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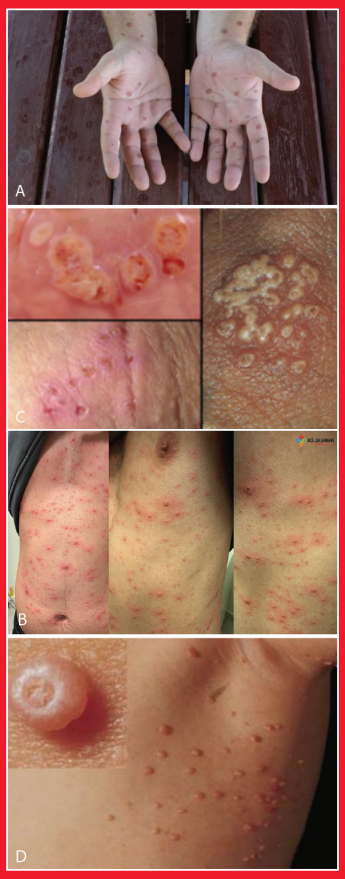

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Publisher Contact
Address: Molla Gürani Mah. Kaçamak Sk. No: 21/1 34093 İstanbul, Türkiye
Phone: +90 (530) 177 30 97
E-mail: info@galenos.com.tr/yayin@galenos.com.tr
Web: www.galenos.com.tr

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Ayşe Filiz GÖKMEN KARASU
Bezmialem Vakıf University Faculty of Medicine, Deparment of Gynecology and Obstetrics, İstanbul, Türkiye
E-mail: afgokmen@gmail.com
ORCID: 0000-0001-7480-4691

Ayşegül DOĞAN DEMİR
İstanbul Medipol University Faculty of Medicine, Department of Social Pediatrics, İstanbul, Türkiye
E-mail: ayseguldogandemir@gmail.com
ORCID: 0000-0002-2536-1422

Bahadır TAŞLIDERE
Bezmialem Vakıf University Faculty of Medicine, Department of Emergency Medicine, İstanbul, Türkiye
E-mail: btaslidere@bezmialem.edu.tr
ORCID: 0000-0002-5920-8127

Burcu OĞLAKÇI ÖZKOÇ
Bezmialem Vakıf University Faculty of Dentistry, Department of Restorative Dental Treatment, İstanbul, Türkiye
Email: burcu923@hotmail.com
ORCID: 0000-0002-6587-5997

Çağla KIZILARSLAN HANÇER
Bezmialem Vakıf University Faculty of Pharmacy, Department of Pharmaceutical Botany, İstanbul, Türkiye
E-mail: c.kizilarslan@gmail.com
ORCID: 0000-0001-5979-2629

Ebru HACIOSMANOĞLU ALDOĞAN
İstanbul-Cerrahpaşa University Faculty of Medicine, Department of Biophysics, İstanbul, Türkiye
E-mail: ebru.aldogan@iuc.edu.tr
ORCID: 0000-0001-9559-4515

Fahri AKBAŞ
Bezmialem Vakıf University Faculty of Medicine, Department of Medical Biology, İstanbul, Türkiye
E-mail: fakbas@bezmialem.edu.tr
ORCID: 0000-0002-3837-250X

Fatma Betül AKÇAKAYA ÖZER
Republic of Türkiye Ministry of Health, Kağıthane District Health Directorate, İstanbul, Türkiye
E-mail: fakcakaya@bezmialem.edu.tr
ORCID: 0000-0003-0079-6574

Mehmet Ali GÜLTEKİN
Bezmialem Vakıf University Faculty of Medicine, Department of Radiology, İstanbul, Türkiye
E-mail: mgultekin@bezmialem.edu.tr
ORCID ID: 0000-0001-7311-6969

Merve MEŞEDÜZÜ
Bezmialem Vakıf University Faculty of Health, Department of Nurse, İstanbul, Türkiye
E-Mail: mmeseduzu@bezmialem.edu.tr
ORCID: 0000-0001-9991-626X

Muhammed Batuhan AYIK
Bezmialem Vakıf University Faculty of Medicine, Department of Psychiatry, İstanbul, Türkiye
E-mail: batuhan.ayik@bezmialem.edu.tr
ORCID: 0000-0002-9322-2336

Muharrem KISKAÇ
Bezmialem Vakıf University Faculty of Medicine, Department of Internal Medicine, İstanbul, Türkiye
E-mail: muharremkiskac@gmail.com
ORCID: 0000-0003-2534-2675

Özlem SU KÜÇÜK
Bezmialem Vakıf University Faculty of Medicine, Department of Dermatology, İstanbul, Türkiye
E-mail: ozlemsukucuk2@yahoo.com.tr
ORCID: 0000-0002-1140-9261

Semiramis ÖZYILMAZ
Bezmialem Vakıf University Faculty of Medicine, Department of Physiotherapy and Rehabilitation, İstanbul, Türkiye
E-mail: sozyilmaz@bezmialem.edu.tr
ORCID: 0000-0002-7788-9739

Ozan Volkan YURDAKUL
Bezmialem Vakıf University Faculty of Medicine, Department of Physical Medicine and Rehabilitation, İstanbul, Türkiye
E-mail: oyurdakul@bezmialem.edu.tr
ORCID: 0000-0003-4567-8133

Yeter DEMİR USLU
İstanbul Medipol University Faculty of Health Sciences, Department of Health Management, İstanbul, Türkiye
E-mail: yuslu@medipol.edu.tr
ORCID: 0000-0002-8529-6466

Biostatistics Consultant

Ömer UYSAL
İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Department of Biostatisitics and Medical Informatics, İstanbul, Türkiye
E-mail: omer.uysal@iuc.edu.tr
ORCID: 0000-0002-8833-697X

Ayşegül YABACI TAK
Bezmialem Vakıf University Faculty of Medicine, Department of Biostatistics and Medical Informatics, İstanbul, Türkiye
E-mail: ayabaci@bezmialem.edu.tr
ORCID: 0000-0002-5813-3397

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Original Articles

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EDITORIAL

Dear Readers;

We are delighted to be with you again with the first issue of Bezmialem Science journal in 2026. Bringing together different disciplines of health sciences, our journal continues to blend the values of the past with the scientific output of today, drawing inspiration from the long-standing foundation tradition of Bezmialem Vakıf University, which blends science and technology with compassion.

The cover image of this issue is selected from the study titled **"Mpox and Public Health in Türkiye: Epidemiology, Diagnostics, Vaccination and Prevention**" by Peşdere S and Uzun SU. This study is a comprehensive review addressing the transformation of mpox from a regional infectious disease to a global public health threat. Particularly in light of the multi-country outbreak in 2022 and the re-emergence of clade I in Central Africa in 2024, this article evaluates the epidemiological, clinical, and diagnostic dimensions of mpox with current data. In the context of Türkiye, the study also draws attention to surveillance, case definitions, treatment, and vaccination strategies. By highlighting inconsistencies in official reporting, the study brings the importance of transparent and sustainable public health approaches back to the forefront.

Other articles featured on the cover include:

"Arterial Stiffness and Mean Arterial Pressure (MAP) and Their Relationship with Renin and Aldosterone Levels in Primary Hyperparathyroidism" by Berber HG et al.

"Electrolyte Disorders: Insights From a Prospective, Multicenter, Observational Cohort Study on Fosfomycin's Impact" by Ayhan YE et al.

"Protective Factors Against Breast Cancer Development: A Retrospective Study on Breastfeeding and Fertility" by Çiflik N et al.

"The Effects of Medications Used in the Treatment of Rheumatological Diseases on Pregnancy and Fertilization: A Single-center Experience" by Karataş B et al.

As we are Bezmialem Science, we don't limit academic value to mere numerical data; we also consider the contribution of the knowledge produced to clinical decision-making processes, patient care, and the healthcare system as a fundamental criterion. In this regard, we value the combination of methodological rigor, applicability to practice, and potential for societal resonance in every study we publish.

I would like to express my sincere gratitude to all the authors who contributed to this issue, to our editors and reviewers who participated in the evaluation process. Their scientific responsibility and dedication are a significant force that enhances the quality of our journal.

I hope that this first issue of the new year will be inspiring and guiding for all researchers working in the field of health sciences; and I wish the Bezmialem Science family and our valued readers a year of health, success, and scientific productivity in 2026.

Sincerely,

Prof. Dr. Adem AKÇAKAYA
Editor-in-Chief

Original Article

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Perceptions of Intensive Care Nurses Regarding Open Visitation Policy in Türkiye: A Qualitative Study

Türkiye'de Yoğun Bakım Hemşirelerinin Açık Ziyaret Politikasına İlişkin Algıları: Nitel Bir Çalışma

Enes BULUT[1], Ayşe SERPİCİ[2], Sema KOÇAN[3], Vahit DALKIZAN[4]

[1]Artvin Çoruh University Faculty of Health Sciences, Department of Emergency Aid and Disaster Management, Artvin, Türkiye
[2]Bursa Uludağ University Faculty of Health Sciences, Department of Nursing, Bursa, Türkiye
[3]Recep Tayyip Erdoğan University Faculty of Health Sciences, Department of Nursing, Rize, Türkiye
[4]University of Health Sciences Türkiye, Bursa City Hospital, Clinic of Anesthesia and Reanimation ICU, Bursa, Türkiye

ABSTRACT

Objective: Patients' families cannot stay with their relatives in intensive care units (ICUs). Consequently, patients and patients' families experience many problems such as insomnia, anxiety, depression. Due to these situations, the recovery period of patient is prolonged and the quality of life of patients' relatives is decreased. To prevent these problems, open visiting policy in ICUs is recommended. Open visiting policy gives patients' families the opportunity to visit their relatives at any time. This policy is recommended by studies, but is not widely implemented in Türkiye. Some reasons are responsible for not applying this policy. The study was conducted to determine the perceptions of intensive care nurses about an open visitation policy.

Methods: The study group consisted of 14 intensive care nurses selected through purposive sampling. Data were collected using a semi-structured interview form, and the interviews were recorded with a voice recorder. Data analysis was performed by content analysis.

Results: Based on the research results, "opportunity to feel family presence," "barriers to open visitation," and "facilitators of open visitation" themes were identified. Participants generally evaluated the open visitation policy positively. However, it was noted that certain arrangements were needed for the implementation of open visiting policy.

ÖZ

Amaç: Hastaların aileleri yoğun bakım ünitelerinde (YBÜ) yakınlarıyla birlikte kalamaz. Bu nedenle hastalar ve aile üyeleri uykusuzluk, anksiyete, depresyon gibi birçok sorun yaşarlar. Bu durumlar nedeniyle hastanın iyileşme süreci uzar ve hasta yakınlarının yaşam kalitesi düşer. Bu sorunları önlemek için YBÜ'de açık ziyaret politikası önerilmektedir. Açık ziyaret politikası aile üyelerine yakınlarını her zaman görme fırsatı verir. Bu politika literatürde önerilmektedir ancak Türkiye'de uygulanmamaktadır. Bu politikanın uygulanmamasının bazı nedenleri vardır. Çalışma yoğun bakım hemşirelerinin açık ziyaret politikası hakkındaki algılarını belirlemek amacıyla yürütülmüştür.

Yöntemler: Çalışma grubu amaçlı örnekleme yoluyla seçilen 14 yoğun bakım hemşiresinden oluşmuştur. Veriler yarı yapılandırılmış görüşme formu kullanılarak toplanmış ve görüşmeler ses kayıt cihazı ile kaydedilmiştir. İçerik analizi kullanılarak veri analizi yapılmıştır.

Bulgular: Araştırma sonuçlarına göre, "aile varlığını hissetme fırsatı", "açık ziyaretlere yönelik engeller" ve "açık ziyaretleri kolaylaştırıcılar" temaları belirlendi. Katılımcılar genel olarak açık ziyaret politikasını olumlu değerlendirdiler. Ancak açık ziyaret politikasının uygulanması için bazı düzenlemelere ihtiyaç duyulduğu belirtildi.

Address for Correspondence: Asst. Prof. Enes Bulut, Artvin Çoruh University Faculty of Health Sciences, Department of Emergency Aid and Disaster Management, Artvin, Türkiye
E-mail: bulutts61@artvin.edu.tr **ORCID ID:** orcid.org/0000-0002-1579-6887
ORCID IDs of the authors: E.B.: 0000-0002-1579-6887, A.S.: 0000-0002-0243-4473, S.K.: 0000-0002-9049-3798, V.D.: 0000-0002-3669-2278

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ABSTRACT

Conclusion: Overall, participants favored open visitation; however, consistent with the literature, successful implementation requires structural (single rooms, privacy), staffing and policy arrangements.

Keywords: Family presence, intensive care nursing, intensive care unit, open visitation, patient, content analysis

ÖZ

Sonuç: Katılımcılar genel olarak açık ziyareti tercih ettiler; ancak literatürle tutarlı olarak, başarılı bir uygulama yapısal (tek kişilik odalar, gizlilik), personel ve politika düzenlemeleri gerektirir.

Anahtar Kelimeler: Aile varlığı, yoğun bakım hemşireliği, yoğun bakım ünitesi, açık ziyaret, hasta, içerik analizi

Introduction

For patients and their families to see each other, a restricted visitation policy is applied in most of the intensive care units (ICUs), and short-term patient visits are allowed at certain time zones of the day. In case of an emergency, the already limited visits can be prevented altogether for a while (1).

The restricted visitation practice has many negative effects on both patients and their families (2-8). To eliminate the negative effects of restricted visitation, an "open visitation" policy has been introduced. Based on the definitions, by open visiting, family or support person, as defined by the patient, has unrestricted access to the patient 24 hours a day, 7 days a week (24/7) in the ICU (7,9-11). Some countries practice an open visitation policy in their ICUs (12). A study conducted in Brazil showed a positive correlation between visitation length and the satisfaction level of the patient's families (7). Various studies have also reported that an open visitation policy helps reduce the incidence of delirium, length of ICU stay, and anxiety in patients (4,13). On the other hand, open visitation has also led to negative situations such as increase in the incidence of burnout among health professionals in the ICU (4,7). Impact may vary depending on context (physical conditions, personnel, policy).

Despite the predominant positive effects of an open visitation policy, some factors can prevent it from being implemented in most ICUs. Some of the barriers are unsuitable physical conditions within the ICUs, insufficient staff, patients' families not acting in accordance with visitation rules or having excessive expectations, patients' families' behaviors that put patient safety risk, negative attitude of health care professionals toward open visitation, and the opinion that open visitation disrupts the daily routines within the ICU and may cause infection (11,14,15). On the other hand, establishment of private rooms for patients in ICUs, legislation of specific internal regulations for families' open visiting and considering nursing as a humanitarian profession facilitate open visiting (14). Yakubu et al. (10) reported that the nurses preferred restricted visitation practices. The study conducted by Alonso-Rodríguez et al. (16) reported that although health care workers believed against an open visitation policy, they thought that open visitation would benefit patients and their families.

Türkiye is a country where open visitation is not practiced in the ICUs. Staff shortage, inappropriate structure of ICUs for open visiting, organizational policies, infection risk, attitudes of patient families towards open visiting and inadequate knowledge and practice level of families regarding intensive care are the reasons not to be applied open visiting policy in Türkiye (1). Besides it is known that the attitudes of health care professionals working in intensive care have a significant impact on the implementation and maintenance of the process.

