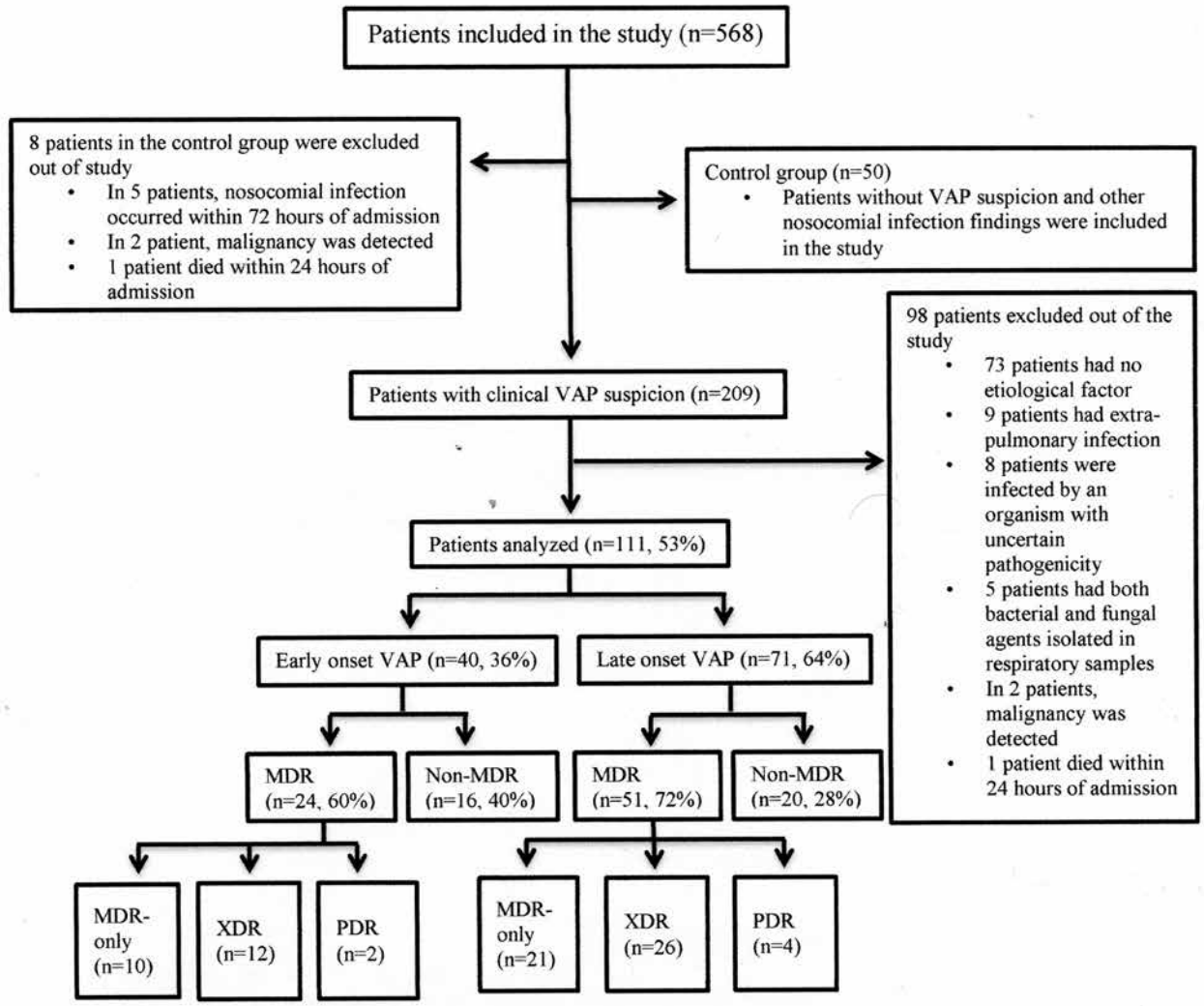

Fig 1: Study profile of included and excluded patients.

Respiratory culture

Samples were collected in a mucus trapper by applying negative pressure through an automated machine. Tracheal aspirates were subjected to microbiological work-up within 15 minutes. Gram stain of a cytocentrifuged layer was performed on all specimens. Specimens were inoculated on blood agar, EMB agar, chocolate agar and Sabouraud dextrose agar plates. All plates were incubated at 37 °C until 24 hours and one plate of Sabouraud dextrose agar was incubated at 25 °C until 72 hours for fungal culture.

Blood culture

For each sample, an aliquot of 5 to 10mL whole blood was inoculated into BACTEC aerobic and anaerobic bottles (Becton Dickinson, Sparks, MD). Two sets from two different sites were collected at the same time. The bottles were incubated in a BACTEC FX automated blood culture system (Becton Dickinson). All bottles that flagged positive within seven days were removed from the instrument and an aliquot was taken for gram stain and culture on solid media (blood agar, EMB agar and chocolate agar plates) for 37 °C until 24 hours.

In addition, sterile urine samples were cultured and growth of $>10^5$ CFU/mL was considered significant.

The empirical antimicrobial therapy was practiced according to the locally modified guidelines[1]. The most frequently isolated pathogens of our institution and their antimicrobial resistance states were taken into consideration. When antimicrobial tests resulted, the empirical antibiotic treatment was revised. Serum lipid profile and inflammatory biomarkers were analyzed from blood samples drawn at the onset of infection for patients in the pneumonia groups and at least 48 hours after the endotracheal intubation for patients in the control group. Since antibiotherapy could affect procalcitonin (PCT) levels[14], blood

samples were received at the time of diagnosis before initiation of empirical therapy and analyzed by Siemens ADVIA Centaur CP Immunoassay System. By using original reagents, Beckman Coulter AU5800 automatic biochemical analyzer and Siemens BN II plasma protein analyzer systems were utilized for measuring serum lipid and C-reactive protein (CRP) levels. Other biomarker levels were measured by standard laboratory operating procedures at the local institution. The organisms isolated via quantitative cultures of endotracheal aspirates were identified according to the standard microbiological methods. Blood and urine cultures were also obtained in order to rule out other possible nosocomial infections. VITEK 2 healthcare system (BioMérieux, Lyon, France) were utilized for antimicrobial susceptibility tests. Minimal inhibitory concentration results were interpreted according to European Committee on Antimicrobial Susceptibility Testing 2018 breakpoints[15].

In compliance with the manufacturer's instructions, VITEK 2 compact system with antimicrobial susceptibility testing (AST)-P640 and AST-P641 card assembly kits for gram-positive (GP) bacteria, AST-ST03 card assembly kit for *Streptococcus species* and AST-N325, AST-N326 and AST-N327 card assembly kits for gram-negative (GN) bacteria were used. Colistin resistance of all GN bacteria were evaluated by manual minimal inhibitory concentration method. *Staphylococcus aureus* (ATCC 29213) and *Escherichia coli* (ATCC 25922) were used as quality control strains for all cards.

The Kirby-Bauer disc diffusion method was applied to *Haemophilus influenzae* isolates (*Haemophilus* Test Medium Agar, Germany, BM) because the reliability of the antibiogram results would be reduced by VITEC 2 compact system due to the fastidious growth characteristic of *H. influenzae.* For determination of the sensitivity, aztreonam, ceftazidime, cefepime, ceftriaxone, penicillin, piperacillin, piperacillin-tazobactam, imipenem, meropenem, ertapenem, gentamicin, amikacin, levofloxacin and fosfomycin antibiotic discs (Antimicrobial Susceptibility Test Discs, Bioanalyse, Turkey) were utilized.

Organisms with intermediate susceptibility were considered as antimicrobial resistant.

Table 1: Baseline characteristics of patients with ventilator-associated pneumonia

Variables	Control	All VAP	Early VAP	Late VAP
Number of patients	50	111	40	71
Age in years	55.8±13.4	58.9±13,6	57.9±15.4	59.5±12.5
Gender, male, n (%)	26 (52)	60 (54)	23 (57)	37 (52)
Co-morbidities, n (%)				
Renal diseases	12 (24)	34 (30)	13 (32)	21 (29)
Neurological diseases	11 (22)	27 (24)	10 (25)	17 (23)
Cardiovascular diseases	17 (34)	38 (34)	15 (37)	23 (32)
Pulmonary diseases	11 (22)	22 (19)	8 (20)	14 (19)
Diabetes mellitus	12 (24)	29 (26)	11 (27)	18.(25)
Main causes of ICU admission, n (%)				
Medical	38 (76)	88 (79)	31 (78)	57(80)
Surgery/Trauma	12 (24)	23 (21)	9 (23)	14 (20)
APACHE II	18.4±1.9	24.7±4.6*	24.3±4.7*	25±4.6*
CPIS	0.0±0.0	7.3±1.2	7.2±1.2	7.4±1.1
PaO_2/FiO_2 ratio	281.7±41.6	190.7±37.6*	196.7±29.5*	187.4±41.3*
Positive blood culture n (%)	0 (0)	9 (8)	3 (7)	6 (8)
Systemic steroids, n (%)	7 (14)	13 (11)	5 (12)	8 (11)
NSAID, n (%)	4 (8)	5 (4)	2 (5)	3 (4)
Vasopressor use, n (%)	5 (10)	24 (21)*	8 (20)*	16 (22)*
Statin use, n (%)	4 (8)	11 (9)	4 (10)	7 (9)
Clinical outcomes				
Duration of intubation prior to VAP (days)	0.0±0.0	6.6±2.9	3.6±0.4	8.3±2.2 ‡
ICU length of stay (days)	12.6±7.6	24±8.3*	22.9±3.1*	24.6±10*
Inapropriate empirical antibiotics during the initial 3 days of treatment, n (%)	0 (0)	44 (39)	14 (35)	30 (42)
Previous antibiotic uses within 7 days prior to VAP onset, n (%)	0 (0)	91 (81)	30 (75)	61 (85)
Days from VAP diagnosis to death	0.0±0.0	9.3±2.4	8.9±2.2	9.5±2.4
28-day ICU mortality, n (%)	0 (0)	52 (46)	17 (42)	35 (49)

Data shown as mean ± standard deviation or n (%).

* Control group vs the other groups; ‡ Early VAP vs Late VAP group, (P <0.05).

VAP: ventilator-associated pneumonia; APACHE II: Acute Physiological and Chronic Health Evaluation; PaO_2/FiO_2: the ratio of arterial oxygen concentration to the fraction of inspired oxygen; ICU: intensive care unit; NSAID: non-steroidal anti-inflammatory drugs; CPIS: Clinical pulmonary infection score

Table 2: Pathogens associated with ventilator-associated pneumonia

Pathogen	All VAP	Early VAP	Late VAP
Number of patients	111	40	71
MDR	75 (68)	24 (60)	51 (72)
Polimicrobial	31 (27)	6 (15)	25 (35)
Monomicrobial			
Acinetobacter baumannii	12 (10)	5 (12)	7 (9)
Klebsiella pneumoniae	11 (9)	4 (10)	7 (9)
Pseudomonas aeruginosa	7 (6)	3 (7)	4 (5)
Staphylococcus aureus	4 (3)	2 (5)	2 (2)
Escherichia coli	3 (2)	1 (2)	2 (2)
Others	7 (6)	3 (7)	4 (5)
Non-MDR	36 (32)	16 (40)	20 (28)
Polimicrobial	4 (3)	1 (2)	3 (4)
Monomicrobial			
Acinetobacter baumannii	7 (6)	3 (7)	4 (5)
Klebsiella pneumoniae	8 (7)	4 (10)	4 (5)
Pseudomonas aeruginosa	6 (5)	3 (7)	3 (4)
Staphylococcus aureus	5 (4)	2 (5)	3 (4)
Escherichia coli	2 (1)	1 (2)	1 (1)
Others	4 (3)	2 (5)	2 (2)

All data shown as n (%)
VAP: ventilator-associated pneumonia; MDR: multi-drug resistant

Statistical analysis

Categorical variables were described as counts and percentages (%), whereas continuous variables were described as means (± standard deviation). Pearson's chi-squared and Fisher's exact tests were used to compare the distribution of the categorical variables. The distribution normality of the continuous variables was analyzed by Kolmogorov-Smirnov test. For normally distributed variables, the statistical differences among the means were analyzed by Independent Samples t-test. For non-normally distributed variables, Mann-Whitney U test was preferred. The correlations (r values) were assessed using Pearson's correlation coefficient. Receiver operating characteristic (ROC) curve was used to analyze the capacity of serum HDL and PCT in differentiating the antimicrobial resistance state. The area under curve (AUC) and 95% confidence interval (CI) were recorded. Youden's indices (sensitivity + specificity – 1) were calculated to determine the best discriminatory cut-off values. All tests of significance were two-tailed with *P*-value <0.05.

RESULTS

During the observation period, 209 patients had clinical VAP suspicion, but 111 patients had microbiologically confirmed VAP and were included in the study (Fig 1). The characteristics of the patients were pointed in Table 1. Forty (36%) of the patients had early-onset VAP, while 71 (64%) of the patients had late-onset VAP. Significant differences between VAP patients and control group as regards APACHE II score, the ratio of arterial oxygen pressure to fraction of inspired oxygen (PaO_2/FiO_2) and vasopressor need were noted. However, no significant difference between early and late-onset VAP groups regarding APACHE II score, PaO_2/FiO_2 ratio and vasopressor need was present. Likewise, no statistical difference between control group and VAP patients was observed for other characteristics. Intubation durations were significantly longer in late-onset VAP group (*P*=0.001). This was probably due to the distinct definitions of early and late-onset VAP. When other clinical outcomes were compared, no significant difference between early and late-onset VAP groups was noticed (Table 1).

MDR-Ps were found to be the causative agents in 75 (68%) of all VAP patients and they were the predominant infectants in both early and late-onset VAP groups. Although rate of MDR infection was higher in late-onset group than early-onset group (72% vs 60%), the difference was not significant (*P*=0.21). Thirty-five (31%) of the VAP patients had polymicrobial infection. The prevalence of polymicrobial infection in late-onset group (n=28, 39%) was significantly higher (*P*=0.01) than early-onset group (n=7, 17%; Table 2).

Serum lipid profiles and inflammatory conditions of VAP and control groups were analyzed. In VAP groups, total cholesterol (TCH), HDL and low-density lipoprotein (LDL) levels decreased but white blood cells (WBC), CRP and PCT levels increased (*P* <0.05). The difference in triglyceride (TG) and erythrocyte sedimentation rate (ESR) levels among VAP and control groups were not significant. There was no significant difference between two VAP groups in terms of inflammatory biomarkers (Table 3).

A significant difference between MDR and non-MDR groups was noted with regard to HDL (*P*=0.002) and PCT (*P*=0.001) levels. However, no statistical difference between groups was observed for other inflammatory biomarkers (Table 4).

Table 3: Serum lipid levels and inflammatory state at VAP diagnosis

Variables	Control	All VAP	Early VAP	Late VAP
No.	50	111	40	71
TCH (mg/dL)	153.3±37.8	126.1±39.3*	129.1±35*	124.5±41.7*
HDL (mg/dL)	41.9±9.5	34±7.7*	33.7±7*	34.2±8.1*
LDL (mg/dL)	91.9±28.9	70.7±29.5*	73.2±15.1*	69.2±35.1*
TG (mg/dL)	133.8±68.2	140.4±66.7	139.4±19.5	141±82.3
WBC ($\times 10^3/\mu l$)	11.6±5.5	14.3±7.7*	13.9±4.7*	14.5±9*
ESR (mm/h)	41.3±32.6	49.1±36.2	49±17.3	49.1±43.5
CRP (mg/L)	48.2±43.3	79.7±73.5*	79.3±40.4*	80±87.1*
PCT (µg/L)	0.3±0.4	15.5±14.8*	14.4±9*	16.1±17.3*

Data shown as mean ± standard deviation
* Control group vs the other groups; ‡ Early VAP vs Late VAP group, (*P* <0.05).
VAP: ventilator-associated pneumonia; TCH: total cholesterol; HDL: high-density lipoprotein cholesterol; LDL: low-density lipoprotein cholesterol; TG: triglycerides; WBC: white blood cells; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; PCT: procalcitonin

Table 4: Inflammatory biomarkers and antimicrobial resistance

Variables	MDR	Non-MDR	*P*-value
No.	75	36	
TCH (mg/dL)	121.3±37.2	136.1±42.1	0.06
HDL (mg/dL)	31.1±7.3	37.5±10.4	0.002*
LDL (mg/dL)	66.5±24.2	79.4±37.1	0.06
TG (mg/dL)	145.8±58.0	131.6±82	0.36
WBC (×10³/μl)	15.2±7.2	12.6±8.4	0.09
ESR (mm/h)	53±32.4	41.6±42.5	0.1
CRP (mg/L)	85.1±69.4	68.7±81.3	0.3
PCT (μg/L)	17.9±11.2	11.1±8.7	0.001*

Data shown as mean ± standard deviation, * *P* <0.05.
MDR: multi-drug resistant; TCH: total cholesterol; HDL: high-density lipoprotein cholesterol; LDL: low-density lipoprotein cholesterol; TG: triglycerides; WBC: white blood cells; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; PCT: procalcitonin

The relation between APACHE II, by which the disease severity was assessed, and the inflammatory responses was analyzed in VAP patients. The correlation analysis showed significant negativity between APACHE II and HDL. In contrast, the correlation was significantly positive for PCT, and weak for other biomarkers. When compared with HDL, the relationship between PCT and APACHE II was more pronounced (r=-0.205, *P*=0.031; r=0.238, *P*=0.012, respectively). In addition, the correlation coefficient of HDL with PCT was studied using bivariate analysis. A significantly negative correlation was observed between HDL and PCT in VAP patients (r=-0.242, *P*=0.01). There was no statistical correlation between HDL and PCT in non-MDR group (r=-0.228, *P*=0.18), but HDL was negatively correlated with PCT in MDR group (r=-0.290, *P*=0.01).

ROC analysis was performed for tracheal aspirate cultures to evaluate the diagnostic accuracy of HDL and PCT in identifying MDR organisms. A serum HDL best cut-off value of 36.2 (sensitivity: 76%; specificity: 63.9%; AUC: 0.727, 95% CI, 0.628-0.826; *P*<0.001) and a serum PCT best cut-off value of 19.8 (sensitivity: 44%; specificity: 94.4%; AUC: 0.689, 95% CI, 0.589-0.789; *P*=0.001) were selected by ROC curve for efficacy analysis. Comparison of the AUC for HDL and PCT revealed there was no statistically significant difference so it could be assumed that HDL and PCT had similar diagnostic values in assessing the infection risk by MDR organisms in VAP patients (difference between areas: 0.037; SE: 0.067; 95% CI, -0.094-0.169; *z*=0.558; *P*=0.58).

The AUC and the sensitivity of serum HDL was higher than serum PCT, while the specificity of serum PCT was higher than HDL. This indicates a combined assessment by HDL and PCT may be a more effective measure in the evaluation of antimicrobial resistance states of VAP patients. Briefly, with the combination

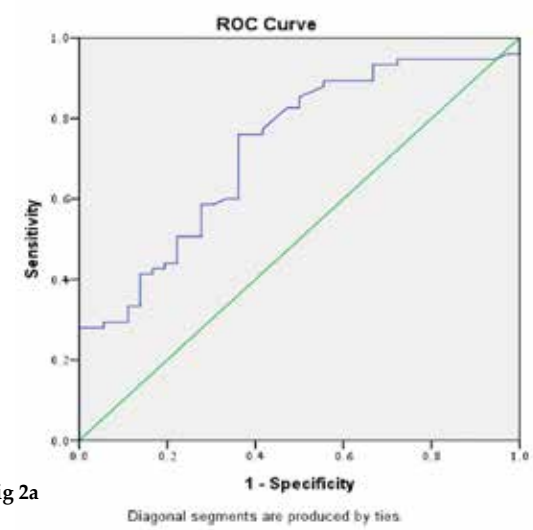

Fig 2a

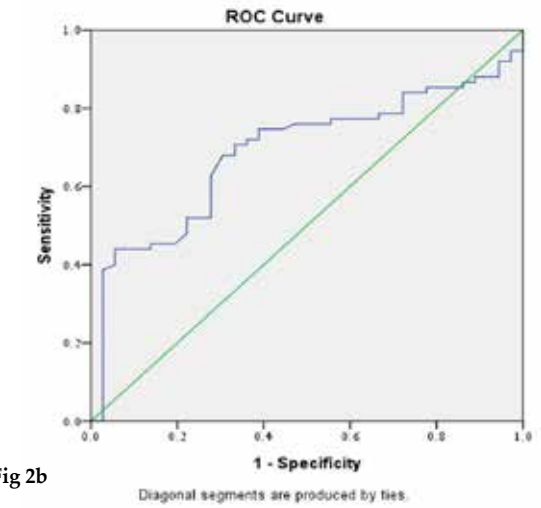

Fig 2b

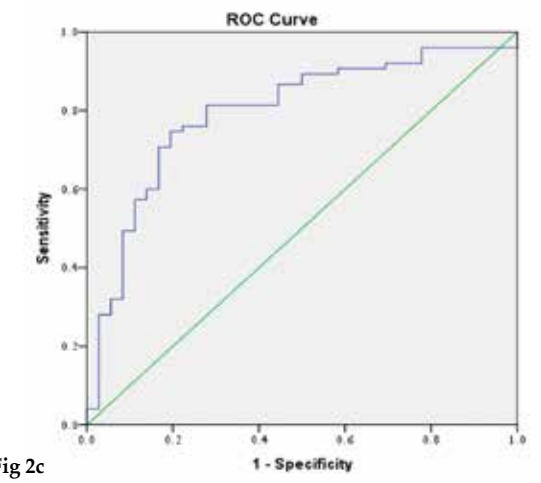

Fig 2c

Fig 2: Receiver operating characteristic (ROC) curves for a) HDL (AUC: 0.727, 95% CI, 0.628-0.826), b) PCT (AUC: 0.689, 95% CI, 0.589-0.789) and c) the combination of HDL and PCT (AUC: 0.796, 95% CI, 0.706-0.885) in patients with VAP to differentiating the antimicrobial resistance state.

of HDL<36.2 mg/dL and PCT>19.8 μg/L to assess antimicrobial resistance, the AUC, sensitivity and specificity reached 0.796, 75% and 81%, respectively (Fig 2).