However, a limited number of articles have been published in the field of intensive care patient visits in Türkiye. Although some of them are reviews, the studies conducted were about the expectations of patients' families who had patients in ICUs in Türkiye regarding patient visits (17,18). Patient visits are very common in Türkiye due to religious and cultural beliefs, therefore, the restricted visitation policy can also cause great difficulties among nurses and family visitors. In light of this information, it is aimed to determine the perceptions of intensive care nurses toward an open visitation policy.

Methods

Research Design

A qualitative content analysis approach was used in this study.

Sample and Setting

In this study, the participants were chosen by using the maximum diversity sampling method, which is a purposive sampling method in state hospitals, university hospitals and private hospitals.

The study group consisted of nurses who had at least one year of intensive care nursing experience and voluntarily participated in the study. Participants with different sociodemographic characteristics (such as age, gender, marital status, work duration, etc.) were included in the sample to create different situations or maximum variety. The study group consisted of nurses working in the ICUs of different types of hospitals (city hospital, training and research hospital). Not wanting to participate in the study was a criterion for exclusion, but we did not encounter such a situation.

Data Collection Tools and Data Collection

The authors had experience in collecting data, conducting and analyzing qualitative research. Data were collected using a form for descriptive characteristics and another for a semi-structured interview.

Descriptive Characteristics Form

This form collects data regarding the descriptive characteristics of the participants and includes seven questions describing age, sex, the mean work duration in the profession, the mean work duration in ICU, experience of being a patient in an ICU, having

a family member in the ICU and the ICU where the participant was working.

Semi-structured Interview Form

This consists of four open-ended questions prepared to determine the participants' perceptions on open visitation by utilizing relevant sources (1,10,14). The questions are provided below. What do you think about the effects of open visitation on patients?

• What do you think about the effects of open visitation on patients' families?

• What do you think about the effects of open visitation practice on nurses/health staff?

• What do you think about whether open visitation should be implemented or not?

Data Collection

Data were collected by the second and fourth authors (A.S. and V.D.) through semi-structured interviews. A.S. is female and her credential is PhD. V.D. is male and he is a registered nurse. A.S. is academical personal at the time of the study while V.D. is nurse. The study group consisted of 14 nurses. There was no relationship between authors and participants prior to the study commencement. The intensive care nurses were called by phone and informed about the study and that the interviews would be recorded. Appointments were made for a semi-structured interview from the nurses called by phone. On the appointment day, the purpose of the meeting, how it would be done and the audio recorded explained again. The participants' consent was then obtained. The interview was conducted in a room suitable for interviewing in the hospital, where only the researcher and the interviewer were present. Smartphones were used to record audio in the interviews.

The research questions were directed to the nurses and they were asked to answer them.

In qualitative research, when the concepts and processes obtained begin to repeat each other, sampling adequacy is confirmed (19). For this reason, data collection continued until the stage when concepts and processes that could answer the research question started to repeat. Three additional interviews confirmed saturation; no new codes emerged; these were excluded from analysis but documented in the audit trail. The interviews were terminated when the nurses had nothing more to say. Then the authors validated the transcripts with the participants. Although the interview duration with each participant varied, the average interview duration was 35 minutes.

Data Analysis

Content analysis can be used in a deductive or inductive manner depending on the purpose of the research. Inductive content analysis was used in our study. The first transcriptions of all interviews were made by the fourth researcher. In this step, the audio recordings kept during the interview were listened to, written verbatim without any changes, and summarized (20). Considering all the written content, the titles in the text were read repeatedly and the comments of the participants were received. Categories for the similar or different titles of the participants' statements were created independently by the first and third authors (E.B. and S.K.), and the resulting categories were compared. Coding was done by focusing on these categories. Then, the codes that were close to each other were reviewed again and 3 main themes were created (Table 1). Finally, the research findings, which included more specific descriptions and quotes from the participants, were written.

Statistical analysis was not used in this study.

Ethical Considerations

Approval to conduct the study was obtained from the Ethics Committee of Artvin Çoruh University (approval no: E-18457941-050.99-41529, date: 02.03.2022). In addition, each participant was informed about the purpose of the study and that the interview would be recorded with a recording program and informed consent of the participant was obtained. Informed consent was obtained and audio-recorded prior to each interview.

Reliability of the Research

In this study, triangulation technique was used to ensure reliability. The data were independently coded, analyzed, and interpreted by E.B. and S.K., the authors. E.B. and S.K. are PhDs too. The authors then compared their perspectives until they agreed on the best interpretation. This method reduced the possibility of researcher bias (21). In order to represent the data accurately and meaningfully, the themes and sub-themes were read over and over by the research team and finalized. Finally, transparency was achieved using reflexivity (22). The guidelines

Table 1. Main and sub-themes

Main themes	Sub-themes
Opportunity to feel family presence	Supporting the patients emotionally
	Supporting the patients' families' emotionally
Barriers to open visitation	Burden of unlimited visits
	Unfavorable physical structures and insufficient number of personnel
	Risk of not protecting patient safety
Facilitators of open visitation	Providing training
	The human aspect of nursing profession

for Consolidated Criteria For Reporting Qualitative Research checklist was followed.

Rigor and Trustworthiness

For the internal validity, the semi-structured interview form was created based on the literature. For external validity, the participants were informed about the research process, including the purpose of the research, its model, data collection method, and data analysis; additionally, interviews were held with the voluntary participants using a purposive sampling method to determine the events and facts as well as their varying features. For internal reliability, all the findings are presented directly in the text without adding any comment; also, the analysis of the data was carried out independently by the two researchers, and then the suitability of the themes was examined, and it was seen that they matched at a high level; and for external reliability, two experts were consulted about the raw data, coding, themes, and findings for confirmation.

Results

The mean age of the participants was 31.86±6.84 years (range, 24-45 years). Of the included participants, 78.6% (n=11) were female. The mean work duration in the profession was 11±8.80 years, and the mean work duration in ICU was 9.57±7.43 years. Moreover, 64.3% (n=9) of the participants were working in the anesthesia and reanimation ICU. None of the participants had been treated in the ICU and had a family member in the ICU.

The three main themes and eight sub-themes generated as a result of the research are provided in Table 1.

Opportunity to Feel Family Presence

This theme was divided into two sub-themes: supporting the patients emotionally and supporting the patients' families' emotionally.

Supporting the Patients Emotionally

Being away from patients' families and not being able to see them increase patients' anxiety. Given that patients and patients' families are part of a whole, the individual should be in a physiological and emotional balance. The majority of participants (n=13) stated that when patients saw their families, they relaxed, felt safe, calmed down, and were discharged from ICU faster. Participants stated that open visits would allow patients to see their families more often. In addition, the participants stated that seeing the family would be good for the psychological health of the patients.

"They feel safe, they can express their problems more easily, and it is of course better to have a family for privacy, patients are not ashamed in front of their families. Also, they can express their problems better without hesitation." [Participant (P) 2]

"Patients in intensive care usually show signs of agitation and delirium. Even after limited visits, I can see that these have diminished. Open visitation will make patients feel better psychologically." (P7)

Some participants (n=3) stated that the patient's condition and the emotional state of the patient's families could negatively affect the patients during the visit.

"If the patient family is agitated or if the patient family is more hopeless than the patient and will wear the patient down, then no visit should be made." (P6)

Supporting Patients' Families Emotionally

There are feelings of fear, anxiety and curiosity between the family waiting outside the ICU and the patient inside. In the ICU, patients' families need to see, support, and be close to their patients. The majority of participants (n=13) stated that the visits calmed the patient families, increased their confidence, and relieved their anxiety. The participants also noted that open visitation could provide rest for patient families.

"Seeing the patient and seeing where the patient is calm down the patient's family. Because they leave their patients in an enclosed place (means intensive care). That's why they don't have a clear picture of what might happen inside. When they see that their patients are being treated, cared for and in a safe environment, the patients' families obviously calm down. The unknown no longer exists." (P1)

"It is also good for the patient family as the patient sees many people and there is a constant circulation. Since the companion constantly changes, patient families can have a rest. Since they can rest, they can support their patient better." (P5)

Some participants (n=3) also stated that open visitation might negatively affect the patients' families.

"Seeing every moment of the patient whenever they want to, having opinions about what they don't know may lead to negative emotions." (P9)

Barriers to Open Visitation

Participants' views on the barriers to open visitation were divided into three sub-themes: the burden of unlimited visits, unfavorable physical structures and insufficient number of personnel, and the risk of not protecting patient safety.

Burden of Unlimited Visits

Nurses who take care of the intensive care patient face many stressors caused by the characteristics of the unit, while on the other hand, they have to deal with the problems of patients and their relatives. The majority of the participants (n=13) stated that the workload in the ICU was excessive and dealing with patients' families with open visitation may increase their workload and make them feel like they are being observed.

"We may also feel as if we are being observed by patients' families all the time." (P3)

"When patients' families pay a visit, we have to accompany them... Open visitation is a practice that will tie the hands of health workers." (P4)

"Case management will be difficult when a sudden event develops. This increases the workload of the staff." (P8)

Some participants (n=4) noted that increased workloads due to open visitation could lead to disruptions in treatment and care.

"When there is an emergency intervention, it will be difficult to manage patients' families. There will definitely be a need to relieve the anxiety experienced by patients' families and to comfort them. Then, intervention to the patient might be delayed." (P9)

Unfavorable Physical Structures and Insufficient Number of Personnel

The suitability of the physical structures of an ICU and the number of staff can determine the applicability of an open visitation policy. Most participants (n=9) stated that open visitation was not feasible due to the unfavorable physical conditions of the ICU and limited number of nurses.

"The number of patients we have to take care of is very high. We are few nurses. If larger areas, larger opportunities were created, perhaps open visitation could be implemented. I also think if patients were in larger single rooms open visitation could be introduced." (P3)

Some participants (n=3) stated that the language difference among migrants in Türkiye posed a problem in communication, which may constitute a barrier to open visitation.

"There is a language difference in our country. We are a country receiving migrants. This is a huge obstacle for the open visitation system. Let our native people come and see their patients, ask their questions during that time and I will answer them, it will take me 5 minutes. However, with someone who speaks a different language , this can take me 1 hour." (P4)

Some participants (n=3) pointed out that violence in health care was increasing and health workers were afraid. They also noted that violence could be a barrier to open visitation.

"There is a lot of violence against health workers. Now we are afraid. The physician is also scared, the nurse is also scared. This is an obstacle to open visitation." (P13)

"Some families of patients can cause unrest. Patients get even worse. Families can shout and scream. There is verbal violence, and sometimes we are even exposed to physical violence." (P11)

Most of the participants (n=11) emphasized that open visitation could be possible after proper planning of the physical conditions of the ICU, increasing the number of staff, and taking appropriate measures.

"Under current conditions of our country, if the physical conditions and the shortage of nurses are improved, maybe it can be done, but security measures should also be taken." (P10)

"...In the area, there are beds separated by curtains. We try to provide privacy with a curtain. Patients' families will not be as comfortable when there is open visitation. We won't be comfortable either. Because sometimes those curtains are not enough when treating or intervening with another patient. There should be a room for each patient and a nurse to accompany the patients' families." (P12)

Risk of Failure to Maintain Patient Safety

Patients hospitalized in ICUs are at higher risk for medical errors and patient safety. Patient safety covers practices such as correct identification of patients, ensuring safe drug administration, reducing the risks caused by falls and ensuring medical device safety. Most participants (n=8) stated that open visitation could increase infection, decrease privacy, and jeopardize patient safety by failing to accompany patient families due to insufficient staff.

"Open visitation can negatively affect patient privacy. Because the patient might be receiving care and an intervention might be carried out. When patients' families visit, they will be allowed to see every patient. It applies to isolated single rooms as well. Because the rooms are single but with glass. We can see the patient inside. It will violate privacy during care or an intervention." (P9)

"Infection is more likely to develop in an open visit. Carrying infection both from the inside out and from the outside in will be more likely." (P12)

"...Without realizing it, a patient family may unknowingly disconnect a patient's vital machine. During any IV application, their hand may touch, pull, tear some part and they may not notice it." (P13)

Facilitators of Open Visitation

The views of the participants on the applicability of open visitation were divided into two sub-themes: providing training, and the human aspect of nursing profession.

Providing Training

By education, it may be possible to create a way of thinking, concepts, beliefs, attitudes, behavior and lifestyle about health and to change in health culture. Some participants (n=6) emphasized the need to raise public awareness on open visitation procedures and provide training to both health care professionals and patients' families/community on what should be followed during open visitation.

"The negative attitude of health workers toward open visitation can be changed. For this, it is necessary to provide the necessary infrastructure and train the personnel on the subject first." (P8)

"Patients' families and health care personnel need to be informed about the issue, and trainings on the subject need to be planned." (P9)

The Human Aspect of the Nursing Profession

Nursing has not been defined as a profession that gives physical care only in any period of the history of nursing. The spiritual peace and pleasure that nurses feel in giving individual care to individuals stems from the respect for the human rights in the nature of the profession and the value of human rights. Some participants (n=6) stated that open visitation would make them feel good spiritually.

"...we would become out of robotization and we would feel better spiritually..." (P3)

"Some people come and pray. That's enough for us, really. The spiritual side is very sufficient for us. They say good things, they wish us well." (P11)

"Patients are more determined, they try much harder to get better and they are happier. Their happiness makes us happy too." (P6)

Discussion

The absence of patients' families in ICUs facilitates physiological and psychological problems in both patients and their families (5,23,24). Participants who participated in this study said that both patients and their families would be emotionally supported. According to a number of studies, nurses believe that family presence is a supportive factor for patients and their families (16,25,26). da Silva Ramos et al. (27) found in their study conducted among ICU staff that more than half of the team members thought that open visitation would accelerate patients' recovery and reduce patient anxiety.

The idea that open visitation will have positive effects on patients and their families is mentioned in the literature (16). Increased emotional support is expected for both patients and families. But there are some obstacles to implementation. They are infrastructure, personnel and security. Despite the prevalence of this idea, open visitation cannot be practiced in ICUs. In our study, participants expressed that the increased workload caused by open visitation, the unfavorable physical conditions within the ICU, the insufficient staff, and the risk of not being able to maintain patient safety hindered the implementation of an open visitation policy. Consistent with our findings, one study showed that according to the intensive care professionals, excessive expectations of families, staff shortages, and the physical structure of the ICU were among the barriers to the implementation of an open visitation policy (14). Similarly, various studies found that the physical structure of ICUs was not specifically designed to protect patient privacy and the possibility of behaviors that may pose a physical threat to the patients by their families constituted an obstacle to open visitation (27-30). Milner et al. (31) found that the frequent entry and exit of some patients' families into and out of ICUs and interruption of patient care were obstacles hindering the switch to an open visitation policy. In a different study, according to more than half of intensive care nurses, patient safety could be better ensured with an open visitation policy (15). In our study, some participants pointed out to violence in health and emphasized that health workers were afraid. They also stated that violence was an obstacle to open visit. Almost 38% of health workers are subjected to physical violence at any time period of their working lives (32). Violence against health workers is performed by most patients or visitors. While violence in health is most commonly defined in North America and the United Kingdom, recent research states that there are similar violence and characteristics in other parts of Europe, Asia, Africa and Australia (33). In a meta-analysis, Liu et al. (34) stated that 42.5% of health workers were exposed to non-physical violence by patients and visitors and 24.4% were subjected to physical violence in the last one year. Contextual differences (room type, visiting protocol, security measures, cultural expectations) determine outcomes.

In our study, the participants identified the physical structure of the ICU, shortage of personnel, increased workload, and risks to patient safety as barriers to open visitation and stated that the implementation of an open visitation policy could be made easier by organizing training programs and improving infrastructure. They also stated that the human aspect of nursing was a facilitating factor in open visitation. A study, whose findings were similar to ours, found that the organization of the physical structure of ICUs to provide private spaces for patients and the presence of consultant health personnel to provide information regarding the patient to the family were factors that facilitated an open visitation policy (14). Zupanets et al. (35) found that an open visitation policy could be implemented by training both health personnel and families.

Implications for Nursing and Health Policy

This study focused on the perceptions of intensive care nurses. But, patients and their relatives are the other important parts of this process. So, to apply open visiting policy, new studies to investigate patients' and patients' families' thoughts should be conducted. Also, by making arrangements in ICUs, this policy can be integrated in ICU visiting process in Türkiye.

Study Limitations

In our study, most of the nurses working in the ICU consisted of young nurses. This is the first limitation of our study. Because age may be an important factor for this study. On the other hand, studies on the open visitation policy in Türkiye have been quantitative in nature. In our study, a complex issue that was not recognized or defined in Türkiye was discussed. Another limitation of our study was that this study was conducted after coronavirus disease 2019 pandemic. So, it is not known that if the nurses' attitudes towards open visiting have changed. The strengths of our study include its qualitative design and information regarding the perceptions of intensive care nurses regarding the open visitation policy.

Conclusion

Our study showed that intensive care nurses generally viewed the open visitation policy positively, but its applicability remained limited without ensuring physical infrastructure, staffing, security and training requirements. To apply open visitation policy, there are some recommendations:

- Single patient rooms should be created in ICUs.
- Patient families should be trained on open visits.
- More nurses should be assigned to inform patient families.

Ethics

Ethics Committee Approval: Approval to conduct the study was obtained from the Ethics Committee of Artvin Çoruh University (approval no: E-18457941-050.99-41529, date: 02.03.2022).

Informed Consent: The participants' consent was then obtained.

Footnotes

Authorship Contributions

Design: E.B., A.S., S.K., V.D., Data Collection or Processing: E.B., A.S., S.K., Analysis or Interpretation: S.K., Literature Search: E.B., A.S., S.K., V.D., Writing: E.B., A.S., S.K., V.D.

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Original Article

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Arterial Stiffness and Mean Arterial Pressure (MAP) and Their Relationship with Renin and Aldosterone Levels in Primary Hyperparathyroidism

Primer Hiperparatiroidizmde Arteriyel Sertlik ve Ortalama Arteriyel Basınç (MAP) ile Renin ve Aldosteron Düzeyleri Arasındaki İlişki

Hatice Gizem BERBER[1], Işılay KALAN SARI[2], Ayça İNCİ[3]

[1]University of Health Sciences Türkiye, Antalya Training and Research Hospital, Department of Internal Medicine, Antalya, Türkiye
[2]University of Health Sciences Türkiye, Antalya Training and Research Hospital, Department of Endocrinology and Metabolic Disorders, Antalya, Türkiye
[3]University of Health Sciences Türkiye, Antalya Training and Research Hospital, Department of Nephrology, Antalya, Türkiye

ABSTRACT

Objective: Primary hyperparathyroidism (PHPT) is associated with cardiovascular mortality and hypertension. Arterial stiffness is a predictor of cardiovascular events. The aim of this study is to investigate arterial stiffness, and daytime and nighttime mean arterial pressures in patients with PHPT using 24-hour ambulatory blood pressure monitoring (ABPM) and to reveal their relationship with renin, aldosterone, and other biochemical parameters.

Methods: Thirty-five patients with PHPT and 32 healthy control subjects participated. All study participants were fitted with an ABPM device for 24 hours. Renin and aldosterone levels were measured and other necessary biochemical tests were performed. Ambulatory pulse wave velocity (PWV) and augmentation index (AIX) were used to evaluate arterial stiffness.

Results: Mean renin levels were statistically higher in patients than in controls ($p<0.05$). Daytime mean arterial pressure and nighttime mean arterial pressure were higher in the patients than in the control group ($p<0.05$). PWV and AIX of the two groups were statistically similar ($p>0.05$). Daytime and nighttime mean arterial pressures were positively correlated with 25-hydroxy vitamin D level, but not with calcium, parathyroid hormone or

ÖZ

Amaç: Primer hiperparatiroidizm (PHPT), kardiyovasküler mortalite ve hipertansiyon ile ilişkilidir. Arteriyel sertlik, kardiyovasküler olayların bir öngörücüsüdür. Bu çalışmanın amacı, PHPT'li hastalarda 24 saatlik ambulatuvar kan basıncı izlemi (ABPM) yöntemi kullanarak, arteriyel sertliği ve gündüz ve gece ortalama arteriyel basınçlarını araştırmak ve bunların renin, aldosteron ve diğer biyokimyasal parametrelerle ilişkisini ortaya koymaktır.

Yöntemler: Çalışmaya PHPT'li 35 hasta ve 32 sağlıklı kontrol katıldı. Tüm çalışma katılımcılarına 24 saatlik ABPM cihazı takıldı. Renin ve aldosteron seviyeleri ölçüldü ve diğer gerekli biyokimyasal testler yapıldı. Arteriyel sertliği değerlendirmek için nabız dalga hızı (PWV) ve augmentasyon indeksi (AIX) kullanıldı.

Bulgular: Hastaların ortalama renin seviyeleri kontrol grubuna göre anlamlı olarak daha yüksekti ($p<0,05$). Hastaların gündüz ve gece ortalama arteriyel basınçları kontrol grubundan anlamlı olarak daha yüksekti ($p<0,05$). İki grubun PWV ve AIX sonuçları arasında istatistiksel olarak bir fark saptanmadı ($p>0,05$). Gündüz ve gece ortalama arter basınçları 25-hidroksi D vitamini seviyesiyle pozitif korelasyon gösterdi, ancak kalsiyum, paratiroid hormonu veya

Address for Correspondence: Asst. Prof. Işılay Kalan Sarı, University of Health Sciences Türkiye, Antalya Training and Research Hospital, Department of Endocrinology and Metabolic Disorders, Antalya, Türkiye
E-mail: isilaykalan@gmail.com
ORCID IDs of the authors: ORCID IDs of the authors: H.G.B.: 0000-0002-5358-1414, I.K.S.: 0000-0002-0391-7848, A.İ.: 0000-0002-7894-8913

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ABSTRACT

renin, aldosterone levels. Five patients were newly diagnosed with hypertension based on ABPM.

Conclusion: Our study shows that arterial stiffness is not elevated in PHPT patients at low cardiovascular risk, as shown by ABPM. PHPT is associated with increased mean arterial pressure and increased renin levels. ABPM may detect hypertension early in PHPT. The finding of a positive correlation of 25-hydroxy vitamin D level with mean arterial pressure in PHPT needs to be supported by further studies.

Keywords: Primary hyperparathyroidism, arterial stiffness, pulse wave velocity (PWV), augmentation index (AIX), renin, aldosterone, mean arterial pressure (MAP)

ÖZ

renin, aldosteron seviyeleriyle anlamlı korelasyon göstermedi. Beş hastaya ABPM'ye göre yeni hipertansiyon tanısı konuldu.

Sonuç: Çalışmamız, düşük kardiyovasküler riske sahip olan PHPT hastalarında ABPM ile saptanan arteriyel sertliğin yüksek olmadığını göstermektedir. PHPT, artmış ortalama arter basıncı ve artmış renin seviyeleri ile ilişkilidir. ABPM, PHPT'de hipertansiyonu erken tespit edebilir. PHPT'de 25-hidroksi D vitamini seviyesi ile ortalama arter basıncı arasındaki pozitif korelasyonun daha fazla çalışma ile desteklenmesi gerekmektedir.

Anahtar Kelimeler: Primer hiperparatiroidizm, arteriyel sertlik, nabız dalga hızı (PWV), augmentasyon indeksi (AIX), renin, aldosteron, ortalama arter basıncı (MAP)

Introduction

Primary hyperparathyroidism (PHPT) is associated with hypertension (HT) and cardiovascular disease (1). There are several studies investigating the effects of parathyroid hormone (PTH) on vascular function, such as vascular reactivity, endothelial cell and vascular smooth muscle cell function, and large vessel compliance (1-4). Arterial stiffness (AS) is a marker of increased cardiovascular disease risk, including myocardial infarction, heart failure, all-cause mortality, stroke and kidney disease (5,6). It is known that pulse wave velocity (PWV) can be used to assess AS, and augmentation index (AIX) is an indicator of AS that can be influenced by hemodynamics and ventricular ejection (7). Twenty-four-hour ambulatory blood pressure monitoring (ABPM) is a non-invasive method to detect arterial changes associated with cardiovascular risk (8). With the advancement of technology, ABPM can be used to perform pulse wave analysis in addition to blood pressure measurement (9). Vascular parameters such as PWV and AIX can be measured in this way (9). Another parameter that can be measured with ABPM is ambulatory pulse pressure, which is known to be associated with AS and cardiovascular outcomes (10). Although AS is measured by different methods in studies, it was found to be elevated in PHPT, even in mild cases (1-4,11). Factors such as diabetes, hyperlipidemia, age, gender, smoking, and HT are known to influence AS (1,12-16). Most studies in the literature have included hypertensive patients with PHPT (17). The aim of this study is to investigate AS and mean arterial pressure (MAP) in patients with PHPT who are at low cardiovascular risk (patients without diabetes, HT, hyperlipidemia and smoking history) using 24-hour ABPM and to reveal their relationship with the levels of renin, aldosterone, calcium (Ca), PTH, phosphorus (P) and 25-hydroxyvitamin D (25OHD).

Methods

This study was conducted by the Department of Endocrinology and Metabolic Diseases and Internal Medicine of the University of Health Sciences Türkiye, Antalya Training and Research Hospital between December 2020 and March 2022. The study was approved by the Ethics Committee of University of Health Sciences Türkiye, Antalya Training and Research Hospital (date: 26/11/2020, number: 18/11) and written informed consent was obtained from all patients. The report followed the Declaration of Helsinki. The study was conducted on newly diagnosed PHPT patients aged 18-75 years and a control group consisting of healthy volunteers. Patients with secondary hyperparathyroidism, diabetes, HT, hyperlipidemia, morbid obesity, coronary heart disease, cerebrovascular disease, primary hyperaldosteronism, congestive heart failure, liver disease, kidney disease or diseases that cause secondary HT (hypothyroidism, hyperthyroidism, congenital adrenal hyperplasia, pheochromocytoma), patients with a history of thyroid or parathyroid surgery, patients who smoke, patients with a 24-hour urinary Ca of less than 100 mg/day and patients taking medications (antihypertensives, diuretics, oral Ca preparations, lithium, etc.) that affect the renin-angiotensin-aldosterone system (RAAS) or Ca and PTH levels were excluded from the study. Thirty-five newly diagnosed PHPT patients and 32 healthy controls who did not smoke, had no medical conditions and were not taking any medications participated in the study, and data from a total of 67 subjects were analysed. The subjects' weight and height were measured, and after a 5-minute rest, blood pressure was measured manually twice. No HT was detected during the manual measurements (blood pressure ≤140/90).

Laboratory Analysis

Blood samples from the entire study group were collected after at least 8 hours of fasting. From the blood samples collected, PTH, Ca, P, magnesium, blood urea nitrogen, creatinine, 25OHD, albumin, total protein, thyroid stimulating hormone (TSH), fasting blood glucose (FBG), total cholesterol, LDL cholesterol, HDL cholesterol, and triglyceride (TG) levels were measured in the laboratory of our hospital. In addition, venous blood samples were simultaneously taken from the patients to determine renin and aldosterone levels. These venous blood samples were centrifuged at 3500 rpm for 10 minutes, and the serums were separated and stored in 1.5-mL lidded Eppendorf tubes at -80 °C for later analysis. The separated serums of all subjects were thawed at room temperature on the study day to determine renin and aldosterone levels. To exclude familial

hypocalciuric hypercalcemia in the patients, 24-hour urinary Ca levels were examined. Renin levels in human serum (LDN immunoassay and services, Nordhorn, Germany) were analyzed with commercial ELISA kits (intraassay coefficient of variation <5%, interassay coefficient of variation <7%, detection range: 0.8-128 pg/mL, sensitivity: 0.8 pg/mL). Aldosterone levels in human serum (DiaMetra, Spello, Italy) were analyzed using commercial ELISA kits (intraassay <10%, interassay <10%, detection range: 86-1520 pg/mL, sensitivity: 80 pg/mL.

Analysis of 24-hour Ambulatory BP Monitoring

All participants in the study were fitted with an ABPM device for 24 hours in the nephrology clinic. All measurements were performed with the Mobil-O-Graph 24-h PWA monitor (I.E.M. Industrielle Entwicklung Medizintechnik und Vertriebsgesellschaft mbH, Stolberg, Germany). This device can be used to perform pulse wave analysis as well as central aortic and brachial BP measurements. A cuff size was chosen that was suitable for the arm of all patients. The device was programmed to measure BP every 30 minutes during the day and once per hour at night during sleep. The following patient values were recorded with ambulatory monitoring: Daytime systolic BP (SBP) and diastolic BP (DBP), and MAP; nighttime SBP, DBP, and MAP, brachial artery PWV, pulse pressure and AIX. PWV and AIX were used to assess AS. Ambulatory HT was identified as 24-hour mean BP ≥130/80 mmHg (18).

Statistical Analysis

Categorical variables were given with frequency (n) and percentage (%). The relationship between categorical variables was examined with the Pearson chi-square test and the Fisher's exact test. The assumption of normal distribution was checked with the Shapiro-Wilk test. Normally distributed continuous variables were presented as mean ± standard deviation and non-distributed ones as median (interquartile range: 25th-75th percentile). The Mann-Whitney U test and the Independent t-test were used to compare continuous variables according to study groups. The Spearman correlation test was performed to determine the relationship between laboratory parameters and ambulatory results of the patients. Data were analyzed with the IBM SPSS 23.0 package program (IBM Corp Armonk, NY). P-values less than 0.05 were considered statistically significant.