DISCUSSION

The duration of the MV is often associated with the type of infecting organism. Antibiotic sensitive pathogens usually cause early-onset VAP, whilst MDR-Ps often lead to late-onset VAP. Kalil *et al* reported that hospitalization of 5 days or more was a risk factor for MDR infection[16]. Nonetheless, this is a controversial subject and it is suggested in recent investigations that the diversity in the infecting organisms of early and late-onset VAP are becoming less prominent. In other words, MDR-Ps are getting more closely related with early-onset VAP, although they are the common agents of late-onset VAP[17].

Martin-Loeches *et al* divided 485 nosocomial pneumonia patients into two groups. Patients in group 1 did not have specific risk factors for MDR infection, yet MDR-Ps were isolated in 50.7% of them. They also figured out that in centers where prevalence of MDR infection was greater than 25%, MDR-Ps were independently associated with pneumonia, sepsis and septic shock[17]. In the large German database, Gastmeier *et al* demonstrated that the causative agents of early and late-onset VAP were akin to each other[18].

The prevalence of MDR-Ps varies intra and inter-institutionally[1]. Restrepo *et al* analyzed the bacterial etiology of 248 early and 248 late-onset VAP patients. They discovered that incidences for MDR infections in early and late-onset VAP were quite close to each other, although late-onset VAP patients had been exposed to more antibiotics in the preceding month and had higher APACHE II scores at the admission[19]. Ferrer *et al* divided 276 ICU acquired pneumonia patients into two groups. Although group 1 had no risk factor for MDR infection according to the criteria specified in 2005 guidelines, potentially drug-resistant microorganisms in 26% of them were isolated[20]. Hu *et al* performed etiological analysis of 95 VAP patients and demonstrated that the isolated pathogens in the cultures were mostly MDR[21]. In our study, 60% of patients in early-onset group and 72% of patients in late-onset group were infected by MDR-Ps. Hence, similar infection rates by MDR-Ps in both groups were recorded.

Uvizl *et al* assessed the relationship between pneumonia types and MV parameters. Having high infection rates by MDR-Ps, late-onset hospital-acquired pneumonia group was associated with more severe lung inflammation and higher rates of complications. They propounded that pulmonary damage and impairment of respiratory functions were directly related with the type of pneumonia and MV parameters[22]. However, in their study, VAP was not considered as a subgroup of hospital-acquired pneumonia and the results of microbiological tests were not analyzed. Therefore, the outcomes of the study were accordingly.

Significant alterations in the lipid profile of patients with acute infection were evinced in the recent studies such as decrease in the levels of TCH, HDL, LDL, apolipoprotein-A1, and apolipoprotein-B and increase in the levels of TG and very low-density lipoprotein[23]. Reguero *et al* evaluated the lipid profile of 60 community-acquired pneumonia (CAP) patients and discovered that their TCH, HDL, apolipoprotein-A1 and apolipoprotein-B levels were significantly lower than those of the control group. Their lipid parameters other than HDL returned to normal 15 days after the infection; however, HDL levels continued to increase for 6 months[8]. Gruber *et al* examined 572 patients, 372 having CAP and 200 having other lower respiratory tract infections (LRTI). In LRTI patients, TCH, HDL and LDL levels were lower at admission than discharge. HDL was equivalent to CRP and better than WBC in distinguishing CAP from other LRTIs and predicting bacteremia[24].

In our study, patients with acute infection had TCH, HDL, and LDL levels decreased and inflammatory serum biomarkers such as WBC, CRP and PCT levels increased. The alterations showed the severity of inflammatory response and were compatible with those discovered in previous investigations. No significant differences were found between early and late-onset pneumonia patients in terms of APACHE II score, inflammatory biomarkers including serum lipids and clinical outcomes. We have thought this owed to the similar infection rates by MDR-Ps in both groups. Therefore, we have tended to investigate whether serum lipid levels of pneumonia patients had relation with the antimicrobial resistance states of the infectants. Eventually, we have compared MDR and non-MDR patients with each other in this aspect. We have hereby found HDL levels decreased and PCT levels increased significantly in MDR patients.

PCT is secreted as part of the systemic inflammatory response to infection. Serum PCT levels vary greatly depending on the type of infection[25]. In sepsis patients, PCT levels increase earlier than CRP and cytokine levels and the increase continues longer in duration. PCT levels also correlate significantly with the severity of infection[26]. Ramirez *et al* conducted their study on 44 patients undergoing MV for more than 48 hours and discovered that PCT was superior to CRP as a biological marker in recognizing VAP[27].

It was pointed out in various studies conducted on patients with pneumonia and sepsis that the

characteristics of the causative agents affected the severity of disease and the density of inflammation[28-30]. Zou *et al* performed their study on 76 sepsis patients and discovered that HDL levels were significantly reduced in GN sepsis compared to GP sepsis. They also found that PCT reflected the inflammatory state but failed to distinguish type of the sepsis[31]. Nonetheless, recent studies have provided evidence that PCT might still be useful in differentiation of GN and GP bacteremia[32-34]. Gomez-Zorilla *et al* assessed acute inflammatory states of 61 patients infected by several *Pseudomonas aeruginosa* strains with variable susceptibilities against antibiotics. Compared to non-MDR-Ps, extensively-drug resistant pathogens (XDR-Ps) were demonstrated to cause further increase in the inflammatory biomarkers[35]. As compatible with the previous studies, we have pointed out significant changes in PCT and HDL levels in MDR patients compare to non-MDR ones. This has been probably due to patients' multifarious acute phase responses against the inflammatory mediators[6,7,9,10].

Some researchers suggested that in patients with systemic inflammatory response syndrome, sepsis and septic shock, decreased HDL level was associated with disease severity[31,36]. Tanaka *et al* studied the relationship between lipid profile and disease severity in septic patients. The disease severity had negative correlation with HDL but no significant relation with LDL or serum triglyceride existed[37]. As the disease severity might be viewed as the direct indicator of inflammation in patients with pneumonia, our results were considered to be consistent with these findings that point out correlations between inflammatory markers and serum HDL since we have found significant relation between APACHE II and serum HDL. Theoretically, the degree of disease severity scored by APACHE II is a reliable indicator of the inflammatory response like in the case of other inflammatory markers. Therefore, parallel to the inverse relations between acute phase proteins and HDL, we may expect a negative correlation between HDL and APACHE II.

In our study, negative correlation of serum HDL and the well-known inflammatory marker which is PCT was found to be significant (P <0.05). In addition, there was a stronger correlation between HDL and PCT in MDR VAP than non-MDR VAP. Therefore, besides being a component of lipid metabolism, HDL can be an inflammatory marker for MDR infections. These results are consistent with the previous studies that reveal the severity of the inflammatory response may vary depending on the characteristics of the causative microorganisms and antimicrobial resistance is associated with an increase in the systemic inflammation.

In the present study, the diagnostic quality of HDL and PCT in MDR pneumonia was appraised. In patients with VAP, HDL cut-off value of 36.2 mg/dL could aid exclude an infection caused by MDR with a sensitivity of 76%. A PCT cut-off value of 19.8 μg/L could help predict an infection caused by MDR with a specificity of 94.4%. At the same time, HDL and PCT showed fair discriminative capacity in MDR VAPs (AUC: 0.727 and 0.689, respectively), and the diagnostic value of both biomarkers was similar (P=0.58). HDL and PCT measured in combination to diagnose VAP demonstrated a higher AUC (0.796) than HDL and PCT measured separately. These data indicated the usefulness of HDL and PCT combination in evaluating the MDR status of VAP patients. Therefore, in patients with clinically suspected VAP and whom microorganisms are detected by direct microscopy of respiratory specimens, HDL and PCT may be useful indicators to determine the appropriate empirical antimicrobial therapy involving agents against MDR-Ps.

Serum TG levels were also shown to be increased by acute phase reactants[6,7]. Besides, ESR was considered as an important acute phase reactant and a marker of inflammation. In our study, VAP patients had higher TG and ESR levels than control group patients, but the difference was not significant. TG and ESR levels increased even more prominently in MDR patients, but there was again no statistically significant difference. Therefore, both biomarkers were not sufficient to assess the inflammatory response of VAP patients against infection.

Tanaka *et al* compared the lipid profile of 50 sepsis and 25 trauma patients in ICU. They discovered that HDL levels were significantly lower in septic patients, but no pronounced difference in trauma patients were detectable[37]. In addition, LDL and TG levels were similar in among sepsis and trauma patients. Although both sepsis and trauma patients were characterized by increased systemic inflammation, a significant decrease only in HDL levels among sepsis patients suggested that HDL had a value to diagnose an infection in trauma patients. Hence, HDL may be an appropriate marker for the evaluation of the inflammatory response of VAP-developing surgery/trauma patients.

According to previous studies, polymicrobial VAP ratio varies greatly. In the studies of Joseph *et al*, Combes *et al* and Patil *et al*, polymicrobial VAP ratios were reported respectively as 30-70%, 48% and 55.4%[3,38,39]. In the study of Tedja *et al*, all patients had late-onset VAP and polymicrobial VAP ratio was 17%[40]. We had 31% of our patients with polymicrobial VAP. Ferrer *et al* divided 256 ICU acquired pneumonia patients into two

as monomicrobial (n=215) and polymicrobial pneumonia groups (n=41). The incidence of MDR and XDR infections in polymicrobial pneumonia group was not increased and systemic inflammatory responses of both groups were similar[13]. Therefore, in our study, the higher polymicrobial infection rate in late-onset group was not thought to cause different inflammatory responses compare to early-onset group (39% vs. 17%).

The current study has several strengths. First, VAP diagnosis was established precisely and confirmed by isolating the microbiological agents. Second, in order to avoid the potential effects of extra-pulmonary infections on biomarker levels, patients with active infection at the diagnosis or developed extra-pulmonary infection within 72 hours were excluded out the study. Third, to the best of our knowledge, this is the first study performed on VAP patients, which relates the alterations in serum lipid levels to the antimicrobial resistance states of infecting organisms. Our study has several limitations also. The variable intra- and inter-institutional prevalence of VAP agents generates the first limitation[1]. Thus, the results of our single-centered study cannot be generalized for other institutions or ICUs. Second, possible concurrent viral infections may cause different inflammatory responses, but our patients were not examined for viral agents. Third, factors that may affect lipid parameters such as race, familial lipid metabolism disorders and nutritional states were not taken into consideration. Fourth, in ICU, diverse diagnostic cut-off points of inflammatory markers may occur due to increased complex inflammatory responses of patients treated by MV.

CONCLUSION

In conclusion, TCH, HDL and LDL levels were lower among VAP patients but did not change in early and late-onset pneumonia types. Decrease in HDL levels was prominent in MDR patients. Serum lipids and PCT could be used as proper markers not only to diagnose VAP, but also to evaluate antimicrobial resistance states of patients.

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Author contributions: Omur Ilban designed the study, collected the data and approved the final version; Aysegul Ilban designed the study and prepared the manuscript; Mehmet Ali Bas created the first draft and performed statistical analysis.

Conflict of interest: None to declare.

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Original Article

Type 3 supracondylar humeral fractures in children: Correlation between cross pin angle and fracture stability

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ABSTRACT

Objectives: Stabilization either in cross configuration or lateral -only are the accepted fixation methods of supracondylar humerus fractures. However, there is no suggestion about the cross-pin configuration regarding stability. We sought to determine the optimum cross-pin configuration regarding stability in the coronal plane in the management of the supracondylar humeral fractures in children.
Design: Retrospective study
Setting: Orthopedics and Traumatology Department, Suleyman Demirel University, Isparta, Turkey
Subjects: A total of 45 children (18 female and 27 male) with a mean age of 6 years (range: 2-10) with Gartland type 3 supracondylar humerus fractures
Intervention: Closed reduction and cross-pinning under fluoroscopic guidance
Main outcome measures: Angular changings in Baumann's angle (BA) and humerocapitellar angle (HA) within 6 weeks postoperatively and the relationship of the angular changing with cross-pin angle
Results: Forty-five children enrolled in the study. The mean age was 6 (2-10) years old. Mean change in BA was 6° (0.6°-23.6°), 5.5° (0.1°-34.8°) in HA and the mean cross pin angle was 71.2° (42.4°-124°). There was displacement in 16 (35.6%) patients in the sagittal plane (HA). There was a statistical significance with a negative correlation between the cross-pin angle and HA (rho= -0.275, *P*=0.020). The cross-pin angles in the coronal plane between 70.58° and 83.23° were the most stable degrees regarding HA with a confidence interval of 95%.
Conclusion: Cross-pin configuration between 70.58° and 83.23°, achieving bicortical fixation, and engaging both fragments with an appropriate size pin seems to be the optimum cross-pin fixation.

KEY WORDS: fixation technique, humerus, pediatric, percutaneous pinning, trauma

INTRODUCTION

Supracondylar humeral fractures (SCHF) are the most common fractures around the elbow during childhood[1,2]. The treatment of the SCHF is a challenge, thus suboptimal treatment leads to complications such as nerve injury, vascular injury and angular deformities[3]. Based on the vast literature, there is consensus that displaced fractures should be reduced either in a closed or open manner and stabilized via percutaneous pin fixation[3]. Stabilization either in cross configuration or lateral-only are the most widely accepted fixation methods[4,5]. However, there is still no consensus on the best pin configuration – cross or lateral entry- despite the several meta-analyses, systematic reviews, biomechanical and clinical studies over the past years[1,3,4,6-8]. Additionally, there is no suggestion about the cross-pin configuration regarding stability in the current literature.

With the present study, we sought to determine the optimum cross-pin configuration regarding stability

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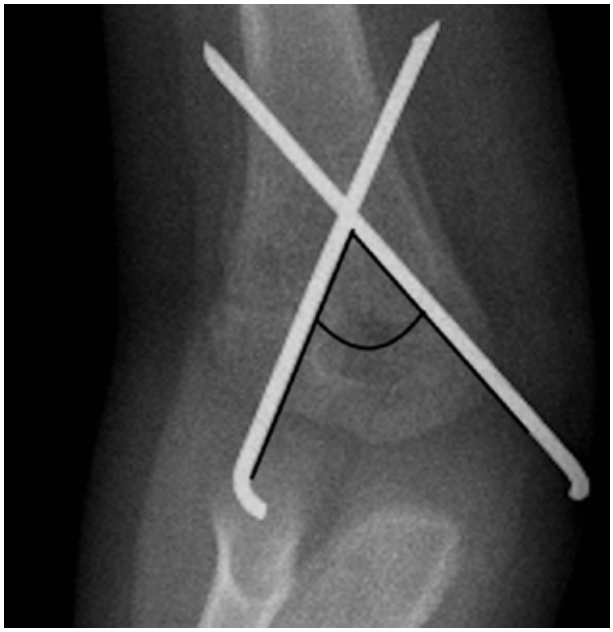

Fig 1a: Cross-pin angle: The angle which is formed by the two cross pins.

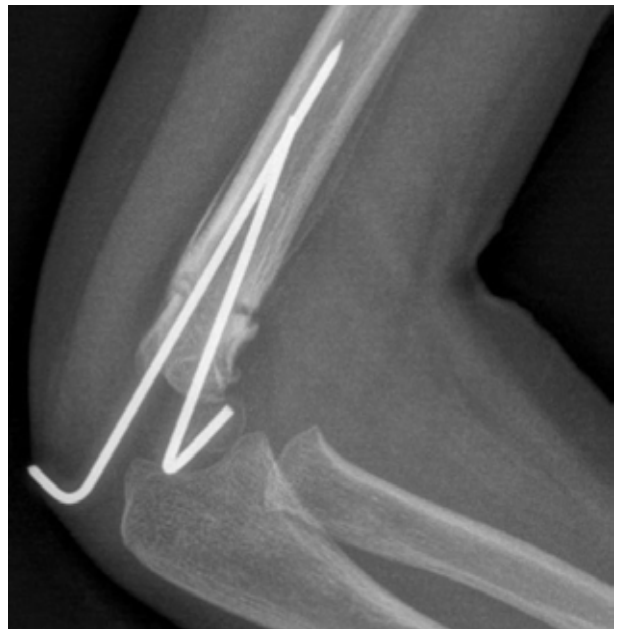

Fig 1b: Post-operative lateral radiograph

in the coronal plane, which may help the surgeon during the operation in the management of the SCHF in children.

SUBJECTS AND METHODS

Children who had extension type 3 Gartland supracondylar fractures and who were managed by closed reduction and percutaneous lateral and medial cross pinning in our institution were retrospectively evaluated after the approval of the local ethics committee (Date: 08/02/2017, No:21). Demographic data including age, gender, side, type of the fracture, neurovascular status, surgical management (either open or close) and pin configuration (lateral / cross) were obtained from the medical files of the patients.

Inclusion criteria were skeletal immaturity (between 2-10 years of age), closed Gartland type 3 extension fractures, and treated within 24 hours of injury via closed reduction and percutaneous cross pinning. Patients who had open fractures, problematic neurovascular situation, had medial wall comminution-unstable, treated after 24 hours of injury, multiple fractures at the same or other extremities and had inadequate early post-operative and/ or control radiographs were excluded.

Surgical technique

Surgery was conducted under general anesthesia in the supine position and pneumatic tourniquet was applied to inflate in case open reduction was required. Reduction and pinning were performed under the guidance of fluoroscopy. 1.5 millimeters (mm) Kirschner wires or 2.0 mm of Steinmann pins were used. The surgeon based on the patients' age and size subjectively chose pin size.

Lateral pin was inserted from the lateral aspect of the hyper flexed elbow to engage the medial cortex firstly. Then the elbow was extended to less than a 90° to avoid the injury of ulnar nerve while inserting the medial pin. The medial pin was inserted from the medial condyle through the finger protecting the ulnar nerve to engage lateral cortex in a closed manner. Placement of a pin across the olecranon fossa was acceptable. Attention was paid to ensure adequate bone fixation both in the proximal metaphyseal and the distal segment. In the sagittal plane, slightly anterior to posterior entry was attempted since the capitellum is anterior to the center of the humerus. After the consideration of acceptable reduction, pinning and stabilization via fluoroscopy either in static and dynamic fashion even with applying varus and valgus stresses pins were bent over the skin. After the surgery, long arm splint was applied approximately at 110°-120° of elbow extension.

During the post-operative period, patients were called for weekly follow-ups. At the 4th week, splint was removed and then, the elbow left free of motion as much as possible with the patients' own pace. At the 6th week, the pins were removed in the clinic after considering the callus formation was enough and the patient was free of pain.

Radiographic evaluation and defining loss of reduction

The type of fracture was considered according to the Wilkins modification of the Gartland classification[9].

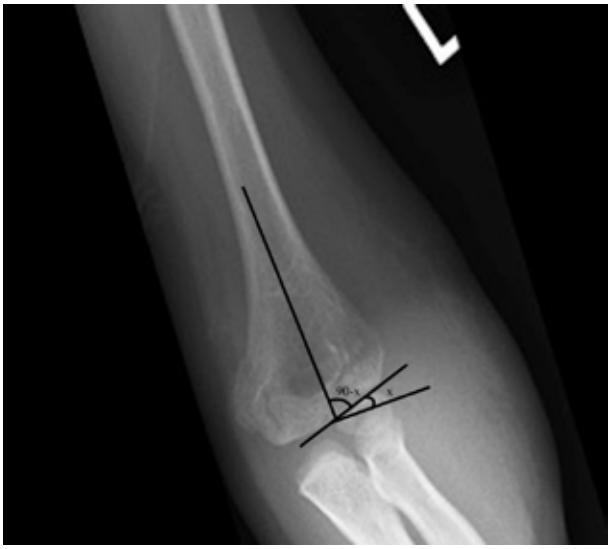

Fig 2: Baumann's angle: The angle which is formed by a line perpendicular to the humeral shaft and a line parallel with the lateral condylar physis. Normative value for Baumann's angle ranges from 8 to 26 degrees.

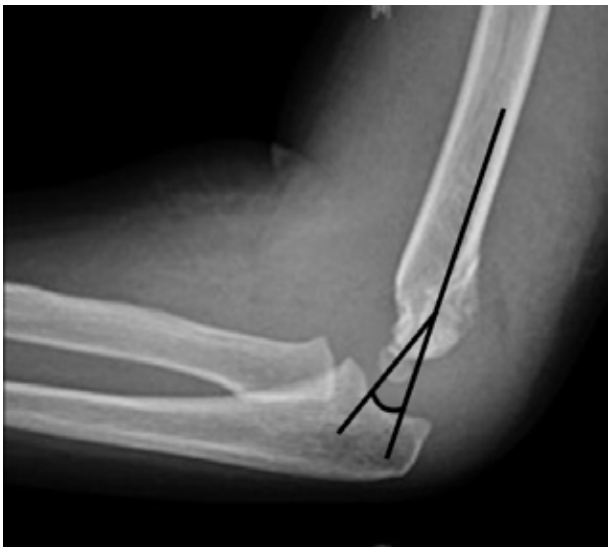

Fig 3: Humerocapitellar angle: The angle which is formed by a line parallel with the anterior cortex of the humerus and a line perpendicular to the physis of the capitellum.

Just after the surgery and during the follow-ups, anteroposterior and lateral radiographs were obtained to check the fracture position and healing.