Results

The general characteristics and laboratory parameters of the patient and control groups are shown in Table 1. The mean age of the patient group was higher than that of the control group. The FBG (p=0.002), TG (p=0.001) and TSH (p=0.012) levels

Table 1. General characteristics and laboratory parameters of the control and patient groups

Variables	Control (n=32)	Patient (n=35)	p
Age (years)	47.31±11.13	55.91±15.57	**0.012**
Gender			
Female	20 (62.5)	27 (77.1)	0.191
Male	12 (37.5)	8 (22.9)	
BMI (kg/m^2)	27.39±3.42	28.86±5.51	0.192
FBG (mg/dL)	88 (83.5-90)	91 (87-95)	**0.002**
Total-C (mg/dL)	205.44±36.74	211.97±43.35	0.510
LDL-C (mg/dL)	128.16±30.72	121.75±33.13	0.416
TG (mg/dL)	101.5 (78.5-136.5)	152 (113-210)	**0.001**
HDL-C (mg/dL)	54.06±11.93	60.06±14.65	0.072
Creatinine (mg/dL)	0.89±0.11	0.88±0.16	0.726
GFR (mL/min./1.73 m^2)	86.25±12.99	80.14±21.54	0.161
Ca (mg/dL)	9.67±0.41	11.27±1.92	**<0.001**
P (mg/dL)	3.4±0.49	2.6±0.51	**<0.001**
25OHD (ug/L)	16.89 (9.43-26.5)	18.32 (14.47-26.27)	0.429
Magnesium (mg/dL)	2.1 (2-2.2)	2.1 (2-2.3)	0.390
PTH (ng/L)	43 (34-54)	136 (84-181)	**<0.001**
TSH (uIU/mL)	1.92±0.59	2.43±0.99	**0.012**
Renin (pg/mL)	5.51 (3.98-14.91)	14.24 (5.7-30.37)	**0.023**
Aldosterone (pg/mL)	81.34 (42.23-176.86)	51.49 (30.9-120.12)	0.082
Urine Ca (mg/day)	-	252 (150-380)	

Results are given as mean ± standard deviation, median (interquartile range), or n (%). Mann-Whitney U test, Independent t-test, Pearson chi-square test, Fisher's exact test. BMI: Body mass index, FBG: Fasting blood glucose, Total-C: Total-cholesterol, LDL-C: Low-density lipoprotein- cholesterol, TG: Triglyceride, HDL-C: High-density lipoprotein-cholesterol, Cholesterol, GFR: Glomerular filtration rate, 25OHD: 25-hydroxyvitamin D, TSH: Thyroid stimulating hormone, Ca: Calcium, P: Phosphorus, PTH: Parathyroid hormone

of the patients were higher than those of the control group. The median renin level of PHPT patients was statistically higher than that of the control group (p=0.023). After adjustment for age, the significance of the parameters TSH (p=0.060), renin (p=0.263) and P (p=0.477) levels disappeared. The results of the participants' ABPM are shown in Table 2. It was found that the daytime MAP, nighttime MAP and nighttime SBP of the patients were significantly higher than those of the control subjects (p=0.012, p=0.003 and p=0.025, respectively). Pulse pressure was increased in PHPT compared to controls (p=0.033). The PWV and AIX of the two groups were not statistically different. After adjusting for age, daytime MAP (p=0.026) and nighttime MAP (p=0.010) were still significantly different between the groups. However nighttime SBP (p=0.064) and pulse pressure (p=0.128) did not differ significantly between groups. There was a positive correlation between nighttime MAP and daytime MAP with 25OHD levels (r=0.410; p=0.014 and r=0.392; p=0.020, respectively). There was no correlation between MAP and Ca, P or PTH levels. The results of the correlation analysis are shown in Table 3. Patients diagnosed with HT were not included in our study. Manual BP measurements were performed twice before ABPM, and patients were confirmed as normotensive with blood pressure measurements and then included in the study. However, in our study, 5 patients were diagnosed with HT using the 24-hour ABPM method (18). In the analysis performed by removing these 5 patients; the age (p=0.051), gender (p=0.189) and BMI (p=0.239) were similar between the groups. Renin levels were higher in patients than controls (p=0.019) (Table 4).

Table 2. Ambulatory results of the control and patient groups

Variables	Control (n=32)	Patient (n=35)	p
Daytime SBP (mmHg)	118.5 (113-128.5)	120 (114-125)	0.451
Daytime DBP (mmHg)	77.5 (70-82)	74 (70-82)	0.985
Daytime MAP (mmHg)	91.5 (83.8-96.1)	97 (90-103)	**0.012**
Nighttime SBP (mmHg)	110.5 (102.5-116)	115 (112-121)	**0.025**
Nighttime DBP (mmHg)	66.5 (62-76)	71 (64-78)	0.336
Nighttime MAP (mmHg)	85 (77.83-90)	92 (86-96)	**0.003**
Pulse pressure (mmHg)	41 (34.5-46)	46 (39-52)	**0.033**
PWV (m/s)	6.5 (5.7-7.05)	6.2 (4.8-7.6)	0.459
AIX (%)	24.13±10.48	25.51±6.22	0.519

Results are given as mean ± standard deviation or median (interquartile range). Mann-Whitney U test, Independent t-test. SBP: Systolic blood pressure, DBP: Diastolic blood pressure, MAP: Mean arterial pressure, PWV: Pulse wave velocity, AIX: Augmentation index

Table 3. Correlation between laboratory findings and the results of ambulatory blood pressure monitoring in the patient group (n=35)

Variables		Daytime SBP (mmHg)	Daytime DBP (mmHg)	Daytime MAP (mmHg)	Nighttime SBP (mmHg)	Nighttime DBP (mmHg)	Nighttime MAP (mmHg)	Pulse pressure (mmHg)	PWV (m/s)	AIX (%)
FBG (mg/dL)	r	0.087	0.065	0.102	0.202	0.156	0.201	-0.099	-0.003	0.183
	p	0.617	0.713	0.559	0.244	0.372	0.247	0.570	0.988	0.293
TG (mg/dL)	r	-0.118	0.129	0.008	-0.213	-0.028	-0.138	-0.169	-0.289	-0.102
	p	0.499	0.461	0.962	0.219	0.872	0.429	0.333	0.092	0.559
Ca (mg/dL)	r	-0.171	-0.029	-0.107	-0.162	-0.150	-0.176	-0.133	-0.238	-0.324
	p	0.326	0.869	0.541	0.352	0.389	0.312	0.448	0.169	0.057
P (mg/dL)	r	-0.010	-0.052	-0.015	-0.047	0.045	0.021	-0.045	0.068	0.199
	p	0.955	0.765	0.934	0.791	0.797	0.907	0.797	0.696	0.252
25OHD (ug/L)	r	0.400	0.282	0.392	0.365	0.384	0.410	0.152	0.550	0.367
	p	**0.017**	0.100	**0.020**	**0.031**	**0.023**	**0.014**	0.384	**0.001**	**0.030**
PTH (ng/L)	r	-0.156	-0.056	-0.173	-0.224	-0.183	-0.162	-0.104	-0.293	-0.524
	p	0.371	0.748	0.320	0.196	0.293	0.353	0.551	0.087	**0.001**
Renin (pg/mL)	r	-0.219	-0.234	-0.256	-0.336	-0.221	-0.293	-0.330	-0.323	-0.378
	p	0.207	0.177	0.138	0.049	0.203	0.088	0.053	0.059	**0.025**

Spearman correlation test. FBG: Fasting blood glucose, Total-C: Total-cholesterol, LDL-C: Low-density lipoprotein- cholesterol, TG: Triglyceride, HDL-C: High-density lipoprotein-cholesterol, GFR: Glomerular filtration rate, 25OHD: 25-hydroxyvitamin D, TSH: Thyroid stimulating hormone, Ca: Calcium, P: Parathyroid hormone,, PTH: Parathormone, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, MAP: Mean arterial pressure, PWV: Pulse wave velocity, AIX: Augmentation index

In ambulatory measurement results; there were no significant differences in PWV, AIX and pulse pressure and daytime MAP (p=0.033) and nighttime MAP (p=0.017) were higher in the patients compared to control group (Table 5).

Discussion

Patients with PHPT have an increased risk of death due to cardiovascular disease (19,20). AS reflects ageing of the cardiovascular system and loss of elastic properties of the arterial wall (21). AS has an independent predictive value for cardiovascular disease morbidity and mortality (21). Studies in the general population show an association between PTH and AS (22,23). A meta-analysis shows elevated AS even with mild PHPT and a significant reduction in AS after parathyroidectomy (21). Ambulatory PWV and AIX are simple and non-invasive measures of AS. Of the methods used to measure AS, they are closely related to cardiovascular structural changes such as atherosclerosis and mortality (24). A study by Schillaci et al. (2) found that PWV was higher in patients with PHPT than in

Table 4. Laboratory findings of control and patient groups after excluding hypertensive patients

Variables	Control (n=32)	Patients (n=30)	p
Age (years)	47.31±11.13	51.85±12.17	0.051
Gender			
Female	20 (62.5)	23 (76.6)	0.189
Male	12 (37.5)	7 (23.3)	
BMI (kg/m²)	27.39±3.42	27.46±4.25	0.239
FBG (mg/dL)	88 (83.5-90)	91 (85.25-95.00)	**0.015**
Total-C (mg/dL)	205.44±36.74	212.37±48.25	0.544
LDL-C (mg/dL)	128.16±30.72	121.52±35.80	0.459
TG (mg/dL)	101.5 (78.5-136.5)	164.0 (106.3-207.5)	**0.003**
HDL-C (mg/dL)	54.06±11.93	60.70±15.58	0.076
Creatinine (mg/dL)	0.89±0.11	0.88±0.15	0.567
GFR (mL/min./1.73 m²)	86.25±12.99	85.20±21.02	0.820
Ca (mg/dL)	9.67±0.41	11.10±2.23	**0.001**
P (mg/dL)	3.4±0.49	2.60±0.49	**<0.001**
25OHD (ug/L)	16.89 (09.28-26.84)	19.17 (12.09-25.16)	0.508
Magnesium (mg/dL)	2.1 (2-2.2)	2.1 (2.0-2.40)	0.091
PTH (ng/L)	43 (34-54)	141.5 (103.2-179.25)	**<0.001**
TSH (uIU/mL)	1.92±0.59	2.20±0.93	0.170
Renin (pg/mL)	5.51 (3.98-14.91)	14.94 (5.85-42.70)	**0.019**
Aldosterone (pg/mL)	81.34 (42.23-176.86)	66.63 (37.72-136.65)	0.325
Urine Ca (mg/day)	-	268 (154.0-394.25)	

Results are given as mean ± standard deviation, median (interquartile range), or n (%). Mann-Whitney U test, Independent t-test. FBG: Fasting blood glucose, Total-C: Total cholesterol, LDL-C: Low-density lipoprotein- cholesterol, TG: Triglyceride, HDL-C: High-density lipoprotein-cholesterol, GFR: Glomerular filtration rate, 25OHD: 25-hydroxyvitamin D, TSH: Thyroid stimulating hormone, Ca: Calcium, P: Phosphorus, PTH: Parathyroid hormone, BMI: Body mass index

Table 5. Comparison of ambulatory results of the control and patient groups after excluding hypertensive patients

Variables	Control (n=32)	Patient (n=30)	p
Daytime SBP (mmHg)	118.5 (113-128.5)	119 (112-125)	0.868
Daytime DBP (mmHg)	77.5 (70-82)	74 (70-82)	0.987
Daytime MAP (mmHg)	91.5 (83.8-96.15)	97 (90-102.5)	**0.033**
Nighttime SKB (mmHg)	110.5 (102.5-116)	115 (109-120)	0.100
Nighttime DKB (mmHg)	66.5 (62-76)	71 (63.25-75.75)	0.595
Nighttime MAP (mmHg)	85 (77.83-90)	92 (86-94.75)	**0.017**
Pulse pressure (mmHg)	41 (34.5-46)	42 (38-47.5)	0.344
PWV (m/s)	6.5 (5.7-7.05)	6.1 (4.65-7.40)	0.182
AIX (%)	24.13±10.48	24.91±6.17	0.746

Results are given as mean ± standard deviation (SD) or median (interquartile range). Independent t-test (AIX), Mann-Whitney U test. Results are given as mean ± SD or median (interquartile range). Mann-Whitney U test, Independent t-test. SBP: Systolic blood pressure, DBP: Diastolic blood pressure, MAP: Mean arterial pressure, PWV: Pulse wave velocity, AIX: Augmentation index

control subjects with similar sex, age and blood pressure values. In their study of 28 hypertensive and 16 normotensive patients with PHPT, Rosa et al. (3) also showed higher PWV and AS, especially in hypertensive patients. In this study, no correlation was found between PWV and Ca or PTH levels. A study by Wetzel et al. (4) showed that there was a direct interaction between PTH levels and PWV. The study by Rubin et al. (17) found a strong correlation between serum PTH levels and AIX, but no correlation between serum Ca levels and AIX. The methods used to measure PWV and AIX were different in the studies, and these studies did not exclude diabetics, smokers or hypertensive patients. In our study, PWV and AIX were statistically similar between the patient and control groups. We can argue that in patients at low risk of cardiovascular disease, AS is not increased in PHPT and that Ca and PTH levels are not independently associated with AS.

Another finding was that patients' blood pressure could be normal when measured manually, but could be high when measured using ABPM. With ABPM, HT could be diagnosed early in these patients. The prevalence of HT is higher in PHPT patients (25), and the study by Letizia et al. (26) showed that almost half of patients with PHPT had HT. There are several mechanisms such as hypercalcemia, high PTH, renal damage, activation of the sympathetic nervous system and RAAS that are responsible for HT in PHPT (5,27,28). Letizia et al. (26) showed a correlation between serum Ca level and mean 24-hour DBP and daytime DBP. A study conducted on 3002 patients over a follow-up period of 9 years showed that higher PTH levels were associated with an increased risk of HT (27). Another study showed that intracellular Ca plays an important role in smooth muscle cell contraction in the pathogenesis of essential HT. In this study, hypertensive patients with PHPT were found to have higher intracellular Ca levels compared with normotensive patients with PHPT and the control group (25). Our ABPM results in PHPT patients without concomitant HT showed that MAP was elevated in PHPT. However, we found no significant difference in systolic and diastolic pressure values between patients and the control group. Since no correlation between MAP and Ca, PTH or renin levels was found in our study, it could not be concluded that the increased MAP in PHPT was related to these parameters. However, the intracellular Ca level, which was not measured in our study, could be related to increased blood pressure, in contrast to the serum Ca levels described in the literature (25).

The study's first analysis revealed a significant difference in pulse pressure between the two groups. Pulse pressure is a sign of deteriorating cardiovascular health and naturally increases with age due to arteriosclerosis (29). However, this analysis shows that the patient group is older than the control group, and the significance of this parameter disappeared in the age-adjusted analysis. Excluding hypertensive patients, the second analysis showed no difference between the groups in pulse pressure results. However, in this analysis, the difference between the two groups in age also disappeared. It is therefore hypothesized that increasing age or the presence of HT are the main factors influencing pulse pressure in PHPT, rather than the disease itself.

A positive correlation was found between 25OHD level and MAP in PHPT. Contemporary studies have generally shown that vitamin D deficiency is associated with HT (30,31). Studies have shown that vitamin D deficiency in PHPT leads to increased Ca and PTH levels (32,33). A study on PHPT conducted in our country also showed that vitamin D deficiency was a risk factor for the development of HT in PHPT (34). Long-term exposure to vitamin D deficiency in PHPT may be associated with an increased risk of HT. However, it appears that there are insufficient studies investigating the risk of HT in PHPT with low vitamin D levels. In our study, the early diagnosis and the small number of patients might be the reasons for this result. However, the limited number of studies on this topic in the literature make it difficult to discuss this finding. Unlike in the general population, new studies are needed to reveal the association between 25OHD levels and HT in PHPT patients.

In our study, we found increased FBG and TG levels in PHPT patients compared to the control group, and this result may confirm the literature. In the study by Luboshitzky et al. (35), the incidence of metabolic syndrome and insulin resistance was significantly higher in patients with severe PHPT than in patients with mild PHPT and the control group. Procopio et al. (36) performed an oral glucose tolerance test in 105 PHPT patients and showed that the prevalence of impaired glucose tolerance and diabetes was higher in the PHPT group than in the healthy control group. Diabetics and patients with morbid obesity were not included in the study, so we cannot comment on the prevalence of these conditions, but we found no significant difference in BMI between patients and controls.