Due to the purpose of the study, the early post-operative radiographs and the radiographs just before the pin extraction were compared in terms of Baumann's angle (BA) and the humerocapitellar angle (HA). Cross-pin angles were measured in the early post-operative radiographs (Figure 1a and b). Reduction was assessed in the coronal plane using BA[10]. This angle is defined as the angle formed by a line perpendicular to the humeral shaft and a line parallel with the lateral condylar physis. A normative value for BA ranges from 8 to 26 degrees[11] (Figure 2). Reduction in the sagittal plane was assessed using the lateral HA. This angle is formed by a line parallel with the anterior cortex of the humerus and a line perpendicular to the physis of the capitellum[12,13] (Figure 3).

We defined the changings in BA and HA as stated by Gaston *et al* in detail[14] and we accepted BA greater than 6° and a change in HA greater than 10° as a true change in reduction. A change in the BA of <6° was defined as no displacement, 6°-12°mild displacement and >12° major loss as stated by Kocher *et al*[4]. We defined displacement in the sagittal plane as >10° of change in the HA. The angles less than 10° was accepted as no change due to statements of Gaston *et al*[14].

Statistical analysis

Statistical analysis was performed using SPSS software package version 20.0 (IBM Corp. Armonk, NY, USA). Descriptive data of continuous variables were expressed as mean, standard deviation, median, minimum and maximum, whereas nominal variables were represented with percentages. Variables with normal distribution were analyzed with the t-test. Continuous variables were compared using Mann-Whitney U test when the data were not normally distributed. Correlations between variables were tested using Pearson correlation coefficient.

RESULTS

Forty-five children were enrolled in the present study and 18 (40%) were female. The mean age of the patients was 6 (2-10) years old. There were neither iatrogenic ulnar nerve injury nor preoperative and post-operative vascular comprise and infection in any patients. Patients' demographics are given in detail in Table 1.

Mean change in BA was 6° (0.6°- 23.6°) and was 5.5° (0.1°-34.8°) in HA and the mean cross pin angle was 71.2° (42.4°-124°) (Table 1). There was a change in BA

Table 1: Demographics of the patients

Variables	Values
Age (years)	6 (2-10)
Gender (Male/ Female)- n	27 /18
Side (Left /Right)- n	30 /15
Mean change in BA (degree)	6º (0.6º- 23.6º)
Mean change in HA (degree)	5.5º (0.1º-34.8º)
Cross pin angle (degree)	71.2º (42.4º-124º)

BA: Baumann angle, HA: Humerocapitellar angle
n: number of the patients, values in the parenthesis are the minimum and maximum values

Table 2: Number of patients who had loss of reduction according to Baumann angle and humerocapitellar angle

Variables	Degrees	n	%
Angular change in BA	< 6º	22	48.9
	≥6º	23	51.1
Angular change in HA	< 10º	29	64.4
	≥10º	16	35.6

BA: Baumann angle, HA: Humerocapitellar angle
n: number of the patients, %: percentage of the patients

less than 6° in 22 patients (48.9%), 6°-12° in 16 patients (35.5%) and more than 12° in 7 patients (15.5%). Change less than 6° is not considered as a real angular change in BA as stated above. When the changing in the HA more than 10° was considered as the real displacement, there was a displacement in 16 (35.6%) of the patients in the sagittal plane (Table 2). When the changings in Baumann and humerocapitellar angles were compared with the cross-pin angle, statistical significance with a negative correlation was found between the cross- pin angle and the HA. Sagittal plane displacement was increasing as the cross-pin angle decreasing (rho= -0.275, *P*=0.020; Table 3). The cross-pin angles in the coronal plane between the 70.58°- 83.23° angles were the most stable degrees regarding HA with a confidence interval of 95%. The coronal plane displacement was not correlated with the cross-pin angle (*P*=0.101; Table 3).

Table 3: Relationship between angular changings (loss of reduction) in BA and HA between cross-pin angle

	Cross pin angle (Mean±SD)	*P*
Angular change in BA		0.101
<6º	76.85º±12.52º	
≥6º	69.07º±17.99º	
Angular change in HA		0.020*
<10º	76.10º±16.62º	
≥10º	65.56º±11.63º	

**P* <0.05 is statistically significant, BA: Baumann angle, HA: Humerocapitellar angl

DISCUSSION

SCHF are very common in pediatric population and the accepted treatment for SCHF is closed reduction and percutaneous pinning[12,15]. The success of these fractures' treatment depends on achieving and maintaining an acceptable reduction until the fracture is healed[8]. Although the cross-pin construct has been used to stabilize these fractures, concerns about the ulnar nerve injury had led the surgeons to lateral entry pin fixation[1,15]. The configurations of the lateral entry pins and the effect on the stability was discussed in many studies previously and additionally, pin spread distance was mentioned[4,7,15-17]. However, the effect of cross-pin angle was discussed in neither of the studies. We performed the present study considering this issue and found that cross-pin angle has an effect on stability in sagittal plane. Cross-pin angles between 70.58°- 83.23° were the most optimum degrees for stable construct.

The suboptimal treatment of the SCHF leads to serious complications including angular deformities[4,14]. Rotation or the tilting of the distal fragment in coronal plane causes cubitus varus and usually associated with cosmetic deformity, but gunstock deformity[3]. On the other hand, any deformity in the sagittal plane causes loss of elbow functions[3,18]. This reality makes sagittal plane stability more important in protecting elbow functions[19].

Several factors such as type 3 fractures, flexion type fractures, medial comminution and fractures with greater obliquity are associated with the loss of reduction[2]. Three technical reasons for loss of reduction related to lateral only pin fixation was stated: 1) failure to engage both fragments; 2) failure to achieve bicortical fixation; and 3) failure to achieve pin separation >2 mm at the fracture site[19]. However, addition of the medial pin was also emphasized to make the construct more stable in fractures prone to loss of reduction[20]. Moreover, cross-pin configuration recommended when the medial cortex comminution is present instead of lateral entry pin fixation[16]. We can neither adapt nor discuss their findings to our pin configuration and there is no suggestion for cross pin angle according to our knowledge in the literature. Yet, Srikumaran *et al* emphasized the importance of cross-pin configuration determining the biomechanical stability in the sagittal plane[18].

When the study of Aarons *et al* is considered, even though the statistically significant association is found only in cross-pin fixation performed type 3 fractures between the pin spread ratio and absolute change in Baumann's angle, they could not state any certain amount of divergence regarding construct stability and confirmed all constructs equally stable[15]. Our study does not support this finding, whereas there is no other study considering this issue. Yet, Pennock *et al* stated the narrow pin spread in the coronal plane related to loss of reduction in the sagittal plane regardless of additional medial pin placement[2]. As the pin spread increases, the angle between the pins will also increase. This issue partly supports our study. The partial support is because, when the pin spread exceeds some degrees, stability will be broken due to reduced grip of the opposite cortex. The present study gave us a chance of reporting certain degrees of pin angle regardless of fracture configuration, which is an important limitation of the study.

Gaston *et al* reported the loss of reduction more in sagittal plane than the coronal plane in the cross-pinning group with a mean change of 5.1° (28% vs 18%), which is comparable to our results[14]. Thus, effect of cross-pinning on sagittal plane stability seems more than on coronal plane stability when Gaston *et al*'s and Srikumaran *et al*'s is considered[14,18,20]. Our results regarding angular changings in both planes are also comparable with the results of a previous study with mean angles of 6.4° 4.8° in Baumann angle and 7.0° 6.9° in humerocapitellar angle[12]. Additionally, we found no correlation between cross-pin angle and coronal plane displacement. There is no other study lightening this issue to compare the results.

Pin width was also stated as an important factor related to loss of reduction[18,20]. Fixation of the supracondylar fractures with larger pins (>0.9mm) was stated as more stable, particularly in sagittal plane than the small ones[20]. In addition, fixation with 1.6 mm of pins in cross fashion was stated as stable as 2.8 mm pins in any fashion considering sagittal plane particularly in a biomechanical study emphasizing the importance of cross-pin fixation[18]. We did not evaluate the pin size, but the pins that were used 1.5 or 2.0 mm. and larger than 0.9 mm which is larger than suggested. Considering the studies of Srikumaran *et al*, we can omit the effect of pin size on stability. Furthermore, no other study except Srikumaran *et al* has addressed this issue as an independent variable[20].

Inclusion of the patients who only had anatomical reduction post-operatively is the strength of this study. Moreover, it was stated that malreduced fractures are not prone to loss of reduction and must be differed from the fractures reduced and fixed anatomically that lost reduction[14]. Additionally, we did not include the fractures with medial comminution and long oblique fractures in the study group.

Main limitations of the present study are retrospective design and no evaluation of the different fracture configurations such as long oblique, short oblique or fractures with medial comminution. Being biomechanically unsupported is another limitation of the present study but can be done as another study subject, including other fracture types such as short, long oblique and with medial comminution.

CONCLUSION

Even though the malalignment in the sagittal plane leads to functional impairments, this issue has not gotten the attention deserved as well as coronal plane alignment in the literature. Nevertheless, there is no existing data evaluating the cross-pin angle except the present study considering stability of the fixation. Cross-pin configuration in a custom angle, achieving bicortical fixation, and engaging both fragments with an appropriate size pin seems to be optimum fixation technique regarding stability when the rotational stability is particularly considered. Therefore, more studies comprising more patients are needed to strengthen our findings, either in fractures having medial comminution and other fracture configurations leading instability.

ACKNOWLEDGMENT

Author contribution: Emrah Kovalak planned, analyzed the data, designed and wrote the manuscript; Tolga Atay designed the study, analyazed and wrote the data; Firat Seyfettinoglu planned and analyzed the data, and wrote the manuscript; Vecihi Kirdemir and Yakup Barbaros Baykal planned and analyzed the data, and checked and edited the manuscript.

Conflict of interest: None.

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Case Report

Brucellosis relapse seven years after first infection in a COVID-19 patient: A case report

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ABSTRACT

Coronavirus disease 2019 (COVID-19) emerged in China and then has spread worldwide. It has been seen in Turkey since March. Brucellosis is a zoonotic disease which is observed in Turkey endemically. Here, we report the firstcase of Brucellosis relapse in a COVID-19 patient.

A 39-year-old female had cough, dispnea, fatigue and backpain and miyalgia for one week was admitted. She had leucopenia and lymphopenia in whole blood count. She had a contact history with her COVID-19 positive sister. COVID-19 polymerase chain reaction (PCR) test resulted positive. She received hydroxychloroquine treatment for five days. Her COVID-19 PCR became negative and laboratory improved. Her miyalgia, back pain and fatigue got worse. When her medical history was elaborated, she had a brucellosis history seven years ago. She was completely treated and her Brucella serology tests were negative in 2015. She stated that she didn't consume any unpasteurized milk product recently. Rose-Bengal and Coombs agglutination tests were positive (1:320 titers). She was initialized on treatment and symptoms started to resolve after 15 days of treatment.

Severe COVID-19 patients show lymphopenia, particularly reduction of T-cells. Cell mediated immunity is crucial against brucellosis. During pandemic, endemic infections like brucellosis can be observed in patients due to lymphopenia. Further immunological studies are needed.

KEY WORDS: brucellosis, COVID-19, leucopenia, lymphopenia

INTRODUCTION

In December 2019, serious illness causing severe pneumonia and deaths were reported from Wuhan, China. Soon after that, the number of cases had increased dramatically and the disease spread across China, and then worldwide[1].

The first COVID-19 case in Turkey was reported on March 11 and has been seen increasingly. The symptoms of COVID-19 include fever, cough, fatigue, vomiting, diarrhea and less commonly headache, sputum production and hemoptysis[2,3]. Brucellosis is a zoonotic disease which is seen wide spread all over the world and caused by *Brucella spp.* that are gram-negative cocobacilli[4]. It is still a public health problem in developing countries, especially in the Mediterranean basin[5]. Brucellosis can affect multiple organs and systems and various clinical signs and symptoms can be observed, as fever, fatigue, myalgia and backpain. Patients can be misdiagnosed, because of the non-specificity of symptoms. After the first infection, it can relapse even after years. Approximately, 10% of brucellosis patients get relapsed, 90% of these occur within one year after discontinuation of antimicrobial treatment[6]. Here, we report the first case of brucellosis relapse in a COVID-19 patient.

CASE REPORT

A 39-year-old female patient, who had complaints of cough, dispnea, fatigue, backpain and myalgia for one week, was admitted to emergency department. She had a history of contact 10 days ago with her sister who is a nurse in another healthcare facility

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and positive for COVID-19. Her blood tests and chest computed tomography (CT) scan were performed with the preliminary diagnosis of COVID-19. She had bilateral widespread ground-glass opacification in her chest CT scan.

She had leucopenia ($2.47x10^3/\mu L$) and lymphopenia ($0.95x10^3/\mu L$) in complete blood count. Her liver enzymes, renal function tests, coagulation tests and inflammatory markers were within normal ranges. She was hospitalized to the infectious diseases ward in the pandemic hospital. Oropharyngeal and nasopharyngeal samples were taken for COVID-19 PCR test. She was initialized on hydroxychloroquine and enoxaparine according to national treatment and management guideline[7]. Her COVID-19 PCR test resulted positive. On the 5th day, hydroxychloroquine treatment was discontinued and control samples were taken repeatedly on the 5th and 6th day and both resulted negative. Laboratory tests were repeated and leucopenia and lymphopenia improved on the 5th day. Despite this improvement, her myalgia, backpain and fatigue got worse. When her medical history was elaborated, she had a medical history of brucellosis seven years ago and she was completely treated. Her medical records were investigated and it was found that Rose Bengal and standard tube agglutination tests were negative in 2015, two years after treatment. Also, she stated that she didn't consume any unpasteurized milk product recently. Rose Bengal serum agglutination and Coombs' agglutination tests were performed. Rose Bengal serum agglutination test was positive and Coombs' agglutination test was 1:320 titers positive. She was initiated on doxycycline and rifampicin treatment. Her symptoms started to resolve after two weeks of antimicrobial treatment.

DISCUSSION

In December 2019, a novel coronavirus which was later named severe acute respiratory syndrome coronavirus 2, unexpectedly emerged in Wuhan, China. It spread across China, and then all over the world. The World Health Organization declared that as a public health threat and emergency of an international concern on January 31, 2020. At the end of April, the disease has been spreading worldwide and has caused over 3 million cases and 200,000 deaths[8]. This disease recently has taken an important place in our daily practice and changed it[9]. Immunological findings about COVID-19 were mainly reported in severe cases. Patients with severe diseases usually showed lymphopenia, particularly reduction of peripheral T lymphocytes[10]. Brucellosis is a zoonotic disease, which can effect many systems and organs, and it is seen endemically in our country. Various signs and symptoms can be observed during disease course. In addition, some laboratory changes like anemia, leucopenia, pancytopenia and elevation of liver enzymes can be seen[5]. The cell-mediated immune responses have a crucial role in host defense against intracellular bacteria like *Brucella spp.* The contribution of antigen-presenting cells (macrophages and dendritic cells) and consequently induction of T-lymphocytes (CD 4+ and CD8+) play a crucial role[11] After first infection, relapse can occur even after many years. In a previous report, relapse of brucellosis was reported with gall bladder involvement after 28 years from the first infection[6].

CONCLUSION

This is the first case of brucellosis relapse in a COVID-19 patient. It was thought that decrease in lypmphocyte count might have caused this relapse. During pandemic, it is important to keep in mind endemic infections like brucellosis for differential and additional diagnosis while symptoms don't improve, despite laboratory improvement in patients.

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Author contributions: Muge Ayhan treated the patient and wrote the manuscript; Ayse Kaya Kalem treated and collected the data; Hatice Rahmet Guner treated and did critical revision of the manuscript.

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Case Report

Amputation of ulnar four fingers due to decompression delay in acute compartment syndrome of the hand in a diabetic patient

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ABSTRACT

Acute compartment syndrome (ACS) of the hand is a surgical emergency. Usually, it follows an injury. Non-traumatic ACS of the hand is relatively rare. In ACS, increased pressure in one or more fascial spaces leads to decreased perfusion pressure and subsequently, muscle and nerve ischemia. In diabetic patients, it occurs even more frequently. Early diagnosis is crucial in hand ACS as decompression delay can impart significant functional loss. We report a case of non-traumatic ACS of the hand in a diabetic patient, where decompression delay resulted in amputations of ulnar four fingers.

KEY WORDS: amputation, diabetic hand, acute compartment syndrome, non-traumatic

INTRODUCTION

Acute compartment syndrome (ACS) of the hand is a surgical emergency. Hand ACS usually follows an injury and presents with progressive worsening of pain and swelling of the hand. Non-traumatic ACS of the hand is under reported in the literature. Among the causes, reperfusion injuries, intravenous (IV) fluid infiltration, hemorrhage associated with anticoagulation medications, sustained compression due to arm position in the setting of an unconscious person, snake envenomation, and insect bites are reported[1].

In ACS, increased pressure in one or more osteo-fascial spaces leads to decreased perfusion pressure and subsequently, muscle and nerve ischemia. In diabetic patients, it occurs even more exponentially due to associated angiopathy and neuropathy. So, it is important to keep a high degree of clinical suspicion to diagnose ACS early, as delay in treatment can translate into debilitating consequences with important functional repercussions[2,3].

We report a case of non-traumatic ACS of the hand, where decompression delay resulted in amputations of ulnar four fingers, which could be avoided if emergency fasciotomies would be done in the earliest possible time.

CASE REPORT

A 70-year-old Bangladeshi female was referred to our medical centre with mild pain and swelling of the left-hand following displacement of IV cannula one day back. Patient was a known case of type II diabetes mellitus and hypertension.

On presentation, the patient's attendant gave a history of stroke three days back and the patient was unconscious. She was initially treated in a local hospital where IV cannula was inserted at the dorsal aspect of the left hand. Unfortunately, IV cannula was inadvertently displaced and there was extravasation of normal saline into the dorsum of the hand which led to swelling. As the patient was disoriented, she did not complain of pain till the next morning. Due

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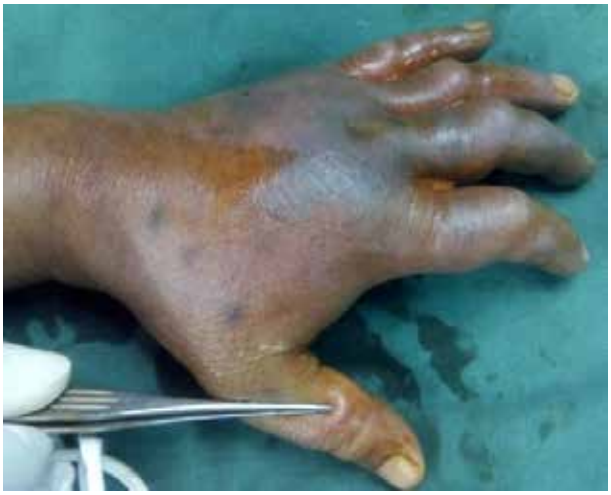

Fig 1: Pre-operative clinical picture of the hand.

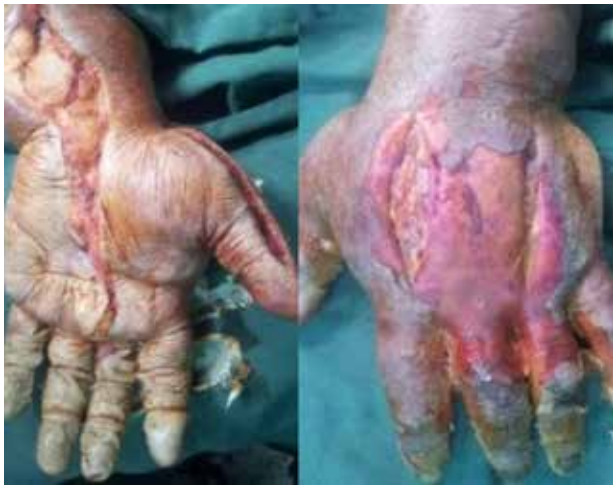

Fig 3: Clinical picture of the hand after 48 hours of fasciotomy

to unavailability of the surgeon at that centre, she was referred to our hospital.

At presentation in our emergency department, her left hand had severe generalized oedema with bluish discoloration of the skin. It was in intrinsic- minus posture (Figure 1). Skin was tense. Tenderness was noted extending to her wrist. She had pain on passive flexion and extension of hand joints. Deep sensation in median and radial nerve distributions was diminished but ulnar nerve distribution was absent. Capillary refill time was within normal limit in thumb but delayed in index finger and absent in other fingers. She was diagnosed clinically as ACS of the hand. Her blood sugar was uncontrolled, serum electrolyte level showed hyponatraemia and ultrasound of the left hand revealed generalized oedema. CT scan of brain showed haemorrhagic stroke. She did not have any previous vascular insufficiency. After consultation with the intensive care unit, she underwent emergency fasciotomies through multiple dorsal and volar hand incisions. Fasciotomies were done over all the digits through mid-lateral incisions. Thenar and hypothenar spaces were released. An extended carpal tunnel release was also performed (Figure 2). However, in total there was a decompression delay of about 36 hours from the appearance of the symptoms to the time of the surgery. During the time of fasciotomy, her fingers showed marked signs of ischaemia. There was no sign of revascularization of the fingers following fasciotomy (Figure 3). After two days of fasciotomy, due to signs of ischaemic gangrene, the ulnar four fingers were amputated along with the

Fig 4: Post-operative picture at follow up clinic after six months of healing of the wound

Fig 2: Clinical picture of the hand after fasciotomies.

debridement of the skin of the dorsal and volar aspect of the hand. Subsequently, the wound was covered with split thickness skin graft. The wound healed and patient developed contracture at the first web space that hampered her thumb function (Figure 4). After six months, functional outcome was measured by Disabilities of the Arm, Shoulder and Hand score, which was 75.

DISCUSSION

Non-traumatic ACS of the hand is not a common presentation, hence less reported[1]. Among the reported causes, ischemia-reperfusion injury, thrombosis, bleeding disorders, vascular disease, anticoagulation, nephrotic syndrome, animal poisonings and bites, extravasation of IV fluid, massive fluid resuscitation, prolonged limb compression, revascularization procedures or treatments are common[4]. In diabetics, due to associated neuropathy and angiopathy, any such condition rapidly leads to ischemia and tissue necrosis. Our patient developed ACS of the hand because of extravasation of fluid from the inadvertent displacement of IV cannula, which was initially unnoticed due to the patient's altered level of consciousness. Early delay of diagnosis and decompression led to ischemia and necrosis.

In the upper limb, the most common site of ACS is the forearm and it presents with the typical physical findings of severe and disproportionate pain to the injury, pain on passive stretching of the wrist and finger flexors and progressive neurological deficits. In contrast, ACS of the hand is usually considered when the hand is significantly swollen in a context where it is difficult to determine if there is more pain than would be expected and usually with no neurological dysfunction[5]. There are also limited objective criteria to assist in diagnosis of hand ACS[5]. However, Ogrodnik *et al* reported that ACS of the hand may present with unique intra-compartmental nerve pain more intensely in the hand than in the forearm, as the median nerve traverses through the carpal tunnel and is potentially at risk of compression[1]. On their review article, they mentioned excessive swelling, taut compartments on palpation, elevated pain level, worsening pain on passive movement of fingers, and handheld in intrinsic-minus posture as the classical physical findings of hand ACS[1]. As she was disoriented due to stroke, classical disproportionate pain on passive stretch of fingers was absent in our patient, which might be a cause of the delay in diagnosis in first hospital.

Once diagnosis of ACS is made, the mainstay of treatment is urgent decompressive fasciotomy. There is traditionally little role for non-operative management in ACS, and delays in surgical intervention result in poorer outcomes. Decompression delays of more than eight hours are consistent with irreversible ischemic damage to muscle tissue and nerve that can result in loss of function, limb, or life[2]. Due to the delay in treatment, our patient lost her four fingers.

CONCLUSION

Timing of the surgical decompression is crucial to prevent severe functional disability in hand ACS. Decompression delay could lead to grave results.

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There is no conflict of interest between the authors. First author is the operating surgeon. Third author is the assistant surgeon. All the three authors worked for manuscript preparation under supervision of the first author.

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Case Report

Primary extragonadal teratoma of retroperitoneum in adult

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ABSTRACT

Teratomas are germ cell neoplasms. They may be found in extragonadal locations such as the intracranial, cervical, mediastinal, sacrococcygeal or retroperitoneal region. A nineteen-year-old woman was referred to our clinic with epigastric minimal pain and abdominal discomfort. The superior mesenteric vein was close with mass but the superior mesenteric artery had surrounded. The tumor was resected successfully with a part of the superior mesenteric artery. After resection, the superior mesenteric artery was anastomosed without graft.

KEY WORDS: mature teratoma, retroperitoneal neoplasms, tumor resection

INTRODUCTION

Teratomas are germ cell neoplasms that contain at least two of ectoderm, mesoderm or endoderm[1]. They can be congenital or acquired. These neoplasms have higher incidents in children, but can occur in adults. They may be found in extragonadal locations such as the intracranial, cervical, mediastinal, sacrococcygeal or retroperitoneal region. Retroperitoneal teratomas represent only 1-11% of primary retroperitoneal tumors[2].

We report a retroperitoneal teratoma that occurred in a middle-aged woman that surrounds the superior mesenteric artery.

CASE REPORT

A nineteen-year-old woman was referred to our clinic with epigastric minimal pain and abdominal discomfort. The physical examination was normal. The laboratory parameters were normal and no abnormalities in the medical history. An abdominal ultrasound was performed and a retroperitoneal mass found behind the pancreas. Contrast enhanced abdominal tomography and magnetic resonance imaging were performed and revealed a solid and internal cystic alternated mass (Figure 1).

An elective laparotomy was performed and encapsulated mass (about 8x8x6 cm) located behind the pancreas was found. The superior mesenteric vein was close with mass, but the superior mesenteric artery was surrounded (Figure 2, 3). The tumor was resected successfully with a part of the superior mesenteric artery. After resection, the superior mesenteric artery was anastomosed without graft (Figure 4-6). The patient was discharged on the 10th day without any complications. The histopathologic evaluation showed skin and its accessories, lymphoid tissues, nerves, fat and bone tissues that were compatible with mature teratoma.

DISCUSSION

Teratomas are more common in neonates and young adults[3]. Primary retroperitoneal teratomas are unusual and account for 4 to 6% of the whole teratomas[2]. The pathogenesis of extragonadal teratomas are unclear. Two competing hypotheses have been proposed. The first is unsuccessful migration of the primordial germ cells along the urogenital ridge to the gonadal ridges during the embryogenesis[4]. The second is the reverse migration of the transformed germ cells from the gonads[5].

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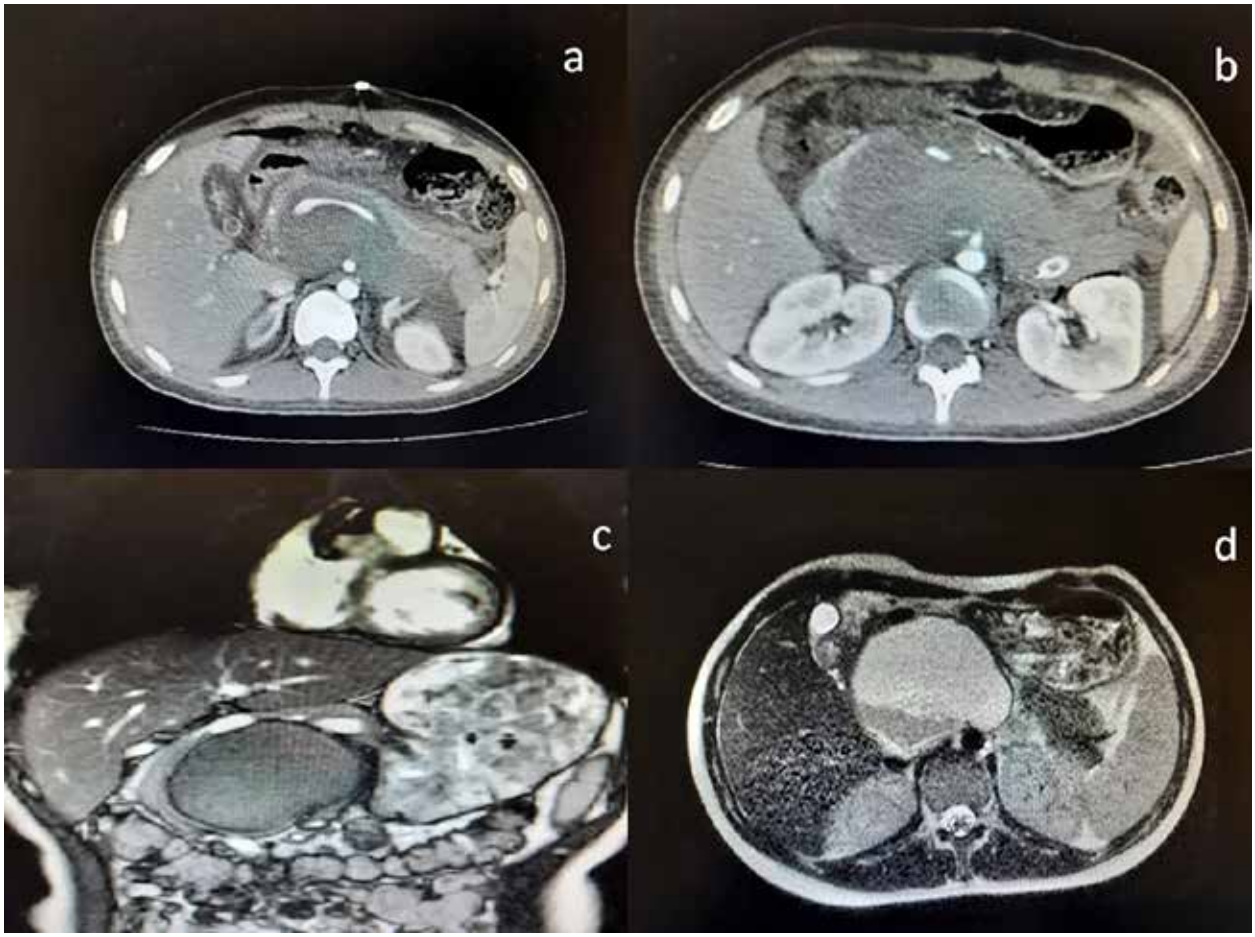

Fig 1: Radiological appearance **a,b:** computed tomography imaging **c,d:** magnetic resonance imaging T2 sekans

It is not clear which gender is more common. In the widest series published by Gatcombe *et al*, 15 of the patients were female and 17 were male[2].

The incidence has two peaks, in the first six months of life and early adulthood. Due to their retroperitoneal location, they are usually asymptomatic and identified only after they grow[2]. The age of our case was 19 and it was among the common age groups of the disease.

When the tumor gets large in size, symptoms such as abdominal pain, genitourinary and gastrointestinal

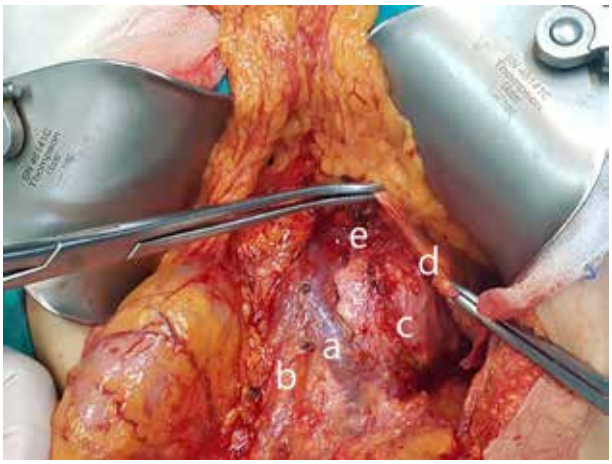

Fig 2: Teratoma under pancreas in the neighborhood of SMV **a:** inferior mesenteric vein **b:** superior mesenteric vein, **c:** teratoma, **d:** corpus of pancreas, **e:** Splenik vein

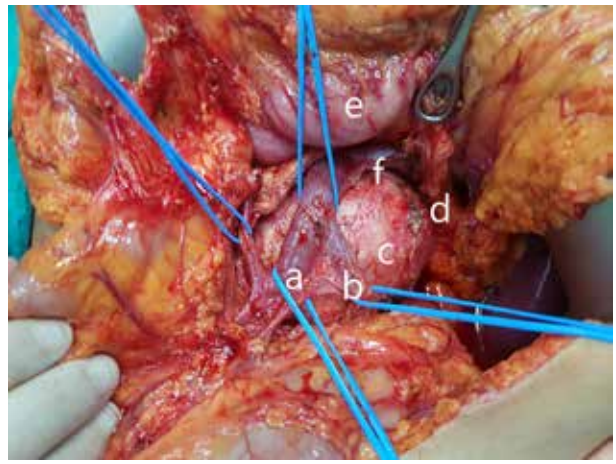

Fig 3: SMV dissection and dissection of teratoma from surrounding tissues. **a:** superior mesenteric vein, **b:** inferior mesenteric vein, **c:** teratoma, **d:** corpus of pancreas, **e:** stomach, **f:** splenic vein

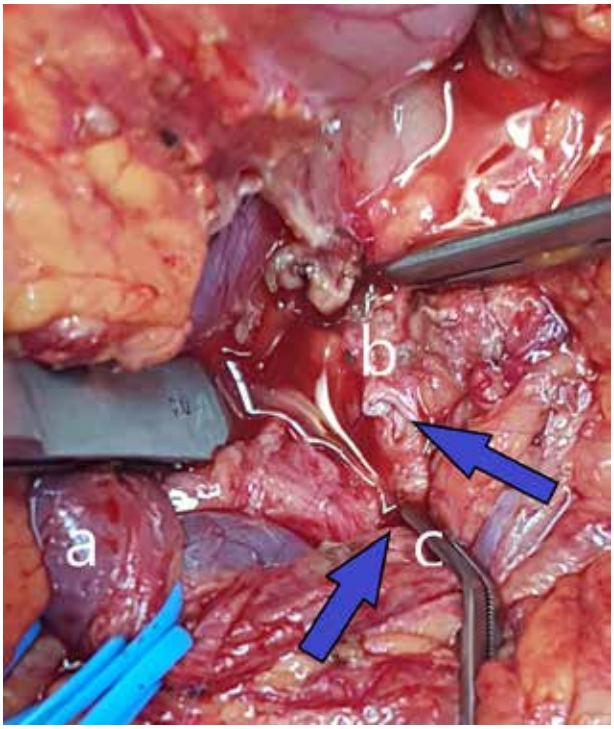

Fig 4: SMA held with clamps after excision of teratoma, **a:** superior mesenteric vein, **b:** upper part of superior mesenteric artery, **c:** lower part of superior mesenteric artery

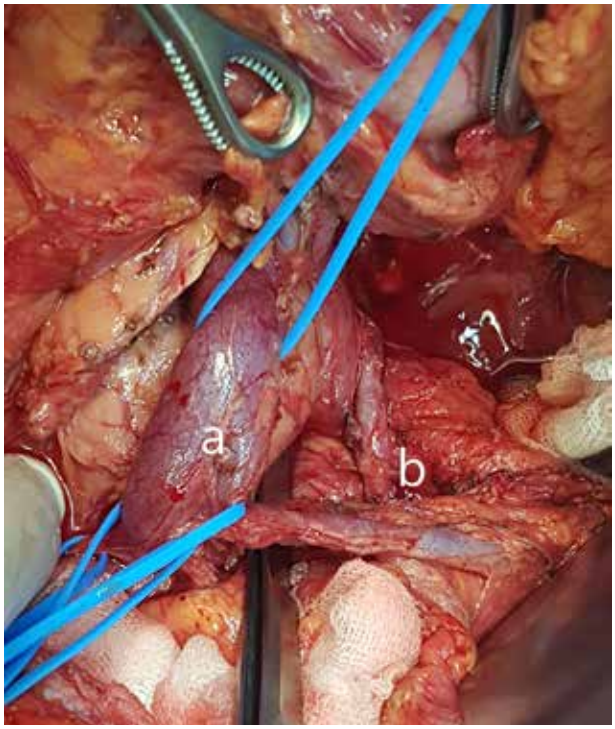

Fig 5: Tumor location after SMA repair **a:** superior mesenteric vein, **b:** superior mesenteric artery

symptoms (vomiting, nausea and constipation can occur)[6,7]. In the case we present, there are complaints related to the tumor's occupying space and partial superior mesenteric artery (SMA) obstruction.

There are two histologic types of teratomas, mature and immature. A mature teratoma consists of an adult-type tumor with differentiated structures and an immature teratoma consists of structures with only partial somatic differentiation. Most retroperitoneal teratomas are benign. The mature teratomas commonly are benign, but can transform into non–germ-cell malignancies such as sarcomas or carcinomas[1]. In histopathological examination of our case, it was determined that there was a benign mature cystic teratoma.

The diagnosis can often be ascertained based on radiologic findings. Imaging tools can show mass that ranges from predominantly cystic to completely solid. Plain abdominal films demonstrate a calcific mass in more than half of patients. The cross-sectional imaging studies are superior to clarify the relationship of the mass to adjacent structures[7]. In our case, plain abdominal film was normal. However, abdominal ultrasound found the mass. Computerized tomography and magnetic resonance imaging demonstrated a bone-like calcific solid cystic mass in the retroperitoneum.

The primary treatment of retroperitoneal teratomas is surgical resection. Point to be considered is that the tumor may be close to the branches of the abdominal aorta and the cava.

Fig 6: Teratoma photograph after resection

Damage to these structures can cause overwhelming hemorrhage, severe postoperative complications, and even death[1]. In our case, the location of the mass was among the main vascular structures. SMA was resected because it was surrounded by mass.

Previous studies have shown that retroperitoneal teratomas have a low risk of malignancy and have reported that laparoscopic excision can be performed if it is possible and not too large[8].

In benign tumors, laparoscopic surgery can provide a better operational view and can be safely applied if local invasion findings are absent in preoperative imaging[9]. Cadeddu *et al* and Wang *et al* reported that they excised a retroperitoneal teratoma laparoscopically[10,11]. Wang *et al* performed laparoscopic resection of the adrenal teratoma, removing the en bloc tumor tissue and preserving the adrenal gland. It is seen that the cases where laparoscopic surgery was successfully applied are cases of teratoma that do not have large vessel invasion and can be easily separated from the surrounding tissues[11]. However, as in our case, this may be risky for tumors that are in close proximity with vascular structures. We did not start laparoscopically because we detected a SMA invasion by imaging.

Literature presents an inconsistent report on the spread-out adhesions and therefore, the ease of resection in these tumors[4,12]. Some reports explain teratomas as detached retroperitoneal tumors, making dissection simple. More reports, however, pronounce teratomas as tumors adherent to the connected viscera making dissection severely problematic. Important adhesions to the stomach, pancreas, hepatic tissue, gall bladder, mesenteric tissue of colon, spleen and diaphragm have been reported[4,12,13]. Resection of the tumor could effect in injury to these structures and may add morbidity.

Totally resected benign teratoma cases have a good prognosis; however, malignant ones do not. Radiotherapy and chemotherapy have sort of small effects in the management of these mass. In adults, the retroperitoneal teratoma normally does not penetrate adjacent forms and can be totally resected without important complications.

CONCLUSION

Retroperitoneal teratomas are very rare. Normally, the mature teratomas are benign, surgery is the best way to get it cured, but they already have the chance for malignant alteration. Although laparoscopic resection can be performed in retroperitoneal teratomas, it may be necessary to avoid laparoscopy in cases including vascular invasion and repair.

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All authors contributed to the design and implementation of the case report, to the analysis of the case and to the writing of the manuscript. All authors discussed the results and contributed to the final manuscript

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Case Report

Rare Pericentrin (PCNT) gene mutation detected in a patient with microcephalic osteodysplastic primordial dwarfism in Turkey

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Kuwait Medical Journal 2022; 54 (4): 517 - 520

ABSTRACT

Background: Microcephalic osteodysplastic primordial dwarfism (MOPD) syndrome is an autosomal recessive syndrome characterized by prenatal and postnatal growth restriction, microcephaly and craniofacial findings such as beak nose, flattened forehead and micrognathia. MOPD type II is the most common form and its clinical features are severe intrauterine growth restriction in prenatal period, short stature in adulthood, microcephaly, mild mental disability, bone dysplasia and tooth development disorders. To date, associated with MOPD, 33 different mutations have been identified.

Case report: In this case report, we present a 6-year-old male patient who was diagnosed as MOPD Type II in the light of clinical and radiological findings. We performed the molecular genetic analysis of the patient by next-generation sequencing. Mutation analysis of the PCNT gene (Pericentrin) in the patient revealed a rare mutation in the exon 18 acceptor splice site. After the Sanger confirmation, we observed that the parents were heterozygous for the same mutation.

Conclusions: The identification of mutations causing MOPD syndrome is important both for the confirmation of the clinical diagnosis and for help in prenatal diagnosis in our country where consanguineous marriages are common in Turkey.

KEY WORDS: microcephalic osteodysplastic primordial dwarfism, microcephaly, PCNT gene, short stature

INTRODUCTION

Microcephalic osteodysplastic primordial dwarfism (MOPD) is an autosomal recessive syndrome defined by prenatal and postnatal growth restriction, microcephaly and craniofacial findings such as beak nose, flattened forehead and micrognathia. According to clinical and radiological findings, MOPD is divided into three classes as Type I, II and III. Later, it was named Taybi-Linder syndrome because types I and III had similar clinical findings[1,2].

MOPD Type II is the most common form and its prominent clinical features are severe intrauterine growth restriction in prenatal period, short stature in adulthood (often height <110 cm), microcephaly, mild mental disability, bone dysplasia and tooth development disorders[3]. It is usually confused with Seckel syndrome due to similar clinical findings. Severe growth restriction, radiological findings, absence of mental disability or mild mental disability support the diagnosis of MOPD. MOPD Type II is the result of mutation in the pericentrin (PCNT) gene localized in 21q22.3 region[4]. To our date, 33 different mutations have been reported in the PCNT gene (www.ncbi.nlm.nih.gov/clinvar).