Some studies have shown that the renin-aldosterone system plays a role in the development of HT in PHPT. In particular, these studies indicate that renin and aldosterone levels tend to be high in hypertensive PHPT patients (37,38). Brinton et al. (37) showed that plasma renin activity was elevated in 4 of 7 patients with PHPT and HT, whereas plasma renin activity was normal in PHPT patients with normal blood pressure. Gennari et al. (38) studied 34 patients with PHPT. Ten of these 34 patients were hypertensive. Plasma renin and aldosterone levels were found to be higher in hypertensive patients with PHPT than in normotensive patients with PHPT. Our results showed that patients with PHPT had higher renin levels than healthy controls, regardless of HT. However, in our study, no significant difference was found between the patient and control groups in terms of aldosterone levels. This could be due to the fact that aldosterone is also controlled by mechanisms other than renin.

Study Limitations

The most important limitation is the small number of patients. In addition, AS was studied using a non-invasive method such as 24-hour ABPM, and no additional methods were used, which is another limitation.

Conclusion

Consequently, in our study, we found that MAP increased in PHPT regardless of HT and age. There was no correlation between MAP with Ca, PTH or renin levels. The finding of a positive correlation of 25OHD level with MAP in PHPT needs to be supported by further studies. PWV, pulse pressure and AIX, which are cardiovascular risk markers, were not elevated in PHPT patients with low cardiovascular risk. New studies with a larger number of patients are needed to substantiate these findings.

Information: This thesis study was presented as an oral presentation at the 44th Endocrinology and Metabolic Diseases Congress (İstanbul, Türkiye).

Ethics

Ethics Committee Approval: The study was approved by the Ethics Committee of University of Health Sciences Türkiye, Antalya Training and Research Hospital (date: 26/11/2020, number: 18/11).

Informed Consent: Written informed consent was obtained from all patients.

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Footnotes

Authorship Contributions

Surgical and Medical Practices: H.G.B., I.K.S., A.İ., Concept: I.K.S., Design: I.K.S., A.İ., Data Collection or Processing: H.G.B., Analysis or Interpretation: I.K.S., A.İ., Literature Search: H.G.B., I.K.S., Writing: H.G.B., I.K.S., A.İ.

Conflict of Interest: No conflict of interest was declared by the authors.

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Original Article

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The Effect of Vaginal Cuff Closure Technique on Postoperative Vaginal Length and Sexual Function: A Prospective Randomized Study

Vajinal Kaf Kapatma Tekniğinin Postoperatif Vajinal Uzunluk ve Cinsel İşlev Üzerine Etkisi: Prospektif Randomize Bir Çalışma

Merve Ecem ALBAYRAK, Mehmet Ata TOPÇUOĞLU

Bolu Abant İzzet Baysal University Training and Research Hospital, Department of Obstetrics and Gynecology, Bolu, Türkiye

ABSTRACT

Objective: After laparoscopic hysterectomy, vaginal cuff closure may lead to shortening of vaginal length and negatively affect sexual function. This prospective randomized study aimed to compare the effects of different vaginal cuff closure techniques on postoperative vaginal length (primary outcome) and female sexual function (secondary outcome).

Methods: This study included 63 patients who underwent total laparoscopic hysterectomy at the Department of Obstetrics and Gynecology, Bolu Abant İzzet Baysal University Training and Research Hospital. Patients were randomized into two groups according to vaginal cuff closure technique: laparoscopic suturing (n=32) and vaginal suturing (n=31). Vaginal length was measured preoperatively and at the 3rd postoperative month using a graduated metal ruler (Hegar bougie with scale) from the hymenal ring to the vaginal vault apex, with the patient in the lithotomy position and without anesthesia. Sexual function was evaluated at the same time points using the Arizona Sexual Experience Scale (ASEX).

Results: The mean reduction in vaginal length was 0.67±0.22 cm in the laparoscopic suturing group and 0.92±0.30 cm in the vaginal suturing group, with a statistically significant difference favoring laparoscopic suturing. The mean change in ASEX scores between preoperative and postoperative assessments was 1.38±1.5 in the laparoscopic group and 1.1±1.1 in the vaginal suturing group, with

ÖZ

Amaç: Laparoskopik histerektomi sonrası vajinal kaf kapatma işlemi vajinal uzunlukta kısalmaya yol açabilir ve cinsel işlevi olumsuz etkileyebilir. Bu prospektif randomize çalışmada, farklı vajinal kaf kapatma tekniklerinin postoperatif vajinal uzunluk (primer sonlanım) ve kadın cinsel işlevi (sekonder sonlanım) üzerindeki etkilerinin karşılaştırılması amaçlandı.

Yöntemler: Bu çalışmaya Bolu Abant İzzet Baysal Üniversitesi Eğitim ve Araştırma Hastanesi Kadın Hastalıkları ve Doğum Kliniği'nde total laparoskopik histerektomi uygulanan 63 hasta dahil edildi. Hastalar vajinal kaf kapatma tekniğine göre laparoskopik sütürasyon (n=32) ve vajinal sütürasyon (n=31) gruplarına randomize edildi. Vajinal uzunluk ölçümü, preoperatif dönemde ve postoperatif 3.ayda, dereceli metal cetvel (skalalı Hegar buji) kullanılarak, himenal halkadan vajinal kaf apeksine kadar, litotomi pozisyonunda ve anestezi uygulanmadan yapıldı. Aynı zaman noktalarında cinsel işlev Arizona Cinsel Yaşantılar Ölçeği (ACYÖ) ile değerlendirildi.

Bulgular: Laparoskopik sütürasyon grubunda ortalama vajinal uzunluk kısalması 0,67±0,22 cm, vajinal sütürasyon grubunda ise 0,92±0,30 cm olarak saptandı ve gruplar arasında istatistiksel olarak anlamlı fark bulundu. Preoperatif ve postoperatif ACYÖ skor farkı laparoskopik grupta 1,38±1,5, vajinal sütürasyon grubunda 1,1±1,1 olup gruplar arasında anlamlı fark saptanmadı. Vajinal uzunluk ve

Address for Correspondence: Merve Ecem Albayrak MD, Bolu Abant İzzet Baysal University Training and Research Hospital, Department of Obstetrics and Gynecology, Bolu, Türkiye
E-mail: mecem_albayrak@yahoo.com.tr
ORCID IDs of the authors: M.E.A.: 0009-0006-3332-8530, M.A.T.: 0000-0002-8929-6973

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ABSTRACT

no statistically significant difference between groups. No significant correlation was found between changes in vaginal length or ASEX scores and demographic variables.

Conclusion: Laparoscopic vaginal cuff suturing results in less postoperative vaginal shortening compared with vaginal suturing. However, vaginal cuff closure technique does not have a significant effect on postoperative sexual function. Further prospective studies with larger sample sizes are warranted.

Keywords: Laparoscopic hysterectomy, vaginal cuff, vaginal length, sexual function, suturing

ÖZ

ACYÖ skor değişimleri ile demografik değişkenler arasında anlamlı korelasyon bulunmadı.

Sonuç: Laparoskopik vajinal kaf sütürasyonu, vajinal sütürasyona kıyasla daha az postoperatif vajinal kısalmaya neden olmaktadır. Bununla birlikte, vajinal kaf kapatma tekniğinin postoperatif cinsel işlev üzerine anlamlı bir etkisi bulunmamaktadır. Daha geniş örneklemli ileri çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Laparoskopik histerektomi, vajinal kaf, vajinal uzunluk, cinsel işlev, sütürasyon

Introduction

Hysterectomy is defined as the surgical removal of the uterus using various approaches. Laparoscopic hysterectomy, in particular, involves the removal of the uterus through the vagina with laparoscopic assistance. It offers advantages such as shorter hospital stay, faster postoperative recovery, less postoperative pain, and better visualization of pelvic structures.

Following hysterectomy, anatomical changes such as vaginal shortening due to vaginal cuff closure can result in sexual dysfunction, including dyspareunia and decreased sexual satisfaction (1). In addition to structural changes, hysterectomy may impact female sexual function through physiological, hormonal, and psychological mechanisms. Physiologically, disruption of pelvic nerve supply and reduced pelvic blood flow may impair arousal and lubrication (2). Hysterectomy may also lead to hormonal imbalances, particularly when oophorectomy is performed or ovarian blood flow is disrupted, resulting in reduced estrogen and progesterone levels (3). Psychologically, changes in body image, mood, and perception of femininity can further contribute to sexual dysfunction. Body image has a determining effect on an individual's eating behaviors, social anxiety levels, sexual behaviors, social relationships, and emotional states, in addition to their self-esteem (4).

Despite these concerns, the impact of hysterectomy on sexual function is often under-addressed during preoperative counseling. Furthermore, the surgical technique used for vaginal cuff closure-vaginal or laparoscopic-may influence postoperative outcomes including vaginal length and sexual function, yet few studies have directly compared these techniques.

In this prospective study, we aimed to compare the effects of two vaginal cuff closure techniques-laparoscopic versus vaginal-on postoperative vaginal length and female sexual function following laparoscopic hysterectomy. Sexual function was assessed using the Arizona Sexual Experience Scale (ASEX), a validated tool frequently used in gynecologic research.

Methods

This was a prospective clinical study conducted at Bolu Abant İzzet Baysal University Ethic Committee after obtaining ethics approval (decision no: 2021/104, date: 01.02.2023). All participants provided written informed consent. A total of 63 patients who underwent laparoscopic hysterectomy for benign gynecologic conditions were included. The vaginal cuff was closed using one of two techniques: laparoscopic intracorporeal suturing or vaginal suturing. Only patients operated on by a single experienced surgeon were included to minimize operator-related variability. Vaginal cuff in patients operated for benign reasonswas closed using a laparoscopic intracorporeal technique using 1/0 vycril or vaginally using 1/0 vycril.

Operation time, vaginal complications, and postoperative outcomes were compared between the two groups. The primary outcome of the study was the difference in baginal length measured preoperatively and at 3 months postoperatively.

Seconder outcomes included changes in sexual function as assessed by ASEX scores, operation time, and postoperative complications.

Operation time, vaginal complications, vaginal length, and postoperative sexual functions were compared between these two groups.

Patients who were operated on at an external center, patients who were operated by other surgeons, patients who developed intraoperative complications, patients who delayed their follow-up and treatment, patients who did not want to participate in the study, patients who were operated on for malignant reasons, patients with presence of a large adnexal mass (>10 cm in ultrasonography, >10 cm myoma on frozen section), patients who were operated on with indications, patients who were not sexually active, patients without a partner, and illiterate patients were not included in the study. Additionally, patients who could not tolerate the high Trendelenburg position, who were not suitable for laparoscopic surgery (patients with chronic obstructive pulmonary disease, restrictive lung disease), and

who underwent laparotomy were excluded from the study. A total of 70 patients participated in the study during the planned 2-year period. However, 3 patients in the 1st group and 4 patients in the 2nd group were excluded from the study because they did not meet the study criteria.

CONSORT flow diagram summary: enrollment: 70 patients assessed for eligibility.

- Excluded: 7 (did not meet criteria or withdrew)

- Randomized: 63 (laparoscopic group: 32, vaginal group: 31)

- Follow-up: No loss to follow-up

- Analysis: 63 included (32+31)

A total of 63 patients were included in the study, 32 in the first group and 31 in the second group. A power analysis was performed based on previously published data showing a minimum expected mean difference of 0.25 cm in vaginal length and 1.5 points in ASEX scores between groups. To achieve 80% power at a 5% significance level (α=0.05), a minimum of 28 participants per group was required. We enrolled 63 patients in total to account for potential dropouts and maintain statistical power.

Patients were randomly assigned to the laparoscopic or vaginal cuff closure group using a computer-generated simple randomization sequence. Allocation was concealed in sequentially numbered, opaque, sealed envelopes that were opened in the operating room after anesthesia induction. This ensured minimization of selection bias.

Sexual function was assessed using the ASEX preoperatively and at 3 months postoperatively. Although several scales are available for evaluating female sexual function, ASEX was chosen for its brevity, ease of use, validation in Turkish populations, and its ability to quantify changes across domains such as sexual drive, arousal, lubrication, orgasm, and satisfaction. Sexual function was assessed using the ASEX, which has demonstrated reliability and validity in Turkish hemodialysis patients (5).

Vaginal length was assessed both preoperatively and at 3 months postoperatively. The measurement was performed with a graduated metal ruler (Hegar dilator with scale), introduced from the hymenal ring up to the vaginal cuff apex. Patients were placed in the lithotomy position without anesthesia during the procedure. All measurements were carried out by the same experienced gynecologist, who was blinded to the patient's cuff closure technique to reduce bias. Although POP-Q parameters were recorded, the total vaginal length (TVL) measurement was used as the reference standard. To improve reproducibility, each measurement was performed twice, and the mean value was recorded. Trial registration: this study was registered at ClinicalTrials.gov (registration number: NCT07228351).

Statistical Analysis

Statistical analyses were performed using IBM SPSS statistics (version 25.0, IBM Corp., Armonk, NY, USA).While evaluating the study data, descriptive statistical methods were evaluated as mean, standard deviation and frequency. Student's t test was used to compare normally distributed parameters between two groups, and Mann-Whitney U test was used to compare non-normally distributed parameters between two groups. Pearson correlation test was used to examine the relationships between parameters. Chi-square test was used to compare qualitative data. The results were evaluated within the 95% confidence interval and the significance level was $p<0.05$.

Results

Our study was conducted with a total of 63 patients, 32 of whom underwent laparoscopic suturing and 31 of whom underwent vaginal suturing. The groups showed comparable characteristics in terms of most demographic variables. However, body mass index (BMI) values were found to be statistically higher in the vaginal suturing group.

As seen in Table 1, the average age of the patients was 46.59±2.80 (years) in the patient group with laparoscopic suturing and 44.74±3.89 (years) in the patient group with vaginal suturing. When the groups were examined, it was determined that the average ages in both groups ranged between 35 and 51 years, and the average ages were close to each other.

As seen in Table 1, the average height of the patients in the patient group with laparoscopic suturing was 161.78±4.79 cm, and the average height of the patients in the patient group with vaginal suturing was 160.74±5.50 cm. When the average weight of the patients in both groups was compared, it was determined that the average weight in the patient group with laparoscopic suturing was 72.09±13.23 kg, and in the patient group with vaginal suturing it was 77.48±12.11 kg. While the highest weight was 102 kg in the patient group with vaginal suturing, the lowest weight was 50 kg in the laparoscopic suturing group. As seen in Table 2 when the operation times between the groups were compared, the average of the laparoscopic suturing group was 81.36±12.5 minutes, and the average of the vaginal suturing group was 88.46 min (minimum)±13.7 min.

As seen in Table 3; in the patient group that underwent laparoscopic suturing, the average pre-operative (pre-op) vaginal length was 8.63±0.97 cm, while the average post-operative vaginal length was 8.00±0.89 cm. The average difference in vaginal length was 0.67±0.22 cm.

In the patient group who underwent vaginal suturing, the average pre-op vaginal length was 8.60±0.90 cm, while the average post-operative vaginal length was 7.67±0.75 cm. The average difference in vaginal length was 0.92±0.30 cm. When the vaginal lengths of the two groups were compared, it was determined that the vaginal length was shortened more in the patient group who underwent vaginal suturing. A statistically significant difference was detected between the two groups (Table 3).

As seen in Table 4; when the complications were compared between the two groups, no vaginal vault hematoma was detected in the patient group with laparoscopic suturing,

while vaginal vault hematoma was detected in 1 patient in the patient group with vaginal suturing. When compared in terms of vaginal vault infection; while infection was detected in 2 patients in the laparoscopic suture group, infection was detected in 4 patients in the vaginal suture group. When compared in terms of vaginal vault dehiscence, one patient in each group was followed up with vaginal vault dehiscence. When evaluated in terms of complications; while vaginal vault hematoma and vaginal vault infection were more common in the patient groups that underwent vaginal suturing, no significant difference was detected between the two groups in terms of dehiscence.