CASE REPORT

We report a patient with severe intrauterine and postnatal growth restriction, microcephaly and facial dysmorphisms, diagnosed at birth as Seckel syndrome, and afterwards approved as MOPD on the

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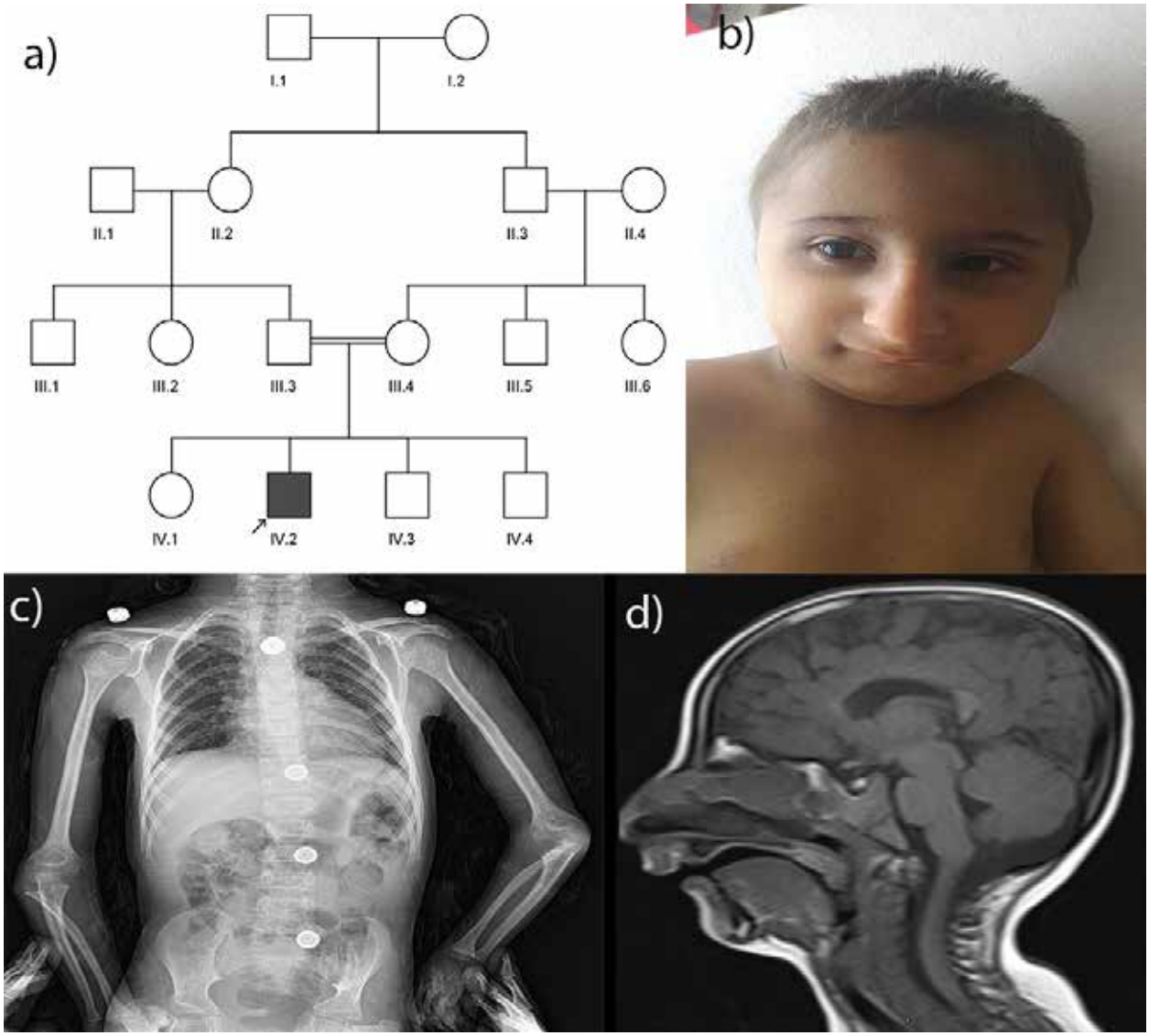

Fig 1: a) Pedigree of family; **b)** The patient with MOPD II; **c&d)** X-Ray and MR imaging of the patient

basis of clinical and radiological features of skeletal dysplasia. He was born to consanguineous parents at 38 weeks gestational age. The pedigree of family is demonstrated in Figure 1a. Prenatal ultrasounds were doubtful for intrauterine growth restriction from 24 weeks of gestational age. Birth weight was 900 g (<3rd centile), length was 38 cm (<3rd centile), and head circumference 34 cm (3rd centile).

At our investigation (6 years, 11 months), he presented height -12.4 standard deviation score (SDS), weight -23.3 SDS, head circumference -6.1 SDS. Abnormalities noted at six years old included microcephaly, hypotelorism, microtia, prominent nose, small mouth, micrognathia, maxillar prognathism, foreshortened extremities (Figure 1b). We observed delayed bone age with respect to chronological age. Skeletal survey revealed short and broad long bones, bilateral coxa vara as shown in Figure 1c. MRI of the brain showed a hypoplasia corpus callosum (Figure 1d). Congenital heart defects including atrial septal defect was detected. Results of blood tests for thyroid hormones, IGF- 1 and complete blood count test were all normal.

Patient blood was subjected to lymphocyte culture. Routine cytogenetic analysis by G-banding techniques at the 550 bands of resolution was performed. The karyotype was 46,XY at standard level. Genomic DNAs were extracted from peripheral blood lymphocytes of patient and parents for next-generation sequencing and PCNT gene sequence analysis. The coding exons and flanking intron regions (exon 1 to 47, 50 PCR products) of the PCNT gene were amplified by PCR using the DNA samples, both strands of the purified PCR products were sequenced and analysed. Mutation analysis of the PCNT gene in the patient using next-generation sequencing revealed a mutation in the exon

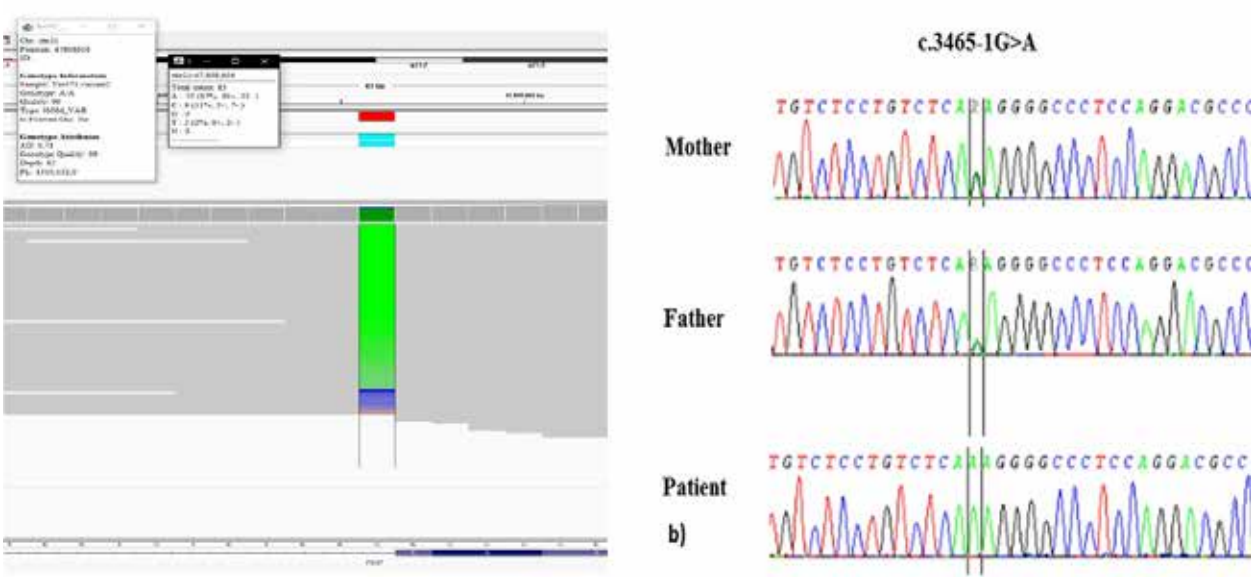

Fig 2: a) Mutation analysis of the PCNT gene in the patient using next-generation sequencing; **b)** Sequence analysis of PCNT gene in the in the family members shows heterozygous c.3465-1G>A mutation in the mother and father, homozygous c.3465-1G>A in the affected individual.

18 acceptor splice site (c.3465-1G>A, homoallelic) as shown in Figure 2a. Mutation analysis approved that the parents were heterozygous for the same mutation (Figure 2b). Informed consents were obtained from the family for the molecular genetic analyses, the publication of photos, and clinical findings.

DISCUSSION

In this case report, we present a 6-year-old male patient who was diagnosed as MOPD Type II in the light of clinical and radiological findings and whose molecular genetic analysis displayed a new mutation in the PCNT gene (c.3465-1G> A). MOPD Type II is a rare disease with autosomal recessive inheritance. Severe growth restriction is detected in the intrauterine period and is also observed in the postnatal period. Among the craniofacial findings, microcephaly, beak nose, flattened forehead, small tooth structure, micrognathy are characteristic and patients speak with high pitched voice. Typical bone dysplasia shows a progressive course. Although growth restriction is generally not observed in patients, mild mental disability may accompany[3].

MOPD Type II is often confused with Seckel syndrome with autosomal recessive inheritance and microcephaly and short stature. Seckel syndrome is defined by markedly proportional short stature without generalized skeletal dysplasia and serious microcephaly often present at birth. Contrarily, MOPD Type II patients present with mesomelic short extremities, disproportionate short stature, generalized skeletal anomalies (short metacarpal bones, metaphyseal flare of distal long bone, proximal femoral epiphysiolysis, radiolucency in metaphysis of long bones, high and narrow pelvis, large pubic bones, coxa vara), and commensurate head size at birth with progression to severe microcephaly[4]. Although Seckel syndrome and MOPD Type II syndrome have different clinical and radiological findings, both syndromes occur as a result of PCNT gene mutation. The PCNT gene is localized in the 21q22.3 region and consists of 122 kb and 47 exons. The PCNT gene encodes a centrosomal protein containing 3336 amino acids, called pericentrin, which is involved in the regulation of mitotic strands for the separation of chromosomes during cell division. As a result of pericentrin mutations, the necessary steps for cell division cannot be formed and consequently cause growth and mental disability[5].

As far as we know, ten genes have been assigned for MOPD, encoding proteins entangled in main cellular processes including genome replication, DNA damage response, mRNA splicing and centrosome function. These genes are origin recognition complex 1 (ORC1), ORC4, ORC6, CDC6, CDT1, ataxia-telangiectasia and Rad3-related (ATR), U4atac, PCNT, CEP152 and CPAP[6,7].

In 2008, Rauch *et al* noticed loss-of-function mutations in the PCNT gene in 28 patients, including 3 with Seckel syndrome and 25 with MOPD II[4]. Willems *et al* studied to clarify the clinical spectrum of patients with PCNT mutations, they analysed PCNT gene in a wide series of patients diagnosed with Seckel syndrome and MOPD II. They observed 13 distinct mutations including five frameshift mutations, five stop mutations, two splice site mutations, and one missense mutation. As a result of the study, it was notified that Seckel syndrome cases with PCNT

mutations have same clinical findings with MOPD type II syndrome[8].

In this case, we diagnosed a patient with MOPD Type II by clinical features and molecular analysis. The genetic mutation (c.3465-1G>A) detected in the PCNT gene is at the beginning of exon 18, activates the cryptic splice site. The same mutation was previously reported in the literature by Weiss *et al*[9].

Weiss *et al* first reported the same pathogenic variant in the Israeli Druze family. They present two patients with diagnosed MOPD Type II. First patient is a boy with dysmorphic features including poor weight gain, prominent nose, small jaw, a long columella, ventricular septal defect, delayed myelination, speech and motor developmental delay, widening of the spheno-occipital suture, left hemiparesis, skin hypopigmentation and malformed teeth. The other MOPD patient has same homozygous c.3465-1G > A variant with facial features that include a micrognathia, long columella below alae nasi, full cheeks, prominent nose with broad nasal bridge, little wide spaced teeth with enamel hypoplasia, simple pinna with attached lobes, nasal prominence, brachydactyly, bilateral inguinal hernia, patent ductus arteriosus, mild kyphoscoliosis and genu varum, delayed bone age, global developmental delay and mild mental disability[9].

In this case report, we show a patient with microcephaly, hypotelorism, microtia, prominent nose, small mouth, micrognathia, maxillar prognathism, and foreshortened extremities. Our patient has similar dysmorphic features with these patients reported by Weiss *et al*. Global developmental delay and mild intellectual disability were also detected in our case. Although cardiac anomalies are very rare in this disease, it was reported in our patient and by Weis *et al*. Therewithal the patients reported by Weiss *et al* have congenital heart defects including ventricular septal defect and patent ductus arteriosus. In addition to this, we detect another congenital heart defect, atrial septal defect, in our patient. Another MOPD Type II case with atrial septal defect has been reported in the literature. This patient has homozygous c.9099+2T>C mutation in PCNT gene[8].

CONCLUSION

As a result of molecular genetic analysis performed with the diagnosis of MOPD Type II with clinical and radiological findings, we identified the same mutation in Turkish patient. Also, clinical findings are very similar to the patients reported by Weiss *et al*. This mutation, which has been described recently in the literature, has been reported for the first time in our country. Identification of new mutations causing MOPD syndrome, confirmation of clinical diagnosis by molecular analysis, elucidation of molecular mechanisms causing disease help in prenatal diagnosis in our country where consanguineous marriages are very common.

ACKNOWLEDGMENT

Authors Contribution: Ozlem Oz collected data and wrote the manuscript; Ataman Gonel edited manuscript.

Conflict of Interests: None

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Selected Abstracts of Articles Published Elsewhere by Authors in Kuwait

Kuwait Medical Journal 2022; 54 (4): 521 - 523

Antenatal Magnesium Sulfate for Preterm Neuroprotection: A Single-Center Experience from Kuwait Tertiary NICU

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Biomed Hub 2022 Jun 30;7(2):80-87. doi: 10.1159/000525431. eCollection 2022 May-Aug.

OBJECTIVES

The study aimed to evaluate the impact of antenatal exposure of magnesium sulfate ($MgSO_4$) on short- and long-term outcomes in preterm neonates born less than 32 weeks gestation.

METHODS

Single-center retrospective cohort study of 229 neonates born between 24 and 32 weeks gestation was conducted from January 2018 through December 2018 in a level III neonatal care unit in Kuwait. Antenatal $MgSO_4$ exposure was collected from the medical records, and the indication was for neuroprotection effect. Brain MRI was done on 212 neonates (median gestational age 36 weeks), and brain injury was assessed using the Miller›s score. Neurodevelopmental outcome was assessed by Bayley-III scales of infant development at 36 months corrected age (N = 146). The association of exposure to MgSO4 with brain injury and neurodevelopmental outcomes was examined using multivariable regression analysis adjusting for gestational age at MRI and variables with p value <0.05 on univariate analysis.

RESULTS

Among the 229 neonates, 47 received antenatal $MgSO_4$. There were no differences between the groups in gestational age and birth weight. $MgSO_4$ exposure was not associated with an increased risk of necrotizing enterocolitis, chronic lung disease, retinopathy of prematurity, and mortality. The incidence of cerebellar hemorrhage was significantly less in the $MgSO_4$ group (0% vs. 16%, p value = 0.002). Neonates who received $MgSO_4$ had lower risks of grade 3-4 intraventricular hemorrhage (IVH) adjusted OR 0.248 (95% CI: 0.092, 0.66), p = 0.006; moderate-severe white matter injury (WMI) adjusted odd ratio 0.208 (95% CI: 0.044, 0.96), p = 0.046; and grade 3-4 IVH and/or moderate-severe WMI adjusted OR 0.23 (95% CI: 0.06, 0.84), p = 0.027. Neurodevelopmental assessment at 36 months corrected age showed better motor (adjusted beta coefficient 1.08 [95% CI: 0.099, 2.06]; p = 0.031) and cognitive composite scores (adjusted beta coefficient 1.29 [95% CI: 0.36, 2.22]; p = 0.007) in the $MgSO_4$ group.

CONCLUSION

Antenatal exposure to $MgSO_4$ in preterm neonates less than 32 weeks was independently associated with lower risks of brain injury and better motor and cognitive outcomes.

A rare presentation of OEIS variant with a recto-bladder neck fistula: A case report and literature review

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Int J Surg Case Rep. 2022 May 4;95:107144. doi: 10.1016/j.ijscr.2022.107144. Online ahead of print.

INTRODUCTION
Omphalocele, bladder extrophy, imperforate anus and spinal defect (known as OEIS) is a very rare congenital anomaly with an unknown etiology. In this report we describe a case of an OEIS variant associated with a wide pubic diastasis, bladder extrophy with a recto-bladder neck fistula and a high ano-rectal malformation. This work has been reported in line with the SCARE 2020 criteria.

PRESENTATION OF THE CASE
A 30-year-old mother delivered a male baby at 39 weeks through a normal vaginal delivery. Examination revealed multiple congenital anomalies in the form of an Omphalocele, extrophied bladder, imperforate anus, ambiguous genitalia and a large pelvic diastasis. Fecal matter was noted at the most inferior point of the extrophied bladder, raising the suspicion of a recto- vesical fistula. An exploratory laparotomy showed a fistula between the rectum and the neck of the extrophied bladder. A sigmoid colostomy was carried out in addition to a mucous fistula. The fascial defect of the Omphalocele was approximated to the upper border of the extrophied bladder. At the age of 2 years, the baby underwent a bladder extrophy repair, a posterior sagittal anorectoplasty and bilateral osteotomies.

DISCUSSION
OEIS complex has been reported to occur with a wide variety of associated anomalies, and this necessitates a thorough investigation in order to formulate an appropriate treatment plan. A prenatal diagnosis of OEIS complex can be made by ultrasound stressing the importance of antenatal follow up and a multidisciplinary approach in management.

CONCLUSION
We described a rare variant of an OEIS complex and management of such anomalies requires a multidisciplinary input.

Prevalence of Hepatitis B Virus infection in the Gulf Cooperation Council: a systematic review and meta-analysis

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[2]Department of Medicine, Faculty of Medicine, Kuwait University, Jabriyah, Kuwait. alali.a@ku.edu.kw.
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BMC Infect Dis. 2022 Nov 7;22(1):819. doi: 10.1186/s12879-022-07806-4.

BACKGROUND
Hepatitis B virus (HBV) infection is a global public-health problem. Since the introduction of an effective vaccine, the epidemiology of HBV infection is changing. We aimed to estimate the prevalence of HBV

infection in the Gulf Cooperation Council (GCC) region and delineate any variation in member-countries, special sub-groups, and over time.

METHODS
This is a systematic review and meta-analysis to review studies of HBV prevalence in the GCC region. Databases were searched and all studies from inception to July 31st, 2021, were considered for inclusion. The pooled HBV prevalence was analyzed using the random-effect model after assessment for heterogeneity. True prevalence was adjusted using the Rogan-Gladen estimator. Pre-defined subgroup analysis was performed, and publication bias was assessed.

RESULTS
Overall, 99 studies (n = 1,944,200 participants) met the inclusion criteria. The overall HBV apparent prevalence was 3.05% (95% CI 2.60, 3.52) and the true prevalence was 1.67% (95% CI 1.66, 1.68). The apparent prevalence varied between subgroups. Over time, the apparent prevalence of HBV infection has declined from 9.38% (95% CI 7.26, 11.74) before 1990 to 1.56% (95% CI 1.07, 2.12) during the period 2010 to 2020.

CONCLUSION
Over the last four decades the overall prevalence of HBV infection in the GCC region has decreased from high- to low-endemicity level. However, due to poor methodology of the included studies, further high-quality community-based studies are needed to obtain more precise estimate of HBV infection in this region.

Forthcoming Conferences and Meetings

Compiled and edited by
Vineetha Elizabeth Mammen

Kuwait Medical Journal 2022; 54 (4): 524 - 532

1423rd International Conference on **Medical and Health Sciences** (ICMHS)
Dec 01, 2022
United Arab Emirates, Dubai
Email: info@iserd.co
Event Website: http: //iserd.co/Conference2022/UAE/10/ICMHS/

1311th International Conference on **Food Microbiology and Food Safety** (ICFMFS)
Dec 01, 2022
Ireland, Dublin
Email: info@theires.org
Event Website: http: //theires.org/Conference2022/Ireland/2/ICFMFS/

1447th International Conference on Recent Advances in **Medical Science** (ICRAMS)
Dec 02, 2022
Germany, Berlin
Email: info@theiier.org
Event Website: http: //theiier.org/Conference2022/Germany/7/ICRAMS/

International Conference on **Medical and Biological Engineering** (ICMBE)
Dec 03, 2022
United Kingdom, Edinburgh
Email: papers.techno@gmail.com
Event Website: http: //technoconferences.com/Conference/7814/ICMBE/

Annual Conference for **Dermatology, Laser and Aesthetic Medicine**
Dec 03-04, 2022
Kuwait, Kuwait city
Event website: http: //www.ksdconference.com

International Conference on **Medical, Medicine and Health Sciences** (ICMMH)
Dec 05, 2022
Turkey, Istanbul
Email: contact.iierd@gmail.com
Event Website: http: //iierd.com/Conference/2116/ICMMH/

International Conference on **Healthcare and Clinical Gerontology** (ICHCG)
Dec 06, 2022
Australia, Adelaide
Email: info.sciencefora@gmail.com
Event Website: http: //sciencefora.org/Conference/13919/ICHCG/

1414th International Conference on **Medical and Biosciences** (ICMBS)
Dec 07, 2022
United Kingdom, Edinburgh
Email: info@researchworld.org
Event Website: http: //researchworld.org/Conference2022/UK/10/ICMBS/

1451st International Conference on Recent Advances in **Medical Science** (ICRAMS)
Dec 09, 2022
Greece, Athens
Email: info@theiier.org
Event Website: http: //theiier.org/Conference2022/Greece/3/ICRAMS/

International Conference on **Cell and Tissue Science** (ICCTS)
Dec 09, 2022
United States, San Jose
Email: info@conferencefora.org
Event Website: http: //conferencefora.org/Conference/34874/ICCTS/

1421st International Conference on Recent Advances in **Medical and Health Sciences** (ICRAMHS)
Dec 12, 2022
France, Paris
Email: info@academicsworld.org
Event Website: http: //academicsworld.org/Conference2022/France/6/ICRAMHS/

International Conference on Recent Advances in **Medical, Medicine and Health Sciences** (ICRAMMHS)
Dec 12, 2022
Qatar, Doha
Email: contact.wrfer@gmail.com
Event Website: http: //wrfer.org/Conference/21303/ICRAMMHS/

4th Annual **Neonatology** Conference
Dec 15-17, 2022
Kuwait, Kuwait city
Event website: http: //www.4neokw.com

International Conference on Recent Advances in **Medical, Medicine and Health Sciences** (ICRAMMHS)
Dec 17, 2022
United States, Cambridge
Email: contact.wrfer@gmail.com
Event Website: http: //wrfer.org/Conference/21140/ICRAMMHS/