As seen in Table 5; pre-op score in the patient group with laparoscopic suturing was 17.53±3.68, post-op score was found 18.53±3.56. The average ASEX score in the surveys conducted in the pre-operative and post-operative periods in patients who underwent laparoscopic suturing was 1.38±1.5. In this group, the lowest score in pre-op patients was 10, while the highest score was 24. The lowest score of post-operative patients were 11 and the highest score was 25. The lowest ASEX score difference measured in pre-op and post-op patients was 0, while the highest was 6. There was no statistically significant difference between the groups in terms of the difference between pre-op and post-op measurements. This showed that the suturing technique in laparoscopic hysterectomy had no effect on the ASEX.

In the patient group who underwent vaginal suturing, the pre-op score was 16.52±4.29 and the post-op score was 17.16±4.98. The average ASEX score in the surveys conducted in the pre-op and post-operative periods in patients who underwent vaginal suturing was 1.1±1.1. In this group, the lowest score in pre-op patients was 8, while the highest score was 26. The lowest score of post-op patients was 8 and the highest score was 29. The lowest ASEX score difference measured in pre-op and post-op patients was 0, while the highest was 4 (Table 5).

As seen in Table 6, there was no significant correlation between the vaginal length and age (r=-0.185, p=0.146), height (r=- 0.04, p=0.975), weight (r=0.008, p=0.949), BMI (demographic factors such as r=0.003, p=0.979), smoking history (r=0.038, p=0.768), comorbidity history (r=0.124, p=0.335), and previous operation history (r=-0.043, p=0.736).

Discussion

Although the specific advantages and disadvantages of laparoscopic hysterectomy have been gradually defined today, it is still not widely applied due to insufficient technical equipment and the lack of well-trained laparoscopically trained personnel.

We know that after hysterectomy, vaginal length shortens due to the removal of the uterus, andas a result, conditions such as dyspareunia and sexual dysfunction may occur. When the literature was examined, it was seen that few studies evaluated vaginal

Table 1. Demographic findings of the laparoscopic suturing and vaginal suturing groups

	Patients who had laparoscopic suturing	Patients who had vaginal suturing	p-value
Age	46.59±2.80 (year)	44.74±3.89 (year)	0.073
Height	161.78±4.79 cm	160.74±5.50 cm	0.373
Weight	72.09±13.23 kg	77.48±12.11 kg	0.097
BMI	27.50±4.71	30.04±4.81	0.039
Cigarette (+)	11 (34.4%)	7 (22.6%)	0.304
Comorbidity DM (+)	2 (6.3%)	5 (16.1%)	0.385
Comorbidity HT (+)	7 (21.9%)	5 (16.1%)	
Comorbidity DM+HT+	1 (3.1%)	2 (6.5%)	
No comorbidities	22 (68.8%)	19 (61.3%)	
Previous operation history+	11 (34.4%)	9 (29.0%)	0.651

BMI: Body mass index, DM: Diabetes mellitus, HT: Hypertension

Table 2. Comparison of operation times of patient groups

	Patients who underwent laparoscopic suturing	Patients who underwent vaginal suturing	p-value
Operation time average	81.36 min±12.5 min	88.46 min±13.7 min	0.651
Operation time min	55 min	65 min	
Operation time max	110 min	130 min	

Table 3. Comparison of vaginal length between groups

	Patients who underwent laparoscopic suturing	Patients who underwent vaginal suturing	p-value
Pre-op vaginal length average	8.63±0.97 cm	8.60±0.90 cm	0.98
Min	7 cm	7 cm	
Max	11 cm	12 cm	
Post-op vaginal length average	8.00±0.89 cm	7.67±0.75 cm	0.125
Min	6.6 cm	6.4 cm	
Max	10.5 cm	10.5 cm	
Average vaginal length difference	0.67±0.22 cm	0.92±0.30 cm	**<0.005***
Min	0.2 cm	0.2 cm	
Max	1.1 cm	1.7 cm	

Data; Shown as mean ± standard deviation, p= Significance level, *: p<0.05, Was considered statistically significant, Pre-op: Pre-operative, Post-op: Post-operative

Table 4. Comparison of complications of patient groups

Complication	Patients who underwent laparoscopic suturing	Patients who underwent vaginal suturing	p-value
Vaginal cuff hematoma	0 (0%)	1 (3.2%)	>0.05*
Vaginal cuff infection	2 (6.3%)	4 (12.9%)	>0.05*
Vaginal cuff dehiscence	1 (3.1%)	1 (3.2%)	>0.05*

*: Comparisons were performed using chi-square or Fisher's exact test as appropriate; no statistically significant difference was observed between groups (p>0.05)

Table 5. Comparison of sexual function between groups

Survey results	Patients who underwent laparoscopic suturing	Patients who underwent vaginal suturing	p-value
Pre-op ASEX	17.53±3.68	16.52±4.29	0.318
Post-op Arizona score	18.53±3.56	17.16±4.98	0.213
Arizona score difference	1.38±1.5	1.1±1.1	0.672

Pre-op: Pre-operative, Post-op: Post-operative, ASEX: Arizona Sexual Experience Scale

length after laparoscopic hysterectomy. Most of these studies evaluated vaginal lengths in different hysterectomy surgeries (vaginal hysterectomy, laparoscopic hysterectomy, abdominal hysterectomy) rather than different cuff closure methods. In some studies in the literature, vaginal cuff closure techniques were compared. In these studies, postoperative complications and operation times of both methods were compared. In a study, preoperative and postoperative vaginal length and sexual function scales were compared (6). In this study, the vaginal length in patients who underwent laparoscopic suturing was found to be longer than the vaginal length in patients who underwent vaginal suturing. In our study, the average pre- operative vaginal length in the patient group who underwent laparoscopic suturing was 8.63±0.97 cm, while the average post-operative vaginal length was 8.00±0.89 cm. The average difference in vaginal length was 0.67±0.22 cm. In the patient group who underwent vaginal suturing, the average pre-op vaginal length was 8.60±0.90 cm, while the average post-operative vaginal length was 7.67±0.75 cm. The average difference in vaginal length was 0.92±0.30 cm. When the vaginal lengths of the two groups were compared, it was determined that the vaginal length was shortened more in the patient group who underwent vaginal suturing. Our data, consistent with the literature, revealed that postoperative vaginal length was shortened regardless of the cuff closure method.

When choosing the patients we included in the study, we made sure that they were similar groups. There was no significant difference in terms of demographic characteristics and surgery indications of the patients in both groups included in the study. This showed that the patients in the groups had a homogeneous structure. In addition, the fact that no significant difference was detected between the groups in terms of previous abdominal and pelvic surgical operations eliminated any possible differences between the groups.

When we looked at the operation times in our study, we noticed that the total operation time was shorter in the patient group who underwent laparoscopic suturing. In patients with laparoscopic suturing, although cuff suturing takes longer; we thought that the shortness of the total operation time was caused by the time loss during the examination of the abdomen with a camera after vaginal cuff suturing. We observed that there were time-consuming steps such as ensuring sterilization in accordance with the abdomen again after vaginal suturing, starting intra-abdominal gas inflation again, setting the appropriate pressure value, and rearranging the camera and other technical elements. Again, since we started working after gaining a certain amount of experience on this subject before laparoscopic suturing, we believed that the operation time of patients who underwent laparoscopic suturing was shorter.

Table 6. Correlation analysis of vaginal length difference with demographic data variables

		Age	Height	Weight	BMI	Cigarette use	Had a disease	Operation
Vaginal length difference	r	-0.185	-0.04	0.008	0.003	0.038	0.124	-0.043
	p	0.146	0.975	0.949	0.979	0.768	0.335	0.736

BMI: Body mass index

In our study, postoperative total ASEX scores were higher in both groups compared to preoperative ASEX scores. (17.5-18.5/16.5-17.1). When all patient groups were examined, it was seen that the ASEX score was high. In our country, 53.1% of women aged 31-45 and 67.9% of women aged 46-55 have sexual dysfunction (7). However, the number of patients admitting for treatment is less. On sexual function; there are influencing factors that cannot be changed, such as the patient's comorbid disease, menopause, and socioeconomic level. The postoperative ASEX form was filled out alone in a private room by the patients in our study, after their vaginal length was measured, when they came for their 3rd month follow-up. The answers here may be considered more realistic. Average ASEX score at the 3rd postoperative month in the patient group who underwent laparoscopic suturing was 18.5, and it was 17.1 in the patient group with vaginal suturing. However, the statistical difference was not significant ($p>0.05$).

One negative aspect of vaginal cuff closure is the increased risk of infection due to vaginal contamination. In our study, vaginal cuff infection was detected in 6.3% of the patient group who underwent laparoscopic suturing, while vaginal cuff infection was detected in 12.9% of the patients who underwent vaginal suturing. However, similar postoperative infection rates are reported in the literature in endoscopic and vaginal cuff closures (8). Infectious factor is an important risk factor for vaginal cuff detachment. When compared in terms of vaginal vault hematoma, no hematoma was detected in any patient in the patient group with laparoscopic suturing, while vaginal vault hematoma was detected in one patient in the patient group with vaginal suturing.

Study Limitations

This study has several limitations:

1. Short follow-up duration: The postoperative evaluation was limited to 3 months. As sexual function may continue to evolve beyond this period, longer follow-up is warranted.
2. Sample size: While powered to detect moderate differences, the relatively small cohort size limited the generalizability of findings.
3. Randomization method: Although computer-based randomization was used, the single-center design and inclusion of only one surgeon might limit external validity.
4. Selection bias: Despite randomization, baseline psychological and relationship factors influencing sexual function could not be fully controlled.
5. Measurement bias: Self-reported ASEX scores might be affected by sociocultural factors or underreporting due to embarrassment or stigma.
6. Choice of assessment tool: While ASEX is validated and practical, more detailed instruments such as the Female Sexual Function Index could offer broader insights into sexual domains. The use of ASEX was chosen for feasibility, but this might be seen as a limitation.

Conclusion

The purpose of our study was to investigate whether vaginal cuff closure techniques commonly used in total laparoscopic hysterectomy had an effect on vaginal length and sexual life, and to determine their superiority over each other, if any. For this purpose, we sutured the vaginal cuff using two different techniques: laparoscopic and vaginal. We found that laparoscopic vaginal cuff suturing shortened the vaginal length less. In terms of sexual life, we found that the vaginal cuff closure technique had no effect on postoperative results.

In terms of complications, although complications were less common in the patient group who underwent laparoscopic suturing in our study, the number of complications was quite low in both patient groups. We think that our findings should be supported by studies with a larger number of cases.

When we compare the two groups in terms of operation times; we found that the operation time was shorter in patients who underwent laparoscopic suturing. We believe that prospective, randomized, larger case series studies are needed to support our findings.

Ethics

Ethics Committee Approval: This was a prospective clinical study conducted at Bolu Abant İzzet Baysal University Ethic Committee after obtaining ethics approval (decision no: 2021/104, date: 01.02.2023).

Informed Consent: All participants provided written informed consent.

Footnotes

Authorship Contributions

Surgical and Medical Practices: M.E.A., M.A.T., Concept: M.E.A., M.A.T., Design: M.E.A., M.A.T., Data Collection or Processing: M.E.A., Analysis or Interpretation: M.E.A., M.A.T., Literature Search: M.E.A., M.A.T., Writing: M.E.A.

Conflict of Interest: No conflict of interest was declared by the authors.

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Original Article

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Reliability and Validity of the Turkish Version of the Arthritis-work Spillover Scale in Individuals with Rheumatoid Arthritis

Romatoid Artritli Bireylerde Artrit-aşırı İş Yükü Ölçeğinin Türkçe Versiyonunun Güvenirliği ve Geçerliği

Duygu Sanem KARA[1], Sebahat Yaprak ÇETİN[1], Ayşe AYAN[2]

[1]Akdeniz University Faculty of Health Sciences, Department of Physiotherapy and Rehabilitation, Antalya, Türkiye
[2]University of Health Science Türkiye, Antalya Training and Research Hospital, Department of Rheumatology, Antalya, Türkiye

ABSTRACT

Objective: The aim of this study is to adapt the arthritis-work spillover (AWS) scale for Turkish and to examine its validity and reliability.

Methods: The study included 60 individuals with rheumatoid arthritis. AWS scale, disabilities of the arm, shoulder and hand questionnaire (DASH) and its subscale DASH-work module (DASH-W), arthritis impact measurement scales (AIMS2), disease activity score 28 (DAS28), and Canadian occupational performance measure (COPM) were administered to the participants. Internal consistency analysis, Cronbach's alpha coefficient, test-retest method, confirmatory factor analysis, convergent validity were used for validity and reliability analysis.

Results: Cronbach's alpha coefficient was used for internal consistency and the result was 0.86. The test-retest reliability coefficient was 0.68 ($p<0.05$). In the convergent validity analysis, moderately significant correlations were observed between the AWS and DASH-W ($r=0.528$, $p<0.05$), AIMS2-role ($r=0.486$, $p<0.05$), COPM-performance ($r=-0.416$, $p<0.05$) and COPM-satisfaction scores ($r=-0.435$, $p<0.05$). The AWS demonstrated good structural fit. High correlations were observed between AWS and AIMS2-symptom, moderate correlations with DASH, AIMS2-physical, AIMS2-affect, and low correlations with DAS28 ($p<0.05$).

Conclusion: The results of this study showed that the Turkish version of the AWS was valid and reliable evaluation. The AWS scale should be used in clinics by clinicians such as physiotherapists,

ÖZ

Amaç: Bu çalışmanın amacı, artrit-aşırı iş yükü (AAİY) ölçeğinin geçerliğini ve güvenirliğini Türk toplumuna uyarlamaktır.

Yöntemler: Çalışmaya romatoid artritli 60 birey dahil edildi. Katılımcılara AAİY ölçeği, kol, omuz ve el engellilik anketi (DASH) ve alt ölçeği DASH-iş modülü (DASH-W), artrit etki ölçüm ölçekleri (AIMS2), hastalık aktivite puanı (DAS28) ve Kanada aktivite ve performans ölçümü (COPM) uygulandı. Geçerlik ve güvenilirlik analizi için iç tutarlılık analizi, Cronbach alfa katsayısı, test-tekrar test yöntemi, doğrulayıcı faktör analizi, yakınsak geçerlilik kullanıldı.

Bulgular: İç tutarlılık için Cronbach alfa katsayısı kullanıldı ve sonuç 0,86 olarak bulundu. Test-tekrar test güvenirlik katsayısı 0,68 ($p<0,05$) olarak bulundu. Yakınsak geçerlilik analizinde AAİY ölçeği ile DASH-W ($r=0,528$, $p<0,05$), AIMS2-rol ($r=0,486$, $p<0,05$), COPM performans ($r=-0,416$, $p<0,05$) ve COPM memnuniyet puanları ($r=-0,435$, $p<0,05$) arasında orta düzeyde anlamlı korelasyonlar gözlendi. AAİY, ölçek yapısının iyi uyumunun kanıtını sağladı. AAİY ile; AIMS2-belirti arasında yüksek korelasyon, DASH, AIMS2-fiziksel, AIMS2-etki arasında orta düzeyde korelasyonlar ve DAS28 ile düşük düzeyde korelasyonlar gözlendi ($p<0,05$).