1243rd International Conference on **Medical & Health Science** (ICMHS)
Dec 19, 2022
United Kingdom, Edinburgh
Email: info@researchfora.com
Event Website: http: //researchfora.com/Conference2022/UK/9/ICMHS/

1458th International Conference on Recent Advances in **Medical Science** (ICRAMS)
Dec 19, 2022
Italy, Florence
Email: info@theiier.org
Event Website: http: //theiier.org/Conference2022/Italy/9/ICRAMS/

International Conference on Recent Advances in **Medical, Medicine and Health Sciences** (ICRAMMHS)
Dec 19, 2022
Ireland, Dublin
Email: contact.wrfer@gmail.com
Event Website: http: //wrfer.org/Conference/21336/ICRAMMHS/

1427th International Conference on Recent Advances in **Medical and Health Sciences** (ICRAMHS)
Dec 21, 2022
Italy, Venice
Email: info@academicsworld.org
Event Website: http: //academicsworld.org/Conference2022/Italy/8/ICRAMHS/

1423rd International Conference on **Medical and Biosciences**
Dec 21, 2022
Czech Republic, Prague
Email: info@researchworld.org
Event Website: http: //researchworld.org/Conference2022/CzechRepublic/2/ICMBS/

1285th International Conference on **Pharma and Food** (ICPAF)
Dec 23, 2022
United States, Houston
Email: info@academicsera.com
Event Website: http: //academicsera.com/Conference2022/USA/19/ICPAF/

International Conference on **Science, Health and Medicine** (ICSHM)
Dec 24, 2022
Canada, Calgary
Email: info@iser.co
Event Website: http: //iser.co/Conference2022/Canada/62/ICSHM/

World Conference on **Pharma Industry and Medical Devices**
Dec 25, 2022
United Arab Emirates, Sharjah
Email: info.ifearpworld@gmail.com
Event Website: http: //ifearp.org/Conference/6693/WCPIMD/

1450th International Conferences on **Medical and Health Science** (ICMHS)
Dec 28, 2022
Kuwait, Kuwait City
Email: info@theires.org
Event Website: http: //theires.org/Conference2022/Kuwait/2/ICMHS/

International Virtual Conference on **COVID-19** and its Effect (IVCCE)
Dec 29, 2022
Russian Federation, Moscow
Email: info.conferenceonline@gmail.com
Event Website: http: //www.conferenceonline.net/Conference/450/IVCCE/

International Conference on Recent advancement in **Medical Education, Nursing, and Health Sciences** (ICRAMNH)
Dec 30, 2022
China, Shanghai
Email: info.irfconference@gmail.com
Event Website: http: //irfconference.org/Conference/14282/ICRAMNH/

1420th International Conference on **Science, Health and Medicine** (ICSHM)
Jan 01, 2023
United Arab Emirates, Dubai
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Event Website: http: //iser.co/Conference2023/UAE/1/ICSHM/

1465th International Conference on Recent Advances in **Medical Science** (ICRAMS)
Jan 01, 2023
Ireland, Dublin
Email: info@theiier.org
Event Website: http: //theiier.org/Conference2023/Ireland/1/ICRAMS/

1429th International Conference on **Medical and Biosciences** (ICMBS)
Jan 02, 2023
Germany, Berlin
Email: info@researchworld.org
Event Website: http: //researchworld.org/Conference2023/Germany/1/ICMBS/

International Conference on Recent Advances in **Medical, Medicine and Health Sciences** (ICRAMMHS)
Jan 03, 2023
United Arab Emirates, Dubai
Email: contact.wrfer@gmail.com
Event Website: http: //wrfer.org/Conference/24537/ICRAMMHS/

International Conference on **Virology** (ICV)
Jan 04, 2023
Japan, Tokyo
Email: papers.itrgroup@gmail.com
Event Website: http: //itrgroup.net/Conference/497/ICV/

1467th International Conference on Recent Advances in **Medical Science** (ICRAMS)
Jan 05, 2023
New Zealand, Auckland
Email: info@theiier.org
Event Website: http: //theiier.org/Conference2023/NewZealand/1/ICRAMS/

International Conference on **Medical, Pharmaceutical and Health Sciences** (ICMPH)
Jan 09, 2023
Japan, Nagoya
Email: info.gsrd@gmail.com
Event Website: http: //gsrd.co/Conference/7768/ICMPH/

International **Cancer** Conference (ICC)
Jan 12, 2023
Thailand, Bangkok
Email: info@biofora.org
Event Website: http: //biofora.org/Conference/121/ICC/

International Conference on **Medical Ethics and Professionalism** (ICMEP)
Jan 15, 2023
Switzerland, Bern
Email: info.sciencefora@gmail.com
Event Website: http: //sciencefora.org/Conference/23169/ICMEP/

International Conference on **Healthcare and Clinical Gerontology** (ICHCG)
Jan 16, 2023
Switzerland, Geneva
Email: info.sciencefora@gmail.com
Event Website: http: //sciencefora.org/Conference/23157/ICHCG/

1452nd International Conference on **Medical and Health Sciences** (ICMHS)
Jan 18, 2023
United Kingdom, London
Email: info@iserd.co
Event Website: http: //iserd.co/Conference2023/UK/1/ICMHS/

Annual Meeting on **Dentistry Endodontics and Hypnodontics** (AMDEH)
Jan 19, 2023
Singapore, Singapore
Email: info@biofora.org
Event Website: http: //biofora.org/Conference/108/AMDEH/

International conference on **Medical Health Science, Pharmacology & Bio Technology** (ICMPB)
Jan 20, 2023
Korea (*South*), Seoul
Email: papers.issrd@gmail.com
Event Website: http: //issrd.org/Conference/17988/ICMPB/

1263rd International Conference on **Medical & Health Science** (ICMHS)
Jan 21, 2023
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Email: info@researchfora.com
Event Website: http: //researchfora.com/Conference2023/CzechRepublic/1/ICMHS/

International Conference on **Virology** (ICV)
Jan 22, 2023
Thailand, Bangkok
Email: papers.itrgroup@gmail.com
Event Website: http: //itrgroup.net/Conference/518/ICV/

1443rd International Conference on **Medical and Biosciences** (ICMBS)
Jan 24, 2023
Australia, Sydney
Email: info@researchworld.org
Event Website: http: //researchworld.org/Conference2023/Australia/1/ICMBS/

1457th International Conference on **Medical, Biological and Pharmaceutical Sciences** (ICMBPS)
Jan 25, 2023
France, Paris
Email: info@iastem.org
Event Website: http: //iastem.org/Conference2023/France/2/ICMBPS/

International Conference on **Endocrinology, Diabetes and Metabolism** (ICEDM)
Jan 26, 2023
Turkey, Istanbul
Email: info.diabetesworld@gmail.com
Event Website: http: //diabetesworld.net/Conference/31/ICEDM/

1482nd International Conference on Recent Advances in **Medical Science** (ICRAMS)
Jan 28, 2023
Kuwait, Kuwait City
Email: info@theiier.org
Event Website: http: //theiier.org/Conference2023/Kuwait/1/ICRAMS/

International Conference on **Healthcare and Clinical Gerontology** (ICHCG)
Jan 28, 2023
Japan, Saitama
Email: info.sciencefora@gmail.com
Event Website: http: //sciencefora.org/Conference/23049/ICHCG/

International Conference on Recent Advances in **Medical, Medicine and Health Sciences** (ICRAMMHS)
Jan 29, 2023
Turkey, Istanbul
Email: contact.wrfer@gmail.com
Event Website: http: //wrfer.org/Conference/24321/ICRAMMHS/

World Conference on **Pharma Industry and Medical Devices** (WCPIMD)
Jan 29, 2023
Saudi Arabia, Jeddah
Email: info.ifearpworld@gmail.com
Event Website: http: //ifearp.org/Conference/7996/WCPIMD/

1460th International Conference on **Medical, Biological and Pharmaceutical Sciences** (ICMBPS)
Jan 30, 2023
Indonesia, Bali
Email: info@iastem.org
Event Website: http: //iastem.org/Conference2023/Indonesia/1/ICMBPS/

International conference on **Medical Health Science, Pharmacology & Bio Technology** (ICMPB)
Jan 30, 2023
Canada, Ottawa
Email: papers.issrd@gmail.com
Event Website: http: //issrd.org/Conference/17927/ICMPB/

International Virtual Conference on **Medical Biological and Pharmaceutical Science** (IVCMBPS)
Jan 31, 2023
Japan, Kyoto
Email: info.conferenceonline@gmail.com
Event Website: http: //conferenceonline.net/Conference/470/IVCMBPS/

1447th International Conference on **Medical and Biosciences** (ICMBS)
Feb 01, 2023
Ireland, Dublin
Email: info@researchworld.org
Event Website: http: //researchworld.org/Conference2023/Ireland/1/ICMBS/

World **Disability** & **Rehabilitation** Conference (WDRC)
Feb 02, 2023
China, Beijing
Email: papers.asar@gmail.com
Event Website: http: //asar.org.in/Conference/39322/WDRC/

International Conference on **Medical and Health Sciences** (ICMHS)
Feb 02, 2023
Scotland, Glasgow
Email: papers.scienceplus@gmail.com
Event Website: http: //scienceplus.us/Conference/25711/ICMHS/

International Conference on **Nutrition & Health** (ICNH)
Feb 03, 2023
Taiwan, Taipei
Email: info.conferenceonline@gmail.com
Event Website: http: //conferenceonline.net/Conference/579/ICNH/

International Conference on Recent Advances in **Medical, Medicine and Health Sciences** (ICRAMMHS)
Feb 05, 2023
India, New Delhi
Email: contact.wrfer@gmail.com
Event Website: http: //wrfer.org/Conference/24232/ICRAMMHS/

1455th International Conference on Recent Advances in **Medical and Health Sciences** (ICRAMHS)
Feb 07, 2023
United Kingdom, Edinburgh
Email: info@academicsworld.org
Event Website: http: //academicsworld.org/Conference2023/UK/3/ICRAMHS/

1451st International Conference on **Medical and Biosciences** (ICMBS)
Feb 08, 2023
Greece, Crete
Email: info@researchworld.org
Event Website: http: //researchworld.org/Conference2023/Greece/2/ICMBS/

International Conference on **Medical, Pharmaceutical and Health Sciences** (ICMPH)
Feb 09, 2023
Qatar, Doha
Email: info.gsrd@gmail.com
Event Website: http: //gsrd.co/Conference/12334/ICMPH/

1315th International Conference on **Pharma and Food** (ICPAF)
Feb 10, 2023
Spain, Madrid
Email: info@academicsera.com
Event Website: http: //academicsera.com/Conference2023/Spain/1/ICPAF/

International Virtual Conference on **Medical Biological and Pharmaceutical Science** (IVCMBPS)
Feb 11, 2023
United Arab Emirates, Dubai
Email: info.conferenceonline@gmail.com
Event Website: http: //conferenceonline.net/Conference/609/IVCMBPS/

International Video Conference on **Healthcare** (IVCH)
Feb 11, 2023
United Arab Emirates, Dubai
Email: info.conferenceonline@gmail.com
Event Website: http: //conferenceonline.net/Conference/604/IVCH/

1446th International Conference on **Science, Health and Medicine** (ICSHM)
Feb 13, 2023
Saudi Arabia, Riyadh
Email: info@iser.co
Event Website: http: //iser.co/Conference2023/SaudiArabia/1/ICSHM/

International Conference on Recent Advances in **Medical Science** (ICRAMS)
Feb 14, 2023
United States, San Francisco
Email: info@theiier.org
Event Website: http: //theiier.org/Conference2023/US/11/ICRAMS/

International Conference on Recent Advances in **Medical, Medicine and Health Sciences** (ICRAMMHS)
Feb 15, 2023
Japan, Fukuoka
Email: contact.wrfer@gmail.com
Event Website: http: //wrfer.org/Conference/26652/ICRAMMHS/

1470th International Conference on **Medical, Biological and Pharmaceutical Sciences** (ICMBPS)
Feb 17, 2023
United States, Las Vegas
Email: info@iastem.org
Event Website: http: //iastem.org/Conference2023/USA/1/ICMBPS/

International Conference on **Medical, Medicine and Health Sciences** (ICMMH)
Feb 18, 2023
Egypt, Cairo
Email: contact.iierd@gmail.com
Event Website: http: //iierd.com/Conference/2205/ICMMH/

World Conference on **Pharma Industry and Medical Devices** (WCPIMD)
Feb 19, 2023
Turkey, Antalya
Email: info.ifearpworld@gmail.com
Event Website: http: //ifearp.org/Conference/9272/WCPIMD/

International **Cancer** Conference (ICC)
Feb 19, 2023
Singapore, Singapore
Email: info@biofora.org
Event Website: http: //biofora.org/Conference/255/ICC/

1473rd International Conference on **Medical, Biological and Pharmaceutical Sciences** (ICMBPS)
Feb 20, 2023
Italy, Rome
Email: info@iastem.org
Event Website: http: //iastem.org/Conference2023/Italy/1/ICMBPS/

1474th International Conference on **Medical and Health Sciences** (ICMHS)
Feb 22, 2023
United States, Chicago
Email: info@iserd.co
Event Website: http: //iserd.co/Conference2023/USA/3/ICMHS/

1324th International Conference on **Sports Nutrition and Supplements** (ICSNS)
Feb 23, 2023
Romania, Bucharest
Email: info@academicsera.com
Event Website: http: //academicsera.com/Conference2023/Romania/1/ICSNS/

1283rd International Conference on **Medical & Health Science** (ICMHS)
Feb 24, 2023
Australia, Sydney
Email: info@researchfora.com
Event Website: http: //researchfora.com/Conference2023/Australia/1/ICMHS/

1456th International Conference on **Science, Health and Medicine** (ICSHM)
Feb 26, 2023
Italy, Milan
Email: info@iser.co
Event Website: http: //iser.co/Conference2023/Italy/4/ICSHM/

International Conference on **Medical and Health Sciences** (ICMHS)
Feb 26, 2023
Greece, Crete
Email: papers.academicsconference@gmail.com
Event Website: http: //academicsconference.com/Conference/30308/ICMHS/

1464th International Conference on **Medical and Biosciences** (ICMBS)
Feb 27, 2023
Kuwait, Kuwait City
Email: info@researchworld.org
Event Website: http: //researchworld.org/Conference2023/Kuwait/1/ICMBS/

1287th International Conference on **Medical & Health Science** (ICMHS)
Mar 01, 2023
Ireland, Dublin
Email: info@researchfora.com
Event Website: http: //researchfora.com/Conference2023/Ireland/1/ICMHS/

1470th International Conference on Recent Advances in **Medical and Health Sciences** (ICRAMHS)
Mar 02, 2023
Germany, Berlin
Email: info@academicsworld.org
Event Website: http: //academicsworld.org/Conference2023/Germany/2/ICRAMHS/

International Conference on **Medical and Health Sciences** (ICMHS)
Mar 02, 2023
Canada, Montreal
Email: papers.academicsconference@gmail.com
Event Website: http: //academicsconference.com/Conference/30264/ICMHS/

2nd Emirates **Allergy & Clinical Immunology** Conference
Mar 03, 2023
United Arab Emirates, Dubai City
Email: allergy@pemsevents.com
Event Website: https: //www.eacic-uae.com/

1481st International Conference on **Medical, Biological and Pharmaceutical Sciences** (ICMBPS)
Mar 04, 2023
Germany, Hamburg
Email: info@iastem.org
Event Website: http: //iastem.org/Conference2023/Germany/2/ICMBPS/

1481st International Conference on **Medical and Health Sciences** (ICMHS)
Mar 06, 2023
New Zealand, Hamilton
Email: info@iserd.co
Event Website: http: //iserd.co/Conference2023/NewZealand/1/ICMHS/

International Conference on Recent advancement in **Medical Education, Nursing, and Health Sciences** (ICRAMNH)
Mar 07, 2023
Japan, Kobe
Email: info.irfconference@gmail.com
Event Website: http: //irfconference.org/Conference/18296/ICRAMNH/

1472nd International Conference on **Medical and Biosciences** (ICMBS)
Mar 09, 2023
Netherlands, Amsterdam
Email: **info@researchworld.org**
Event Website: http: //researchworld.org/Conference2023/Netherlands/1/ICMBS/

6th Kuwait **Neurology** Conference
Mar 10-11, 2023
Kuwait, Kuwait city
Event website: http: //www.kuwaitneurology.com

1336th International Conference on **Pharma and Food** (ICPAF)
Mar 12, 2023
France, Paris
Email: info@academicsera.com
Event Website: http: //academicsera.com/Conference2023/France/3/ICPAF/

2nd Edition of World Congress and Expo on **Surgery and Anesthesia**
Mar 13, 2023
France, Paris
Email: surgerymeeting2023@gmail.com
Event Website: https: //www.medwideconferences.com/surgery-surgicaltechniques/

World Conference on **Pharma Industry and Medical Devices** (WCPIMD)
Mar 19, 2023
Turkey, Antalya
Email: info.ifearpworld@gmail.com
Event Website: http: //ifearp.org/Conference/9158/WCPIMD/

1341st International Conference on **Sports Nutrition and Supplements** (ICSNS)
Mar 20, 2023
Italy, Rome
Email: info@academicsera.com
Event Website: http: //academicsera.com/Conference2023/Italy/1/ICSNS/

1493rd International Conference on **Medical, Biological and Pharmaceutical Sciences** (ICMBPS)
Mar 22, 2023
Spain, Madrid
Email: info@iastem.org
Event Website: http: //iastem.org/Conference2023/Spain/3/ICMBPS/

1482nd International Conference on **Medical and Biosciences** (ICMBS)
Mar 23, 2023
United States, Miami
Email: info@researchworld.org
Event Website: http: //researchworld.org/Conference2023/USA/4/ICMBS/

World **Disability & Rehabilitation** Conference (WDRC)
Mar 25, 2023
India, Bengaluru
Email: papers.asar@gmail.com
Event Website: http: //asar.org.in/Conference/39487/WDRC/

1474th International Conference on **Science, Health and Medicine** (ICSHM)
Mar 27, 2023
Canada, Ottawa
Email: info@iser.co
Event Website: http: //iser.co/Conference2023/Canada/2/ICSHM/

World Conference on **Pharma Industry and Medical Devices** (WCPIMD)
Mar 28, 2023
Saudi Arabia, Mecca
Email: info.ifearpworld@gmail.com
Event Website: http: //ifearp.org/Conference/9110/WCPIMD/

1497th International Conference on **Medical, Biological and Pharmaceutical Sciences** (ICMBPS)
Mar 29, 2023
Italy, Milan
Email: info@iastem.org
Event Website: http: //iastem.org/Conference2023/Italy/4/ICMBPS/

International Conference on **Obesity and Chronic Diseases** (ICOCD)
Mar 29, 2023
United States, Washington D.C
Email: info.iared.org@gmail.com
Event Website: http: //iared.org/Conference/351/ICOCD/

1306th International Conference on **Medical & Health Science** (ICMHS)
Mar 30, 2023
Canada, Vancouver
Email: info@researchfora.com
Event Website: http: //researchfora.com/Conference2023/Canada/2/ICMHS/

1488th International Conference on Recent Advances in **Medical and Health Sciences** (ICRAMHS)
Apr 01, 2023
Ireland, Dublin
Email: info@academicsworld.org
Event Website: http: //academicsworld.org/Conference2023/Ireland/1/ICRAMHS/

International Conference on **Cell and Tissue Science** (ICCTS)
Apr 01, 2023
Oman, Salalah
Email: info@conferencefora.org
Event Website: http: //conferencefora.org/Conference/44647/ICCTS/

1526th International Conference on Recent Advances in **Medical Science** (ICRAMS)
Apr 02, 2023
United Arab Emirates, Abu Dhabi
Email: info@theiier.org
Event Website: http: //theiier.org/Conference2023/UAE/2/ICRAMS/

1308th International Conference on **Medical & Health Science** (ICMHS)
Apr 03, 2023
Germany, Hamburg
Email: info@researchfora.com
Event Website: http: //researchfora.com/Conference2023/Germany/3/ICMHS/

International Conference on **Virology** (ICV)
Apr 04, 2023
Japan, Tokyo
Email: papers.itrgroup@gmail.com
Event Website: http: //itrgroup.net/Conference/821/ICV/

International Conference on **Medical and Health Sciences** (ICMHS)
Apr 05, 2023
United States, Boston
Email: papers.scienceplus@gmail.com
Event Website: http: //scienceplus.us/Conference/24586/ICMHS/

International Conference on **Nursing Ethics and Medical Ethics** (ICNEME)
Apr 06, 2023
Australia, Adelaide
Email: info.sciencefora@gmail.com
Event Website: http: //sciencefora.org/Conference/22202/ICNEME/

1504th International Conference on **Medical, Biological and Pharmaceutical Sciences** (ICMBPS)
Apr 10, 2023
Bahrain, Manama
Email: info@iastem.org
Event Website: http: //iastem.org/Conference2023/Bahrain/1/ICMBPS/

International Virtual Conference on **COVID-19** and its Effect (IVCCE)
Apr 11, 2023
United Arab Emirates, Dubai
Email: info.conferenceonline@gmail.com
Event Website: http: //conferenceonline.net/Conference/726/IVCCE/

1520th International Conferences on **Medical and Health Science** (ICMHS)
Apr 13, 2023
France, Cannes
Email: info@theires.org
Event Website: http: //theires.org/Conference2023/France/1/ICMHS/

International Conference on Recent Advances in **Medical Science** (ICRAMS)
Apr 15, 2023
United States, Massachusetts
Email: info@theiier.org
Event Website: http: //theiier.org/Conference2023/US/32/ICRAMS/

1357th International Conference on **Pharma and Food** (ICPAF)
Apr 16, 2023
United States, Boston
Email: info@academicsera.com
Event Website: http: //academicsera.com/Conference2023/USA/5/ICPAF/

International Conference on **Nutrition & Health** (ICNH)
Apr 16, 2023
Japan, Tokyo
Email: papers.asar@gmail.com
Event Website: http: //asar.org.in/Conference/38596/ICNH/

International Conference on **Nursing Science and Healthcare** (ICNSH)
Apr 16, 2023
France, Paris
Email: info.iared.org@gmail.com
Event Website: http: //iared.org/Conference/432/ICNSH/

Global **Cardiology and Healthcare** Summit (GCHS)
Apr 16, 2023
Thailand, Bangkok
Email: info@biofora.org
Event Website: http: //biofora.org/Conference/343/GCHS/

1358th International Conference on **Pharma and Food** (ICPAF)
Apr 18, 2023
United Kingdom, London
Email: info@academicsera.com
Event Website: http: //academicsera.com/Conference2023/UK/2/ICPAF/

4th Global Conference on **Pharma Industry and Medical Devices**
Apr 19, 2023
United Arab Emirates, Dubai
Email: igrnetconference@gmail.com
Event Website: http: //www.gcpimd.igrnet.org/282/united-arab-emirates/

World **Disability & Rehabilitation** Conference (WDRC)
Apr 20, 2023
New Zealand, Auckland
Email: papers.asar@gmail.com
Event Website: http: //asar.org.in/Conference/38564/WDRC/

1528th International Conferences on **Medical and Health Science** (ICMHS)
Apr 25, 2023
France, Paris
Email: info@theires.org
Event Website: http: //theires.org/Conference2023/France/2/ICMHS/

International **Cancer** Conference (ICC)
Apr 29, 2023
United States, New York
Email: info@biofora.org
Event Website: http: //biofora.org/Conference/262/ICC/

International Conference on **Medical and Health Sciences** (ICMHS)
Apr 30, 2023
Qatar, Doha
Email: info.inderscience.org@gmail.com
Event Website: http: //inderscience.org/Conference/538/ICMHS/

WHO-Facts Sheet

1. Ambient (outdoor) air pollution
2. Crimean-Congo haemorrhagic fever
3. Injuries and violence
4. Mental health at work
5. Rheumatic heart disease

Compiled and edited by
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1. Ambient (outdoor) air pollution

KEY FACTS

- Air pollution is one of the greatest environmental risk to health. By reducing air pollution levels, countries can reduce the burden of disease from stroke, heart disease, lung cancer, and both chronic and acute respiratory diseases, including asthma.
- The lower the levels of air pollution, the better the cardiovascular and respiratory health of the population will be, both long- and short-term.
- The WHO Air Quality Guidelines: Global Update 2021 provide an assessment of health effects of air pollution and thresholds for health–harmful pollution levels.
- In 2019, 99% of the world population was living in places where the WHO air quality guidelines levels were not met.
- Ambient (outdoor air pollution) in both cities and rural areas was estimated to cause 4.2 million premature deaths worldwide in 2016.
- Some 91% of those premature deaths occurred in low- and middle-income countries, and the greatest number in the WHO South-East Asia and Western Pacific regions.
- Policies and investments supporting cleaner transport, energy-efficient homes, power generation, industry and better municipal waste management would reduce key sources of outdoor air pollution.
- In addition to outdoor air pollution, indoor smoke is a serious health risk for some 2.4 billion people who cook and heat their homes with biomass, kerosene fuels and coal.

Background

Outdoor air pollution is a major environmental health problem affecting everyone in low-, middle-, and high-income countries.

Ambient (outdoor) air pollution in both cities and rural areas was estimated to cause 4.2 million premature deaths worldwide per year in 2016; this mortality is due to exposure to fine particulate matter of 2.5 microns or less in diameter (PM2.5), which cause cardiovascular and respiratory disease, and cancers.

People living in low- and middle-income countries disproportionately experience the burden of outdoor air pollution with 91% (of the 4.2 million premature deaths) occurring in low- and middle-income countries, and the greatest burden in the WHO South-East Asia and Western Pacific regions. The latest burden estimates reflect the very significant role air pollution plays in cardiovascular illness and death. More and more, evidence demonstrating the linkages between ambient air pollution and the cardiovascular disease risk is becoming available, including studies from highly polluted areas.

WHO estimates that in 2016, some 58% of outdoor air pollution-related premature deaths were due to ischaemic heart disease and stroke, while 18% of deaths were due to chronic obstructive pulmonary disease and acute lower respiratory infections respectively, and 6% of deaths were due to lung cancer.

Some deaths may be attributed to more than one risk factor at the same time. For example, both smoking and ambient air pollution affect lung cancer. Some lung cancer deaths could have been averted by improving ambient air quality, or by reducing tobacco smoking.

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A 2013 assessment by WHO's International Agency for Research on Cancer (IARC) concluded that outdoor air pollution is carcinogenic to humans, with the particulate matter component of air pollution most closely associated with increased cancer incidence, especially lung cancer. An association also has been observed between outdoor air pollution and increase in cancer of the urinary tract/bladder.

Addressing all risk factors for noncommunicable diseases – including air pollution – is key to protecting public health.

Most sources of outdoor air pollution are well beyond the control of individuals and demands concerted action by local, national and regional level policy-makers working in sectors like transport, energy, waste management, urban planning, and agriculture.

There are many examples of successful policies in transport, urban planning, power generation and industry that reduce air pollution:

- **for industry:** clean technologies that reduce industrial smokestack emissions; improved management of urban and agricultural waste, including capture of methane gas emitted from waste sites as an alternative to incineration (for use as biogas);
- **for energy:** ensuring access to affordable clean household energy solutions for cooking, heating and lighting;
- **for transport:** shifting to clean modes of power generation; prioritizing rapid urban transit, walking and cycling networks in cities as well as rail interurban freight and passenger travel; shifting to cleaner heavy-duty diesel vehicles and low-emissions vehicles and fuels, including fuels with reduced sulfur content;
- **for urban planning:** improving the energy efficiency of buildings and making cities more green and compact, and thus energy efficient;
- **for power generation:** increased use of low-emissions fuels and renewable combustion-free power sources (like solar, wind or hydropower); co-generation of heat and power; and distributed energy generation (e.g. mini-grids and rooftop solar power generation);
- **for municipal and agricultural waste management:** strategies for waste reduction, waste separation, recycling and reuse or waste reprocessing; as well as improved methods of biological waste management such as anaerobic waste digestion to produce biogas, are feasible, low cost alternatives to the open incineration of solid waste. Where incineration is unavoidable, then combustion technologies with strict emission controls are critical.

In addition to outdoor air pollution, indoor smoke from household air pollution is a serious health risk for some 2.4 billion people who cook and heat their homes with biomass fuels and coal. Some 3.2 million premature deaths were attributable to household air pollution in 2016. Almost all of the burden was in low-middle-income countries. Household air pollution is also a major source of outdoor air pollution in both urban and rural areas, accounting for up to 50% in some regions of the world.

The *WHO Global air quality guidelines* offer global guidance on thresholds and limits for key air pollutants that pose health risks.

The Guidelines apply worldwide to both outdoor and indoor environments and are based on expert evaluation of current scientific evidence for:

- particulate matter (PM)
- ozone (O_3)
- nitrogen dioxide (NO_2)
- sulfur dioxide (SO_2).

The Guidelines also include qualitative good practice recommendations for black carbon/elemental carbon, ultrafine particles (<=1um) and particles derived from sand and dust storms.

Particulate matter (PM)

Definition and principal sources

PM is a common proxy indicator for air pollution. It affects more people than any other pollutant. The major components of PM are sulfate, nitrates, ammonia, sodium chloride, black carbon, mineral dust and water. It consists of a complex mixture of solid and liquid particles of organic and inorganic substances suspended in the air. While particles with a diameter of 10 microns or less, ($\leq PM_{10}$) can penetrate and lodge deep inside the lungs, the even more health-damaging particles are those with a diameter of 2.5 microns or less, ($\leq PM_{2.5}$). $PM_{2.5}$ can penetrate the lung barrier and enter the blood system. Chronic exposure to particles contributes to the risk of developing cardiovascular and respiratory diseases, as well as of lung cancer.

Air quality measurements are typically reported in terms of daily or annual mean concentrations of PM_{10} particles per cubic meter of air volume (m^3). Routine air quality measurements typically describe such PM concentrations in terms of micrograms per cubic meter ($\mu g/m^3$). When sufficiently sensitive measurement tools are available, concentrations of fine particles ($PM_{2.5}$ or smaller), are also reported.

Health effects

There is a close, quantitative relationship between exposure to high concentrations of small particulates (PM_{10} and $PM_{2.5}$) and increased mortality or morbidity, both daily and over time. Conversely,

when concentrations of small and fine particulates are reduced, related mortality will also go down – presuming other factors remain the same. This allows policy-makers to project the population health improvements that could be expected if particulate air pollution is reduced.

Small particulate pollution has health impacts even at very low concentrations – indeed no threshold has been identified below which no damage to health is observed. Therefore, the WHO Global guideline limits aimed to achieve the lowest concentrations of PM possible.

In addition to guideline values, the *WHO Global air quality guidelines* provide interim targets for concentrations of PM_{10} and $PM_{2.5}$ aimed at promoting a gradual shift from high to lower concentrations.

If these interim targets were to be achieved, significant reductions in risks for acute and chronic health effects from air pollution can be expected. Achieving the guideline values, however, should be the ultimate objective.

The effects of PM on health occur at levels of exposure currently being experienced by many people both in urban and rural areas and in developed and developing countries – although exposures in many fast-developing cities today are often far higher than in developed cities of comparable size.

In low- and middle- income countries, exposure to pollutants in and around homes from the household combustion of polluting fuels on open fires or traditional stoves for cooking, heating and lighting further increases the risk for air pollution-related diseases, including acute lower respiratory infections, cardiovascular disease, chronic obstructive pulmonary disease and lung cancer.

There are serious risks to health not only from exposure to PM, but also from exposure to ozone (O_3), nitrogen dioxide (NO_2) and sulfur dioxide (SO_2). As with PM, concentrations are often highest largely in the urban areas of low- and middle-income countries. Ozone is a major factor in asthma morbidity and mortality, while nitrogen dioxide and sulfur dioxide also can play a role in asthma, bronchial symptoms, lung inflammation and reduced lung function.

Ozone (O_3)

Ozone at ground level – not to be confused with the ozone layer in the upper atmosphere – is one of the major constituents of photochemical smog. It is formed by the reaction with sunlight (photochemical reaction) of pollutants such as nitrogen oxides (NO_x) from vehicle and industry emissions and volatile organic compounds (VOCs) emitted by vehicles, solvents and industry. As a result, the highest levels of ozone pollution occur during periods of sunny weather.

Health effects

Excessive ozone in the air can have a marked effect on human health. It can cause breathing problems, trigger asthma, reduce lung function and cause lung diseases.

The current WHO guideline value of 10 μg/m^3 (annual mean) was set to protect the public from the health effects of gaseous nitrogen dioxide.

Definition and principal sources

NO_2 is the main source of nitrate aerosols, which form an important fraction of $PM_{2.5}$ and, in the presence of ultraviolet light, of ozone. The major sources of anthropogenic emissions of NO_2 are combustion processes (heating, power generation, and engines in vehicles and ships).

Health effects

Epidemiological studies have shown that symptoms of bronchitis in asthmatic children increase in association with long-term exposure to NO_2. Reduced lung function growth is also linked to NO_2 at concentrations currently measured (or observed) in cities of Europe and North America.

Sulfur dioxide (SO_2)

Studies indicate that a proportion of people with asthma experience changes in pulmonary function and respiratory symptoms after periods of exposure to SO_2 . Health effects are now known to be associated with much lower levels of SO_2 than previously believed. A greater degree of protection is needed. Although the causality of the effects of low concentrations of SO_2 is still uncertain, reducing SO_2 concentrations is likely to decrease exposure to co-pollutants.

Definition and principal sources

SO_2 is a colourless gas with a sharp odour. It is produced from the burning of fossil fuels (coal and oil) and the smelting of mineral ores that contain sulfur. The main anthropogenic source of SO_2 is the burning of sulfur-containing fossil fuels for domestic heating, power generation and motor vehicles.

Health effects

SO_2 can affect the respiratory system and the functions of the lungs, and causes irritation of the eyes. Inflammation of the respiratory tract causes coughing, mucus secretion, aggravation of asthma and chronic bronchitis and makes people more prone to infections of the respiratory tract. Hospital admissions for cardiac disease and mortality increase on days with higher SO_2 levels. When SO_2 combines with water, it forms sulfuric acid; this is the main component of acid rain which is a cause of deforestation.

WHO response

WHO Member States recently adopted a resolution (2015) and a road map (2016) for an enhanced global response to the adverse health effects of air pollution.

WHO is custodial agency for 3 air pollution-related Sustainable Development Goals indicators:

- 3.9.1 Mortality from air pollution
- 7.1.2 Access to clean fuels and technologies
- 11.6.2 Air quality in cities.

WHO develops and produces air quality guidelines recommending exposure limits to key air pollutants (indoor and outdoor).

WHO creates detailed health-related assessments of different types of air pollutants, including particulates and black carbon particles, and ozone.

WHO produces evidence regarding the linkage of air pollution to specific diseases, such as cardiovascular and respiratory diseases and cancers, as well as burden of disease estimates from existing air pollution exposures, at country, regional, and global levels.

WHO develops tools such as AirQ+ for assessing the health impacts from various pollutants, but also the Health Economic Assessment Tool (HEAT) to assess walking and cycling interventions, the Green+ tool to raise importance of green space and health, the Sustainable Transport Health Assessment Tool (STHAT) and the Integrated Transport and Health Impact Modelling Tool (ITHIM).

WHO has developed a Clean Household Energy Solutions Toolkit (CHEST) to provide countries and programmes with the tools needed to create or evaluate policies that expand clean household energy access and use, which is particularly important as pollutants released in and around the household (household air pollution) contribute significantly to ambient pollution. CHEST tools include modules on needs assessment, guidance on standards and testing for household energy devices, monitoring and evaluation, and materials to empower the health sector to tackle household air pollution.

WHO assists Member States in sharing information on successful approaches, on methods of exposure assessment and monitoring of health impacts of pollution.

WHO is leading the Joint Task Force on the Health Aspects of Air Pollution within the Convention on Long-range Transboundary Air Pollution to assess the health effects of such pollution and to provide supporting documentation.

The WHO co-sponsored Pan European Programme on Transport Health and Environment (PEP), has built a model of regional, Member State, and multisectoral cooperation for mitigation of air pollution and other health impacts in the transport sector, as well as tools for assessing the health benefits of such mitigation measures.

2. Crimean-Congo haemorrhagic fever

KEY FACTS

- The Crimean-Congo haemorrhagic fever (CCHF) virus causes severe viral haemorrhagic fever outbreaks.
- CCHF outbreaks have a case fatality rate of up to 40%.
- The virus is primarily transmitted to people from ticks and livestock animals. Human-to-human transmission can occur resulting from close contact with the blood, secretions, organs or other bodily fluids of infected persons.
- CCHF is endemic in Africa, the Balkans, the Middle East and Asia, in countries south of the 50th parallel north.
- There is no vaccine available for either people or animals.

Overview

Crimean-Congo haemorrhagic fever (CCHF) is a widespread disease caused by a tick-borne virus (*Nairovirus*) of the *Bunyaviridae* family. The CCHF virus causes severe viral haemorrhagic fever outbreaks, with a case fatality rate of 10–40%.

CCHF is endemic in Africa, the Balkans, the Middle East and Asian countries south of the 50th parallel north – the geographical limit of the principal tick vector.

The Crimean-Congo haemorrhagic fever virus in animals and ticks

The hosts of the CCHF virus include a wide range of wild and domestic animals such as cattle, sheep and goats. Many birds are resistant to infection, but ostriches are susceptible and may show a high prevalence of infection in endemic areas, where they have been at the origin of human cases. For example, a former outbreak occurred at an ostrich abattoir in South Africa. There is no apparent disease in these animals.

Animals become infected by the bite of infected ticks and the virus remains in their bloodstream for about one week after infection, allowing the tick-animal-tick cycle to continue when another tick bites. Although a number of tick genera are capable of becoming infected with CCHF virus, ticks of the genus *Hyalomma* are the principal vector.

Transmission

The CCHF virus is transmitted to people either by tick bites or through contact with infected animal blood or tissues during and immediately after slaughter. The majority of cases have occurred in people involved in the livestock industry, such as agricultural workers, slaughterhouse workers and veterinarians.

Human-to-human transmission can occur resulting from close contact with the blood, secretions, organs or other bodily fluids of infected persons. Hospital-acquired infections can also occur due to improper sterilization of medical equipment, reuse of needles and contamination of medical supplies.

Signs and symptoms

The length of the incubation period depends on the mode of acquisition of the virus. Following infection by a tick bite, the incubation period is usually one to three days, with a maximum of nine days. The incubation period following contact with infected blood or tissues is usually five to six days, with a documented maximum of 13 days.

Onset of symptoms is sudden, with fever, myalgia, (muscle ache), dizziness, neck pain and stiffness, backache, headache, sore eyes and photophobia (sensitivity to light). There may be nausea, vomiting, diarrhoea, abdominal pain and sore throat early on, followed by sharp mood swings and confusion. After two to four days, the agitation may be replaced by sleepiness, depression and lassitude, and the abdominal pain may localize to the upper right quadrant, with detectable hepatomegaly (liver enlargement).

Other clinical signs include tachycardia (fast heart rate), lymphadenopathy (enlarged lymph nodes), and a petechial rash (a rash caused by bleeding into the skin) on internal mucosal surfaces, such as in the mouth and throat, and on the skin. The petechiae may give way to larger rashes called ecchymoses, and other haemorrhagic phenomena. There is usually evidence of hepatitis, and severely ill patients may experience rapid kidney deterioration, sudden liver failure or pulmonary failure after the fifth day of illness.

The mortality rate from CCHF is approximately 30%, with death occurring in the second week of illness. In patients who recover, improvement generally begins on the ninth or tenth day after the onset of illness.

Diagnosis

CCHF virus infection can be diagnosed by several different laboratory tests:

- enzyme-linked immunosorbent assay (ELISA) ;
- antigen detection;
- serum neutralization;
- reverse transcriptase polymerase chain reaction (RT-PCR) assay; and
- virus isolation by cell culture.

Patients with fatal disease, as well as in patients in the first few days of illness, do not usually develop a measurable antibody response and so diagnosis in these individuals is achieved by virus or RNA detection in blood or tissue samples.

Tests on patient samples present an extreme biohazard risk and should only be conducted under maximum biological containment conditions. However, if samples have been inactivated (e.g. with virucides, gamma rays, formaldehyde, heat, etc.), they can be manipulated in a basic biosafety environment.

Treatment

General supportive care with treatment of symptoms is the main approach to managing CCHF in people. The antiviral drug ribavirin has been used to treat CCHF infection with apparent benefit. Both oral and intravenous formulations seem to be effective.

Prevention and control

Controlling CCHF in animals and ticks

Ticks of the genus Hyalomma are the principal vector of Crimean-Congo haemorrhagic fever.

It is difficult to prevent or control CCHF infection in animals and ticks as the tick-animal-tick cycle usually goes unnoticed and the infection in domestic animals is usually not apparent. Furthermore, the tick vectors are numerous and widespread, so tick control with acaricides (chemicals intended to kill ticks) is only a realistic option for well-managed livestock production facilities.

For example, following an outbreak at an ostrich abattoir in South Africa (noted above), measures were taken to ensure that ostriches remained tick free for 14 days in a quarantine station before slaughter. This decreased the risk for the animal to be infected during its slaughtering and prevented human infection for those in contact with the livestock.

There are no vaccines available for use in animals.

Reducing the risk of infection in people

Although an inactivated, mouse brain-derived vaccine against CCHF has been developed and used on a small scale in eastern Europe, there is currently no safe and effective vaccine widely available for human use.

In the absence of a vaccine, the only way to reduce 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 virus.

Public health advice should focus on several aspects.

- Reducing the risk of tick-to-human transmission:
  - wear protective clothing (long sleeves, long trousers);
  - wear light coloured clothing to allow easy detection of ticks on the clothes;
  - use approved acaricides (chemicals intended to kill ticks) on clothing;
  - use approved repellent on the skin and clothing;

- regularly examine clothing and skin for ticks; if found, remove them safely;
- seek to eliminate or control tick infestations on animals or in stables and barns; and
- avoid areas where ticks are abundant and seasons when they are most active.

- Reducing the risk of animal-to-human transmission:
  - wear gloves and other protective clothing while handling animals or their tissues in endemic areas, notably during slaughtering, butchering and culling procedures in slaughterhouses or at home;
  - quarantine animals before they enter slaughterhouses or routinely treat animals with pesticides two weeks prior to slaughter.
- Reducing the risk of human-to-human transmission in the community:
  - avoid close physical contact with CCHF-infected people;
  - wear gloves and protective equipment when taking care of ill people;
  - wash hands regularly after caring for or visiting ill people.

Controlling infection in health-care settings

Health-care workers caring for patients with suspected or confirmed CCHF, or handling specimens from them, should implement standard infection control precautions. These include basic hand hygiene, use of personal protective equipment, safe injection practices and safe burial practices.

As a precautionary measure, health-care workers caring for patients immediately outside the CCHF outbreak area should also implement standard infection control precautions.

Samples taken from people with suspected CCHF should be handled by trained staff working in suitably equipped laboratories.

Recommendations for infection control while providing care to patients with suspected or confirmed Crimean-Congo haemorrhagic fever should follow those developed by WHO for Ebola and Marburg haemorrhagic fever.

WHO response

WHO is working with partners to support CCHF surveillance, diagnostic capacity and outbreak response activities in Europe, the Middle East, Asia and Africa.