Sonuç: Bu çalışmanın sonuçları AAİY ölçeğinin Türkçe versiyonunun geçerli ve güvenilir bir değerlendirme olduğunu göstermiştir. AAİY ölçeği, fizyoterapistler, hekimler, ergoterapistler ve psikologlar gibi klinisyenler tarafından kliniklerde kullanılmalı

Address for Correspondence: Assoc. Prof. Sebahat Yaprak Çetin, Akdeniz University Faculty of Health Sciences, Department of Physiotherapy and Rehabilitation, Antalya, Türkiye
E-mail: fzt.ycetin@gmail.com
ORCID IDs of the authors: D.S.K.: 0000-0002-0098-8966, S.Y.Ç.: 0000-0002-7467-1398, A.A.: 0000-0001-9488-2611

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ABSTRACT

physicians, occupational therapists and psychologists etc. to determine the problems experienced by patients in their professional lives and could also be a guide in planning work and occupational programmes of patients.

Keywords: Rheumatoid arthritis, work, functionality, validity, reliability

ÖZ

ve hastaların mesleki yaşamlarında yaşadıkları sorunları belirlemede ve ayrıca hastaların iş ve mesleki programlarını planlamada bir rehber olabilir.

Anahtar Kelimeler: Romatoid artrit, iş, işlevsellik, geçerlik, güvenilirlik

Introduction

Having a job is highly beneficial for individuals with physical limitations by strengthening a sense of purpose, improving economic and emotional well-being, and promoting self-efficacy (1). Although current treatment approaches have improved the lives of individuals with arthritis, research shows that there are still work limitations (2). The challenges of working with rheumatoid arthritis (RA) include dealing with disease symptoms, as well as activity limitations in work tasks. Work can also be made more efficient by physically hard tasks, fast-paced work, little job control, and commuting. Two of the challenges of working with RA include managing the disease's symptoms and activity limitations in professional tasks. People with RA may also experience difficulties at work due to physically demanding jobs, fast-paced work environments, a lack of job control, and transportation (3). Higher levels of discomfort are associated with higher rates of disease leave and decreased productivity (4).

Syngle et al. (3) observed that 73% of individuals with RA were affected in their work capacity. There was a decrease in working hours in 48% of individuals, 17% left the labour force early and 8% changed their jobs. Of the people who are currently working, 15% are incapacitated in 1 year, 27% in 5 years, and this increases to more than 50% in 10 years (4,5). Many workplace exposures lead to serious financial consequences and increased social security costs for the individual with RA and his/her family. Economically problems experienced may lead to deterioration in the emotional states of individuals, conflicts in the family environment and lead to decreases in health-related quality of life (6-8). Patient health related reports are increasingly being used in clinical studies because they are an important factor in the perception of health and disability status of patients (9). Validity and reliability studies contribute to the quality and credibility of the research as they ensure that the research accurately measures what it is intended to measure and that the results are consistent and reproducible (10).

The arthritis-work spillover (AWS) was developed by Gignac et al. (11) in 2006. It was created to examine the reciprocal effects of work on arthritis in individuals and to evaluate the relationship between demographic, disease and work-related variables and AWS. In the original study all factor loadings were ≥0.69. The factor explains for 62.1% of variance and the alpha value for reliability measurement was 0.88 (11). However, no validity and reliability study has been conducted in another language yet.

To the best knowledge there is no scale translated into Turkish to reciprocal effects of arthritis on work in individuals. The aim of this study was to adapt the AWS to Turkish culture and to examine whether it was valid and reliable.

Methods

The study was approved by the Ethic Committee of the University of Health Sciences Türkiye, Antalya Training and Research Hospital (decision no: 8/6, date: 14.04.2022). The study was conducted between 1 June 2022 and 1 December 2022 in the Internal Medicine Rheumatology Outpatient Clinic of University of Health Science Türkiye, Antalya Training and Research Hospital. Informed consent form was obtained from the individuals who agreed to participate in the study. This study was conducted in accordance with the Declaration of Helsinki.

Translation and Cultural Adaptation

Permission was obtained from Monique Gignac for the Turkish version of the AWS. The Turkish version was created in 5 steps (12).

Translation: The AWS was translated into Turkish by a physiotherapist and a linguist who are native Turkish speakers and fluent in English. These translators created their translations independently of each other.

Synthesis: The first translations were evaluated together by the people who created them and a one translation was created.

Back-translation: The Turkish translation of AWS was translated back into English independently by two linguists who are native English speakers and fluent in Turkish.

Expert committee review: All translations created at this stage were examined by a team consisting of 3 physiotherapists and 2 linguists whose native language is English. After the evaluations, it was decided that the scale was compatible with the original and the pre-final version of the scale was obtained before the pilot study.

Pilot study and creation of final version: The pre-final version of the scale was applied to 20 patients with RA in a pilot study. All participating individuals stated that they had no difficulty in understanding the questions. Thus, the final version of the scale was obtained.

Participants

Sixty individuals aged 18-64 years who were diagnosed with RA by a rheumatologist at the Internal Medicine Rheumatology Outpatient Clinic of University of Health Science Türkiye, Antalya Training and Research Hospital were included in the study. Inclusion criteria were determined as patients with RA for at least 1 year, being employed in a paid job, no comorbidities causing physical disability, being over 18 years old, volunteering to participate in the study and giving consent. Exclusion criteria were determined as patients with hand involvement due to diseases other than a known rheumatological disease, co-morbidities causing physical and cognitive disability, communication problems, illiterate patients and patients not giving consent to participate in the study.

Measures

Participants were asked to complete a demographic form that included age, gender, body mass index, etc. were recorded. Occupation was grouped according to the most recent international standard classification of occupations classification of the international labour organisation. Accordingly, professions are divided into; "professionals, clerical support workers", "services and sales workers", "skilled agricultural, forestry and fishery workers", "craft and related trades workers", "plant and machine operators and assemblers" and "elementary occupations" (13).

AWS, disabilities of the arm, shoulder and hand questionnaire (DASH) and DASH-work module (DASH-W), arthritis impact measurement scales (AIMS2), disease activity score 28 (DAS28), and Canadian occupational performance measure (COPM) were applied to the individuals whose demographic information was recorded. AWS was re-applied to the individuals 7 days later for test-retest (14,15).

AWS

The AWS was developed by Gignac et al. (11). It is a single-dimensional scale consisting of six items. Six items are designed to assess the extent to which the demands of arthritis affect work performance and the extent to which working life interferes with managing arthritis. The items are scored on a 5-point Likert-type scale (1-strongly disagree, 2-disagree, 3-neither agree or disagree, 4-agree and 5-strongly agree). First three items assess the impact of employment on arthritis. Last three items assess the impact of arthritis on work. In scoring, an average score can be calculated over the six items or a total score can be used. In this study, a total score was obtained (11).

DASH and DASH-W

The DASH evaluates upper extremity symptoms and activities of daily living (16,17). It has a 5-point Likert-type scoring (1-no difficulty, 2-mild difficulty, 3-moderate difficulty, 4-severe difficulty, 5-unable). The DASH questionnaire consists of 30 questions. To calculate the DASH score, the total score is divided by the number of questions answered, subtract one and multiply by twenty-five. In addition to these 30 questions, the optional DASH-W is created (16,17). The DASH-W assesses the level of disability in working life and consists of 4 questions. For the DASH-W score, the total score is divided by four, subtract one and multiply by twenty-five (16,17).

AIMS2

The AIMS2 scale is a comprehensive and sensitive measure to assess the health status of patients with arthritis (18). In this scale, the last 1 month is questioned. The AIMS2 scale is a 78-item questionnaire and consists of 12 subscales. The results of AIMS2 can be presented in 3 or 5 component models. The 5-component model groups the AIMS2 subscales into the general categories of physical, affect, symptom, social interaction and role. The 3-component model groups the subscales into the general categories of physical, affect and symptom. In AIMS2, specific formulae for each subscale are used for scoring. Higher scores represent poorer health status (18).

DAS28

The DAS28 is an assessment method based on the calculation of swelling and tenderness in 28 joints including proximal interphalangeal joints, metacarpophalangeal joints, wrist, elbow, shoulder and knee joints, together with erythrocyte sedimentation rate (ESR) and patient's global health assessment [visual analogue scale (VAS) 0-100 mm] score, using a special formula (19,20). DAS28 = [(0.56 x $\sqrt{}$(tender joints) + (0.28 x $\sqrt{}$(swollen joints) + (0.70 x Ln (ESR))] + (0.014 x visual analog scaleVAS for global health). A high score indicates high disease activity: high disease activity: >5.1; moderate disease activity: 3.2<DAS28≤5.1; low disease activity: ≤3.2; remission: <2.6 (19-21).

COPM

The COPM is a measurement created to measure individuals' activity performance and performance satisfaction (22). This measurement is applied with a semi-structured interview method. In the first stage, individuals are asked to determine the activities they do, want to do or have difficulty in their daily lives. Then, they are asked to give these activities an importance score from 1 to 10. The most important 5 activities are selected and they are asked to give a performance score and satisfaction score from 1 to 10 to these activities. Then the performance and satisfaction scores are totalled separately and averaged. As a result, performance and satisfaction scores are obtained (22).

Statistical Anaylsis

International Business Machines (IBM) Statistical Package for Social Science (SPSS) 25.0 (IBM SPSS Statistics 25.0) was used for data analyses. Jamovi version 2.3.21. was used for confirmatory factor analysis. Demographic and clinical characteristics were expressed as mean ± standard deviation (SD) or percent (%). For the sample size, based on the validity and internal consistency recommendations of the COSMIN criteria (23,24), it was decided that the number of cases should be 60 individuals with a maximum of 10 times the number of questions. Spearman correlation analysis was performed to examine the relationship between the AWS and the other scales used. Validity was analysed using convergent analysis and confirmatory factor

analysis. For convergent validity, Spearman correlation analyses were performed with DASH-W, AIMS2-role component and COPM. For reliability analysis, internal consistency and test-retest method were applied. Cronbach's alpha coefficient was used for internal consistency analysis. Spearman correlation analysis was used for test-retest. Correlation coefficients: 1.00 to 0.80 very high correlation; 0.80 to 0.60 high correlation; 0.60 to 0.40 moderate correlation; 0.40 to 0.20 low correlation; 0.20 to 0 very low correlation (25,26). Cronbach's alpha coefficient: ≥0.90 excellent; 0.90 to 0.80 good; 0.80 to 0.70 acceptable; 0.70 to 0.60 doubtful; 0.60 to 0.50 poor; ≤0.50 unacceptable (27). Statistical significance was accepted as $p<0.05$.

Results

Demographic data and findings of outcome measures are shown in Table 1.

Internal Consistency

Cronbach's alpha was used for internal consistency analysis. Cronbach's alpha coefficient was 0.86. According to these values, the scale had good reliability. It was observed that Cronbach's alpha value decreased when the items were removed from the scale. Based on these results, it was noted that each item in the scale contributed to the Cronbach's alpha value (Table 2).

Test-retest Reliability

Spearman correlation analysis was performed for test-retest and correalation coefficient was found 0.68 ($p<0.05$) (Table 2).

Confirmatory Factor Analysis

According to confirmatory factor analysis (CFA) results, the goodness of fit indices of the first model was not among desired values. In the CFA, the programme suggested modification between the fourth and sixth items for a better fit of the model. Since the fourth and sixth items consisted of similar expressions, the modification suggestion was applied. After the modifications it was observed that the model showed a good fit with the data [chi-square/degree of freedom (χ^2/sd)=1.0875, root mean square error of approximation (RMSEA)=0.000, standardized root mean square residual (SRMR)=0.041, comparative fit index (CFI)=0.995, Tucker-Lewis index (TLI)=0.992] (Table 3). The path diagram of the AWS after the second CFA model is shown in Figure 1.

Spearman Correlation Analysis

In the convergent validity a moderate positive correlation was found between AWS and DASH-W and AIMS2-role, and a moderate negative correlation was found between COPM-performance and COPM-satisfaction scores ($p<0.05$, Table 4). A good positive correlation was observed between AWS and AIMS2-symptom component ($p<0.05$, Table 4). A moderate positive correlation was observed between the scale and DASH, AIMS2-physical, AIMS2-affect measures. DAS28 showed a low positive correlation ($p<0.05$, Table 4). A low positive correlation was found with AIMS2-social Interaction, but this relationship was not statistically significant ($p>0.05$, Table 4).

Table 1. Demographic and outcome data of participants

Characteristics (n=60)	
Gender n (%)	
Women/men	52 (86.7)/8 (13.3)
Education n (%)	
Primary/middle school/high school/ university	9 (15)/13 (21.7)/27 (45)/11 (18.3)
Occupation n (%)	
Professionals	7 (11.7)
Clerical support workers	5 (8.3)
Services and sales workers	20 (33.3)
Skilled agricultural, forestry and fishery workers	5 (8.3)
Craft and related trades workers	3 (5)
Plant and machine operators and assemblers	3 (5)
Elementary occupations	17 (28.3)
Additional responsibilities of occupation n (%)	
Overtime/shift work/work travelling	27 (45)/13 (21.7)/2 (3.3)
Age (year), mean ± SD	51.92±9.21
Height (cm), mean ± SD	162.12±7.68
Weight (kg), mean ± SD	71.60±15.35
BMI (kg/m²), mean ± SD	27.26±5.85
Durations (year), mean ± SD	11.28±7.06
Hours of work per week (h), mean ± SD	42.82±4.31
Outcome measures, mean ± SD	
AWS	20.32±6.44
DASH	32.18±19.54
DASH-W	47.60±26.64
AIMS2-physical	3.01±5.33
AIMS2-affect	4.00±1.78
AIMS2-symtom	4.89±2.29
AIMS2-social ınteraction	3.08±1.45
AIMS2-role	3.40±2.32
DAS28	3.98±1.39
COPM-performance	4.06±2.18
COPM-satisfaction	2.92±2.35

SD: Standard deviation, AWS: Arthritis-work spillover scale, DASH: Disabilities of the arm, shoulder and hand questionnaire, DASH-W: DASH-work module, AIMS2: Arthritis impact measurement scales 2, DAS28: Disease activity score 28, COPM: Canadian occupational performance measure, BMI: Body mass index

Table 2. Internal consistency analysis Cronbach's alpha results and test-retest reliability of AWS

Cronbach's alpha			**0.86**
Items		**Cronbach's alpha if item deleted**	**r**
1- The demands of my job make it difficult for me to take good care of my arthritis.		0.844	0.633
2- It takes a great deal of my energy and time to manage my work demands.		0.835	0.673
3- My condition suffers because of the demands of my work.		0.840	0.646
4- The demands of my arthritis make it difficult for me to do as good a job at my work as I would like.		0.845	0.626
5- It takes a great deal of my energy and time to manage the demands of my condition.		0.836	0.675
6- The quality of my work suffers because of the demands of my arthritis.		0.833	0.688
		AWS (second)	
AWS (first)	**Correlation coefficient**	0.683	
	Sig. (2-tailed)	0.000*	

*: p<0.05; Spearman correlation analysis, AWS: Arthritis-work spillover scale

Table 3. CFA goodness of fit indices of AWS

	x^2/sd	**RMSEA**	**SRMR**	**TLI**	**CFI**
Model 1	3.289	0.169	0.067	0.780	0.868
Model 2	1.0875	0.000	0.041	0.992	0.995

x^2/sd: Chi-square/degree of freedom, AWS: Arthritis-work spillover scale, RMSEA: Root mean square error of approximation, SRMR: Standardized root mean square residual, TLI: Tucker-Lewis index, CFI: Comparative fit index; Spearman correlation analysis, CFA: Confirmatory factor analysis

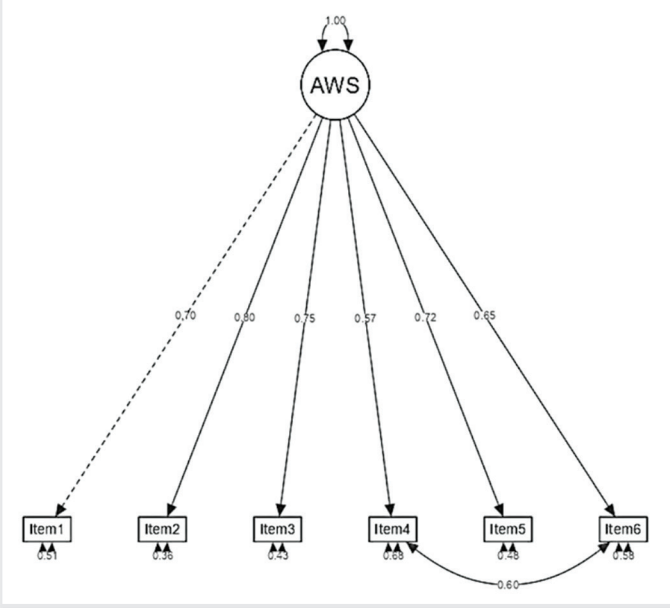

Figure 1. Path diagram of the AWS in confirmatory factor analysis

AWS: Arthritis-work spillover

Discussion

This study examined the validity and reliability of the Turkish cultural adaptation of the AWS scale. According to the results of the study, AWS was found to be valid and reliable.