WHO also provides documentation to help disease investigation and control, and has created an aide–memoire on standard precautions in health care, which is intended to reduce the risk of transmission of bloodborne and other pathogens.

3. Injuries and violence

KEY FACTS

- Injuries – both unintentional and violence-related – take the lives of 4.4 million people around the world each year and constitute nearly 8% of all deaths.
- For people age 5-29 years, 3 of the top 5 causes of death are injury-related, namely road traffic injuries, homicide and suicide.
- Injuries and violence are responsible for an estimated 10% of all years lived with disability.
- Injuries and violence place a massive burden on national economies, costing countries billions of US dollars each year in health care, lost productivity and law enforcement.
- Preventing injuries and violence will facilitate achievement of several Sustainable Development Goal (SDG) targets.

Overview

Injuries result from road traffic crashes, falls, drowning, burns, poisoning and acts of violence against oneself or others, among other causes.

Of the 4.4 million injury-related deaths, unintentional injuries take the lives of 3.16 million people every year and violence-related injuries kill 1.25 million people every year. Roughly 1 in 3 of these deaths result from road traffic crashes, 1 in 6 from suicide, 1 in 10 from homicide and 1 in 61 from war and conflict.

For people age 5-29 years, 3 of the top 5 causes of death are injury-related, namely road traffic injuries, homicide and suicide. Drowning is the sixth leading cause of death for children age 5-14 years. Falls account for over 684,000 deaths each year and are a growing and under-recognized public health issue.

Tens of millions more people suffer non-fatal injuries each year which lead to emergency department and acute care visits, hospitalizations or treatment by general practitioners and often result in temporary or permanent disability and the need for long-term physical and mental health care and rehabilitation. For example, there has been a significant rise in road traffic injuries in the African region since 2000, with an almost 50% increase in healthy life-years lost.

Impact

Beyond death and injury, exposure to any form of trauma, particularly in childhood, can increase the risk of mental illness and suicide; smoking, alcohol and substance abuse; chronic diseases like heart disease, diabetes and cancer; and social problems such as poverty, crime and violence. For these reasons, preventing injuries and violence, including

by breaking intergenerational cycles of violence, goes beyond avoiding the physical injury to contributing to substantial health, social and economic gains.

Injuries and violence are a significant cause of death and burden of disease in all countries; however, they are not evenly distributed across or within countries – some people are more vulnerable than others depending on the conditions in which they are born, grow, work, live and age. For instance, in general, being young, male and of low socioeconomic status all increase the risk of injury and of being a victim or perpetrator of serious physical violence. The risk of fall-related injuries increases with age.

Twice as many males than females are killed each year as a result of injuries and violence. Worldwide, about three quarters of deaths from road traffic injuries, four fifths of deaths from homicide, and two thirds of deaths from war are among men. In many low- and middle-income countries, however, women and girls are more likely to be burned than men and boys, in large part due to exposure to unsafe cooking arrangements and energy poverty. Across all ages, the three leading causes of death from injuries for males are road traffic injuries, homicide and suicide, while for females they are road traffic injuries, falls and suicide.

Poverty also increases the risk of injury and violence. About 90% of injury-related deaths occur in low- and middle-income countries. Across the world, injury death rates are higher in low-income countries than in high-income countries. Even within countries, people from poorer economic backgrounds have higher rates of fatal and non-fatal injuries than people from wealthier economic backgrounds. This holds true even in high-income countries.

The uneven distribution of injuries that makes them more prevalent among the less advantaged is related to several risk factors. These include living, working, travelling and going to school in more precarious conditions, less focus on prevention efforts in underprivileged communities, and poorer access to quality emergency trauma care and rehabilitation services. These issues are explained in more detail below.

Risk factors and determinants

Risk factors and determinants common to all types of injuries include alcohol or substance use; inadequate adult supervision of children; and broad societal determinants of health such as poverty; economic and gender inequality; unemployment; a lack of safety in the built environment, including unsafe housing, schools, roads and workplaces; inadequate product safety standards and regulations; easy access to alcohol, drugs, firearms, knives and pesticides; weak social safety nets; frail criminal justice systems; and inadequate institutional policies to address injuries in a consistent and effective manner, in part due to the availability of sufficient resources. In settings where emergency trauma care services are weak or there is inequitable access to services, the consequences of injuries and violence can be exacerbated.

Prevention

Injuries and violence are predictable and there is compelling scientific evidence for what works to prevent injuries and violence and to treat their consequences in various settings. This evidence has been collated into technical documents that can serve as a guide to support decisions for scaling up injury and violence prevention efforts – see:

- *Save LIVES: a road safety technical package*
- *Preventing drowning: an implementation guide*
- *Violence prevention: the evidence*
- *INSPIRE: seven strategies for preventing violence against children*
- *RESPECT women: preventing violence against women*
- *LIVE LIFE: suicide prevention implementation package*
- *SAFER: a world free from alcohol related harms*

Analysis of the costs and benefits for several selected injury and violence prevention measures shows that they offer significant value for money, making investment in such measures of great societal benefit. For example, with regard to child injury prevention, a study found that every US$ 1 invested in smoke detectors saves US$ 65, in child restraints and bicycle helmets saves US$ 29, and in-home visitation saves US$ 6 in medical costs, loss productivity and property loss. In Bangladesh, teaching school-age children swimming and rescue skills returned US$ 3000 per death averted. The social benefits of injuries prevented through home modification to prevent falls have been estimated to be at least six times the cost of intervention. It is estimated that in Europe and North America, a 10% reduction in adverse childhood experiences could equate to annual savings of 3 million Disability Adjusted Life Years or US$ 105 billion.

Post-injury care

For all injuries and violence, providing quality emergency care for victims can prevent fatalities, reduce the amount of short-term and long-term disability, and help those affected to cope physically, emotionally, financially and legally with the impact of the injury or violence on their lives. As such, improving the organization, planning and access to trauma care systems, including telecommunications, transport to hospital, prehospital and hospital-based care, are important strategies to minimize fatalities and disabilities from injury and violence.

Providing rehabilitation for people with disabilities, ensuring they have access to assistive products such as wheelchairs, and removing barriers to social and economic participation are key strategies to ensure that people who experience disability as the result of an injury or violence may continue a full and enjoyable life.

WHO response

WHO supports efforts to address injuries and violence in many ways, including by:

- developing and disseminating guidance for countries on evidence-based policy and practice including those listed above;
- providing technical support to countries through programmes such as the Bloomberg Initiative for Global Road Safety and the Global Partnership to End Violence against Children;
- documenting and disseminating successful injury prevention approaches, policies and programmes across countries;
- monitoring progress towards achieving the Sustainable Development Goal targets linked to injury, violence prevention, mental health and substance use – namely targets 3.4, 3.5, 3.6, 5.2, 5.3, 16.1 and 16.2 – through global status reports on road safety and violence prevention, and on alcohol and health, and world reports on preventing suicide;
- through informal networks chaired by WHO such as the UN Road Safety Collaboration and the Violence Prevention Alliance, and others towards which WHO contributes like the Global Partnership to End Violence against Children, coordinating global efforts across the UN system including decades of action, ministerial conferences and weeks and days dedicated to injury-related topics to improve road safety and end violence;
- clarifying the role of Ministries of Health as part of multi-sectoral injury-prevention efforts, as reflected in *Preventing injuries and violence: a guide for ministries of health*, including its role in collecting data; developing national policies and plans; building capacities; facilitating prevention measures; providing services for victims, including emergency trauma care; promulgating legislation on key risks; and training journalists to improve reporting on these issues with a focus on solutions and by co-hosting biannual global meetings and regional meetings of Ministry of Health focal points for violence and injury prevention; and
- co-hosting and serving on the International Organizing Committee for the series of biannual World Conferences on Injury Prevention and Safety Promotion, the 14th edition of which will take place in Adelaide, Australia, in 2022.

4. Mental health at work

KEY FACTS

- Decent work is good for mental health.
- Poor working environments – including discrimination and inequality, excessive workloads, low job control and job insecurity – pose a risk to mental health.
- 15% of working-age adults were estimated to have a mental disorder in 2019.
- Globally, an estimated 12 billion working days are lost every year to depression and anxiety at a cost of US$ 1 trillion per year in lost productivity.
- There are effective actions to prevent mental health risks at work, protect and promote mental health at work, and support workers with mental health conditions.

Work can protect mental health

Almost 60% of the world population is in work (1). All workers have the right to a safe and healthy environment at work. Decent work supports good mental health by providing:

- a livelihood;
- a sense of confidence, purpose and achievement;
- an opportunity for positive relationships and inclusion in a community; and
- a platform for structured routines, among many other benefits.

For people with mental health conditions, decent work can contribute to recovery and inclusion, improve confidence and social functioning.

Safe and healthy working environments are not only a fundamental right but are also more likely to minimize tension and conflicts at work and improve staff retention, work performance and productivity. Conversely, a lack of effective structures and support at work, especially for those living with mental health conditions, can affect a person's ability to enjoy their work and do their job well; it can undermine people's attendance at work and even stop people getting a job in the first place.

Risks to mental health at work

At work, risks to mental health, also called psychosocial risks, may be related to job content or work schedule, specific characteristics of the workplace or opportunities for career development among other things.

Risks to mental health at work can include:

- under-use of skills or being under-skilled for work;
- excessive workloads or work pace, understaffing;
- long, unsocial or inflexible hours;
- lack of control over job design or workload;

- unsafe or poor physical working conditions;
- organizational culture that enables negative behaviours;
- limited support from colleagues or authoritarian supervision;
- violence, harassment or bullying;
- discrimination and exclusion;
- unclear job role;
- under- or over-promotion;
- job insecurity, inadequate pay, or poor investment in career development; and
- conflicting home/work demands.

More than half the global workforce works in the informal economy (2), where there is no regulatory protection for health and safety. These workers often operate in unsafe working environments, work long hours, have little or no access to social or financial protections and face discrimination, all of which can undermine mental health.

Although psychosocial risks can be found in all sectors, some workers are more likely to be exposed to them than others, because of what they do or where and how they work. Health, humanitarian or emergency workers often have jobs that carry an elevated risk of exposure to adverse events, which can negatively impact mental health.

Economic recessions or humanitarian and public health emergencies elicit risks such as job loss, financial instability, reduced employment opportunities or increased unemployment.

Work can be a setting which amplifies wider issues that negatively affect mental health, including discrimination and inequality based on factors such as, race, sex, gender identity, sexual orientation, disability, social origin, migrant status, religion or age.

People with severe mental health conditions are more likely to be excluded from employment, and when in employment, they are more likely to experience inequality at work. Being out of work also poses a risk to mental health. Unemployment, job and financial insecurity, and recent job loss are risk factors for suicide attempts.

Action for mental health at work

Government, employers, the organizations which represent workers and employers, and other stakeholders responsible for workers' health and safety can help to improve mental health at work through action to:

- prevent work-related mental health conditions by preventing the risks to mental health at work;
- protect and promote mental health at work;
- support workers with mental health conditions to participate and thrive in work; and
- create an enabling environment for change.

Action to address mental health at work should be done with the meaningful involvement of workers and their representatives, and persons with lived experience of mental health conditions.

Prevent work-related mental health conditions

Preventing mental health conditions at work is about managing psychosocial risks in the workplace. WHO recommends employers do this by implementing organizational interventions that directly target working conditions and environments. Organizational interventions are those that assess, and then mitigate, modify or remove workplace risks to mental health. Organizational interventions include, for example, providing flexible working arrangements, or implementing frameworks to deal with violence and harassment at work.

Protect and promote mental health at work

Protecting and promoting mental health at work is about strengthening capacities to recognize and act on mental health conditions at work, particularly for persons responsible for the supervision of others, such as managers.

To protect mental health, WHO recommends:

- **manager training for mental health**, which helps managers recognize and respond to supervisees experiencing emotional distress; builds interpersonal skills like open communication and active listening; and fosters better understanding of how job stressors affect mental health and can be managed;
- **training for workers** in mental health literacy and awareness, to improve knowledge of mental health and reduce stigma against mental health conditions at work; and
- **interventions for individuals** to build skills to manage stress and reduce mental health symptoms, including psychosocial interventions and opportunities for leisure-based physical activity.

Support people with mental health conditions to participate in and thrive at work

People living with mental health conditions have a right to participate in work fully and fairly. The UN Convention on the Rights of Persons with Disabilities provides an international agreement for promoting the rights of people with disabilities (including psychosocial disabilities), including at work. WHO recommends three interventions to support people with mental health conditions gain, sustain and participate in work:

- **Reasonable accommodations** at work adapt working environments to the capacities, needs and preferences of a worker with a mental health

condition. They may include giving individual workers flexible working hours, extra time to complete tasks, modified assignments to reduce stress, time off for health appointments or regular supportive meetings with supervisors.

- **Return-to-work programmes** combine work-directed care (like reasonable accommodations or phased re-entry to work) with ongoing clinical care to support workers in meaningfully returning to work after an absence associated with mental health conditions, while also reducing mental health symptoms.
- **Supported employment initiatives** help people with severe mental health conditions to get into paid work and maintain their time on work through continue to provide mental health and vocational support.

Create an enabling environment for change

Both governments and employers, in consultation with key stakeholders, can help improve mental health at work by creating an enabling environment for change. In practice this means strengthening:

- **Leadership** and commitment to mental health at work, for example by integrating mental health at work into relevant policies.
- **Investment** of sufficient funds and resources, for example by establishing dedicated budgets for actions to improve mental health at work and making mental health and employment services available to lower-resourced enterprises.
- **Rights** to participate in work, for example by aligning employment laws and regulations with international human rights instruments and implementing non-discrimination policies at work.
- **Integration** of mental health at work across sectors, for example by embedding mental health into existing systems for occupational safety and health.
- **Participation** of workers in decision-making, for example by holding meaningful and timely consultations with workers, their representatives and people with lived experience of mental health conditions.
- **Evidence** on psychosocial risks and effectiveness of interventions, for example by ensuring that all guidance and action on mental health at work is based on the latest evidence.
- **Compliance** with laws, regulations and recommendations, for example by integrating mental health into the responsibilities of national labour inspectorates and other compliance mechanisms.

WHO response

WHO is committed to improving mental health at work. The *WHO global strategy on health, environment and climate change* and *WHO Comprehensive mental health action plan (2013–2030)* outline relevant principles, objectives and implementation strategies to enable good mental health in the workplace. These include addressing social determinants of mental health, such as living standards and working conditions; reducing stigma and discrimination; and increasing access to evidence-based care through health service development, including access to occupational health services. In 2022, *WHO's World mental health report: transforming mental health for all*, highlighted the workplace as a key example of a setting where transformative action on mental health is needed.

The *WHO guidelines on mental health at work* provide evidence-based recommendations to promote mental health, prevent mental health conditions, and enable people living with mental health conditions to participate and thrive in work. The recommendations cover organizational interventions, manager training and worker training, individual interventions, return to work, and gaining employment. The accompanying policy brief by WHO and the International Labour Organization, *Mental health at work: policy brief* provides a pragmatic framework for implementing the WHO recommendations. It specifically sets out what governments, employers, organizations representing employers and workers, and other stakeholders can do to improve mental health at work.

1. World employment and social outlook - Trends 2022. Geneva: International Labour Organization; 2022 (https://www.ilo.org/global/research/global-reports/weso/trends2022/WCMS_834081/lang--en/index.htm, accessed 26 August 2022)
2. Women and men in the informal economy: a statistical picture. Geneva: International Labour Organization; 2018 (https://www.ilo.org/global/publications/books/WCMS_626831/lang--en/index.htm, accessed 26 August 2022).

5. Rheumatic heart disease

KEY FACTS

- Rheumatic heart disease is the most commonly acquired heart disease in people under age 25.
- Rheumatic heart disease and claims over 288 348 lives each year - the large majority in low- or middle-income countries.
- The disease results from damage to heart valves caused by one or several episodes of rheumatic fever, an autoimmune inflammatory reaction to throat infection with group A streptococci

(streptococcal pharyngitis or strep throat). It most commonly occurs in childhood, and can lead to death or life-long disability.
- Rheumatic heart disease can be prevented by preventing streptococcal infections, or treating them with antibiotics when they do occur.

What is rheumatic heart disease?

Rheumatic heart disease starts as a sore throat from a bacterium called *Streptococcus pyogenes* (group A streptococcus) which can pass easily from person to person in the same way as other upper respiratory tract infections. Strep infections are most common in childhood.

In some people, repeated strep infections cause the immune system to react against the tissues of the body including inflaming and scarring the heart valves. This is what is referred to as rheumatic fever. Rheumatic heart disease results then from the inflammation and scarring of heart valves caused by rheumatic fever.

Who is at risk?

Rheumatic fever mostly affects children and adolescents in low- and middle-income countries, especially where poverty is widespread and access to health services is limited. People who live in overcrowded and poor conditions are at greatest risk of developing the disease.

Where rheumatic fever and rheumatic heart disease are endemic, rheumatic heart disease is the principal heart disease seen in pregnant women, causing significant maternal and perinatal morbidity and mortality. Pregnant women with rheumatic heart disease are at risk of adverse outcomes, including heart arrythmias and heart failure due to increased blood volume putting more pressure on the heart valves. It is not uncommon for women to be unaware that they have rheumatic heart disease until pregnancy.

Despite it being eradicated in many parts of the world, the disease remains prevalent in sub-Saharan Africa, the Middle East, Central and South Asia, the South Pacific, and among immigrants and older adults ~~in~~ high-income countries, especially in indigenous peoples.

What are the signs and symptoms?

Rheumatic fever symptoms can include:
- fever
- painful joints especially knees ankles, elbows and wrists
- pain that moves between different joints
- fatigue
- jerky uncontrollable body movements called 'chorea'
- painless nodules under the skin near joints and/or a rash consisting of pink rings with a clear centre (both rare)
- heart murmur

Symptoms of heart valve damage that is associated with rheumatic heart disease may include:
- chest pain or discomfort
- shortness of breath
- swelling of the stomach, hands or feet
- fatigue
- rapid or irregular heart beat

How is rheumatic heart disease treated?

There is no cure for rheumatic heart disease and the damage to the heart valves are permanent. Patients with severe rheumatic heart disease will often require surgery to replace or repair the damages valve or valves. Depending on the severity of disease, medication may also be needed to treat symptoms of heart failure or heart rhythm abnormalities. Medications which thin the blood to reduce the risk of blood clots may also be needed. In the case of serious disease surgery may be required to repair or replace the heart valves. This is often not available in low-income settings, or when it is available the costs may be too high if not covered as part of national health plans, putting families under increased financial strain.

Rheumatic heart disease is preventable.

Since rheumatic heart disease results from rheumatic fever, an important strategy is to prevent rheumatic fever from occurring. Treatment of strep throat with appropriate antibiotics will prevent rheumatic fever.

Once a patient has been identified as having had rheumatic fever, it is important to prevent additional streptococcal infections as this could cause a further episode of rheumatic fever and additional damage to the heart valves. The strategy to prevent additional streptococcal infection is to treat the patient with antibiotics over a long period of time. The antibiotic treatment that is most effective in preventing further infection is benzathine penicillin G, which is given by intramuscular injection every 3-4 weeks over many years.

For countries where rheumatic heart disease is endemic, the main strategies for prevention, control and elimination include: improving standards of living; expanding access to appropriate care; ensuring a consistent supply of quality-assured antibiotics for primary and secondary prevention; and planning, developing and implementing feasible programmes for prevention and control of rheumatic heart disease, supported by adequate monitoring and surveillance, as an integrated component of national health systems responses.

Challenges

Rheumatic heart disease can be prevented by effective management of streptococcal sore throat, however treatment at this early stage is often not achieved. Families may not have the time or money to access a healthcare facility, or may not seek care due to low awareness of the potential risk of untreated 'strep throat'. Healthcare workers may also not have the necessary knowledge to appropriately diagnose and manage a 'strep throat'. If left untreated, rheumatic fever may then ensue**.**

Currently a large proportion of those suffering rheumatic heart disease are not diagnosed, or are diagnosed at a late stage when damage to the heart is very severe. Rheumatic heart disease remains the leading cause of maternal cardiac complications in pregnancy. In many rheumatic heart disease-endemic countries there is little or no access to life-saving heart valve surgery. Measures to halt the progression to severe rheumatic heart disease require long-term treatments and a well-functioning health system to deliver this service. Additionally, because treatment is long-term, it can be costly and challenging for patients to regularly visit a healthcare facility, and some patients may avoid the injections due to discomfort or fear of adverse events.

A steady supply of benzathine penicillin G is an essential prerequisite for treatment of sore throat and to prevent recurrent infection. However, the antibiotic is prone to global shortages. High manufacturing costs and low purchase prices have pushed some manufacturers out of the market while demand for the drug is rising. When the medication is not available on the shelf, necessary long-term treatment regimens are disrupted.

Investing in the secure supply of quality assured benzathine penicillin G will prevent the recurrence of global shortages and contribute to global efforts to increase access to quality-assured, safe, effective, and affordable essential medicines, as part of universal health coverage.

WHO Response

In 2018, the World Health Assembly adopted resolution WHA 71.14 calling for WHO to launch a coordinated global response to rheumatic heart disease and rheumatic fever. The Organization is working to develop clinical guidelines for rheumatic heart disease and with the help of WHO regional offices, a workplan is being developed to put interventions in place to prevent rheumatic heart disease and care for people already living with it.

Ensuring a steady, quality supply of benzathine penicillin is also a key priority in the 13th WHO General Programme of Work, specifically the strategic priority on universal health coverage; access to medicines, vaccines and health products. Additionally, the *WHO Road map for access to medicines, vaccines and other health products 2019-2023* and the WHO Benzathine Penicillin Technical Working Group are working to address global supply and demand issues for benzathine penicillin and ensure a quality-assured, safe and effective product is available on the shelves when needed.

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