Table 4. Spearman correlations of AWS with outcomes data

	AWS	
	r_s	**p-value**
DASH-W	0.528	0.000*
AIMS2-role	0.486	0.000*
COPM-performance	-0.416	0.003*
COPM-satisfaction	-0.435	0.002*
DASH	0.495	0.000*
AIMS2-physical	0.525	0.000*
AIMS2-affect	0.435	0.001*
AIMS2-symptom	0.619	0.000*
AIMS2-social interaction	0.138	0.294
DAS28	0.261	0.044*

*: p<0.05, AWS: Arthritis-work spillover scale, DASH: Disabilities of the arm, shoulder and hand questionnaire, DASH-W: DASH-work module, AIMS2: Arthritis impact measurement scales 2, DAS28: Disease activity score, COPM: Canadian occupational performance measure

Since the AWS is a Likert-type scale, Cronbach's alpha method was preferred to apply the internal consistency analysis. In the study, the coefficient of the AWS was found to be 0.86 (Table 2) and thus the scale was found to be reliable. In the original study, the alpha coefficient of the scale was found to be 0.88 (11).

The coefficient of the Turkish scale with the original study similarities were detected.

As suggested in the original study (11), we applied test-retest to assess whether the scale was stable and sensitive over time. In test-retest reliability good relationship was found between the two measurements (r=0.683; p=0.000) (Table 2). This method was not applied while creating the original version of the scale. In the light of the informations obtained, it was determined that the AWS was reliable.

In confirmatory factor analysis RMSEA and SRMR are interpreted between 0 (perfect fit) and 1 (no fit); TLI and CFI are interpreted between 0 (no fit) and 1 (perfect fit) (28-30). In addition χ^2/sd less than 2 indicates excellent fit, RMSEA less than 0.05 indicates excellent fit, SRMR less than 0.08 indicates good fit, CFI and TLI values bigger than 0.90 indicate good fit. The structure that meets these values shows that the model and data are compatible (28-30). In this study the goodness of fit indices of the first model was not among desired values. After the modification of the model good fit was observed with χ^2/sd (1.0875), good with RMSEA value (0.000), good with SRMR value (0.041), good with CFI value (0.995), and good with TLI value (0.992) (Table 3). Based on all these values, it was observed that the model showed a good fit with the data. Confirmatory factor analysis was not applied when the original version of the scale was developed (11).

In the study, DASH-W, AIMS2-rol and COPM measurements were used for convergent validity. DASH-W is used to assess disability in individuals' working life (16,17). The AIMS2-role component also assesses problems experienced in working life (18). The COPM is used to assess the activity performance and satisfaction of individuals (22). The relationship between DASH-W and AWS was positive and moderately significant (r=0.528; p=0.000) (Table 4). The relationship of the scale with the AIMS2-role component also showed positive moderate significance (r=0.486; p=0.000) (Table 4). The relationship of AWS with COPM-performance (r=-0.416; p=0.003) and COPM-satisfaction (r=-0.435; p=0.002) scores showed negative moderate relationship (Table 4). According to these results, it was seen that the validity of AWS was achieved. Many symptoms of RA such as pain, morning stiffness, swelling and muscle weakness have a direct impact on functional disability and reductions and limitations in physical functions can affect working capacity and make quality of life more fragile (31-33). In addition it was seen that good muscle strength and physical performance led to better job opportunities (31). This study also showed that the relationship between AWS and the physical, affect, symptom and role components of AIMS2, DASH and DASH-W were similar to the literature. The negative correlation with COPM-performance and COPM-satisfaction may explain that AWS scores are negatively affected by losses in physical function.

Studies have shown that work capacity is more affected by functionality than disease activity, and although those with moderate to high levels of disease activity are often associated with problems in work capacity, a significant proportion of those with active disease do not experience impairment in work capacity (3,34). Various studies have indicated that factors such as economic status, occupational type, medications used, duration of the disease may have significant effects on working capacity other than disease activity (6,35,36). These results may support the weak association of AWS with DAS28 in this study.

The current study did not show a significant relationship between AWS and the social interaction component of AIMS2. In various studies, it has been observed that loss of independence and self-confidence and loss of social skills occur with deterioration in working capacity in individual with RA (37,38). However, it has also been observed that the COVID-19 pandemic in recent years has affected social interactions due to social distance and physical isolation (39). In addition it was stated that the character structures of the individual and the people in their close environment and the support they provide might lead the individual to exhibit more social behaviours (40,41). Based on all this information, it can be considered that many factors other than the disease affect the social interaction of individuals. In order to explain the relationship between AWS and social interaction, studies in which various factors such as disease effect, environmental factors, personality structure or social influence are evaluated together are needed.

The AWS scale may assist clinicians in identifying specific domains of work-related disability, allowing for tailored interventions. It has the advantage of being short and easy to administer.

Study Limitations

Our study had several limitations. The first one was that the number of women was much higher than the number of men. This may have led to gender bias and prevented generalisation of the findings to a wider population. Another limitation was the short duration of the study. Longer studies may help to elucidate the causality of factors affecting work capacity. Another limitation of our study was that we did not assess differences in ethnicity. The diversity of individuals from different geographical regions may have influenced the answers to the questions as they may have different life views (42,43). Another limitation was that individuals were not assessed in terms of their occupation. If the occupation required physical labour or was a desk-based job, it may have had a positive or negative effect on the answers given by the individuals, depending on the situation. As this was a cross-sectional study, the responsiveness or sensitivity to change overtime of the AWS was not evaluated. Future studies with AWS should be planned according to ethnicity and work performed, and studies comparing gender differences should be conducted.

Conclusion

The AWS scale was found to be a valid and reliable scale for assessing work affect in individuals with RA. It is also advantageous that the scale can be applied in a short time. The AWS scale should be used in clinics by clinicians such as physiotherapists, physicians, occupational therapists and psychologists etc. to determine the

problems experienced by patients in their professional lives and can also be a guide in planning work and occupational programmes of patients.

Ethics

Ethics Committee Approval: The study was approved by the Ethic Committee of the University of Health Sciences Türkiye, Antalya Training and Research Hospital (decision no: 8/6, date: 14.04.2022).

Informed Consent: Informed consent form was obtained from the individuals who agreed to participate in the study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: A.A., Concept: S.Y.Ç., A.A., Design: S.Y.Ç., Data Collection or Processing: D.S.K., Analysis or Interpretation: S.Y.Ç., Literature Search: D.S.K., Writing: D.S.K.

Conflict of Interest: No conflict of interest was declared by the authors.

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Original Article

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Electrolyte Disorders: Insights from a Prospective, Multicenter, Observational Cohort Study on Fosfomycin's Impact

Elektrolit Bozuklukları: Fosfomisinin Etkisi Üzerine Prospektif, Çok Merkezli, Gözlemsel Bir Kohort Çalışmasından Elde Edilen Veriler

Yunus Emre AYHAN[1], Canan ÇULHA[2], Nilay AKSOY[3], Ömer Faruk ÖZKANLI[4], Barış DEMİRKOL[5], Ramazan ŞAHİN[5], Öznur ALTIPARMAK[6], Büşra ERGEN[4], Zeynep Ülkü GÜN[7], Mesut SANCAR[4]

[1]University of Health Sciences Türkiye, Prof. Dr. Cemil Taşçıoğlu City Hospital, Department of Clinical Pharmacy, İstanbul, Türkiye
[2]Mersin University Faculty of Pharmacy, Department of Clinical Pharmacy, Mersin, Türkiye
[3]Altınbaş University Faculty of Pharmacy, Department of Clinical Pharmacy, İstanbul, Türkiye
[4]Marmara University Faculty of Pharmacy, Department of Clinical Pharmacy, İstanbul, Türkiye
[5]University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital, Department of Chest Diseases, İstanbul, Türkiye
[6]Ege University Faculty of Pharmacy, Department of Clinical Pharmacy, İzmir, Türkiye
[7]Trakya University Faculty of Pharmacy, Department of Clinical Pharmacy, Edirne, Türkiye

ABSTRACT

Objective: Intravenous (IV) fosfomycin is widely used in combination therapies for resistant pathogens. This study aims to investigate the frequency and risk factors of electrolyte disorders (EDs) associated with IV fosfomycin in hospitalized patients.

Methods: This was a prospective, multicenter, observational cohort study, conducted in six centers from February 2023 to February 2024. The Naranjo adverse drug reaction probability scale (NADRPS) was used to evaluate the relationship between IV fosfomycin use and EDs.

Results: A total of 54 patients with a median age [interquartile range (IQR)] of 60 (35-73) years were included in the study. Most patients (38.8%) were admitted to the intensive care unit (ICU). The median IV fosfomycin dose was 12 g (IQR: 12-18), and the mean treatment duration was 13.2±7.2 days. Hypokalemia occurred in 28 patients (51.8%), and hypernatremia in 10 patients (18.5%). NADRPS scores were consistent with a probable

ÖZ

Amaç: İntravenöz (IV) fosfomisin, dirençli patojenler için kombinasyon tedavilerinde yaygın olarak kullanılmaktadır. Bu çalışma, hastaneye yatırılmış hastalarda IV fosfomisin'in neden olduğu elektrolit bozuklukları (EB) sıklığını ve risk faktörlerini araştırmayı amaçlamaktadır.

Yöntemler: Bu çalışma, 2023 Şubat ile 2024 Şubat tarihleri arasında altı farklı merkezde gerçekleştirilen prospektif, çok merkezli, gözlemsel bir kohort çalışmasıdır. Naranjo advers ilaç reaksiyonu olasılık ölçeği (NADRPS), EB ile IV fosfomisin kullanımı arasındaki ilişkiyi değerlendirmiştir.

Bulgular: Çalışmaya toplamda yaş ortalaması [çeyrekler arası aralık (ÇAA)] 60 (35-73) yıl olan 54 hasta dahil edilmiştir. Hastaların çoğu (%38,8) yoğun bakım ünitesinde (YBÜ) yatırılmıştır. IV fosfomisin medyan (ÇAA) dozu 12 g (ÇAA: 12-18) olup tedavi süresi ortalama 13,2±7,2 gündür. Hipokalemi 28 hastada (%51,8) ve hipernatremi 10 hastada (%18,5) görülmüştür. NADRPS

Address for Correspondence: Yunus Emre Ayhan MD, University of Health Sciences Türkiye, Prof. Dr. Cemil Taşçıoğlu City Hospital, Department of Clinical Pharmacy, İstanbul, Türkiye
E-mail: eczyunusemreayhan@gmail.com
ORCID IDs of the authors: Y.E.A.: 0000-0001-6093-0849, C.Ç.: 0000-0002-7714-7444, N.A.: 0000-0002-6990-1945, Ö.F.Ö.: 0000-0002-7048-8879, B.D.: 0000-0001-5585-3842, R.Ş.: 0009-0007-5193-9762, Ö.A.: 0000-0003-1261-1944, B.E.: 0000-0001-5223-3787, Z.Ü.G.: 0000-0002-7131-6585, M.S.: 0000-0002-7445-3235

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ABSTRACT

association between fosfomycin use and EDs. The incidence of hypokalemia was significantly higher in ESBL-positive patients (63.4% vs. 30.7%, p=0.04). The incidence of hypernatremia was significantly higher among patients with hypokalemia than among those without hypokalemia (90% vs. 46.1%, p=0.013). Mortality was significantly higher in patients with EDs than in those without, with an odds ratio (OR) of 6.25 [95% confidence interval (CI): 1.82-20, p=0.002]. Furthermore, the presence of ESBL and positive fluid balance were associated with increased ED risk, with ORs of 3.77 (95% CI: 1.09-13.10, p=0.032) and 5.40 (95% CI: 1.12-26.04, p=0.03), respectively.

Conclusion: The correlation between IV fosfomycin and electrolyte abnormalities requires careful consideration, especially in ICU patients. Clinicians must regularly monitor electrolyte levels while administering IV fosfomycin to minimize potential risks while ensuring patient safety.

Keywords: Fosfomycin, electrolyte disorders, hypernatremia, hypokalemia, intensive care unit

ÖZ

skorları, hastaların EB'leri ile uyumlu bulunmuştur. ESBL pozitif hastalarda hipokalemi insidansı daha yüksekti (%63,4 vs. %30,7, p=0,04). Hipokalemik hastalarda hipernatremi insidansı, hipokalemisi olmayanlardan anlamlı derecede yüksekti (%90 vs. %46,1, p=0,013). EB'li hastalarda mortalite oranı, EB'siz hastalara göre anlamlı derecede yüksekti ve odds oranı (OR) 6,25 [%95 güven aralığı (GA): 1,82-20, p=0,002] olarak bulunmuştur. Ayrıca, ESBL (+) varlığı ve pozitif sıvı dengesi, sırasıyla OR'leri 3,77 (%95 GA: 1,09-13,10, p=0,032) ve 5,40 (%95 GA: 1,12-26,04, p=0,03) ile artmış EB riski ile ilişkilendirilmiştir.

Sonuç: IV fosfomisin ile elektrolit anormallikleri arasındaki ilişki, özellikle YBÜ hastalarında dikkatle değerlendirilmelidir. Klinik uzmanlar, IV fosfomisin tedavisi sırasında elektrolit düzeylerini düzenli olarak izlemeli, potansiyel riskleri en aza indirirken hasta güvenliğini sağlamalıdır.

Anahtar Kelimeler: Fosfomisin, elektrolit bozukluğu, hipernatremi, hipokalemi, yoğun bakım ünitesi

Introduction

Electrolyte homeostasis is maintained through a complex system involving the coordinated action of various hormones and organs (1). Moreover, several medications used in clinical practice can lead to electrolyte disorders (EDs) (1-3).

Fosfomycin is a bactericidal antibiotic with broad-spectrum activity against both gram-positive and gram-negative pathogens. Notably, it is effective against challenging strains such as carbapenemase- and extended-spectrum beta-lactamases (ESBL) producing *Enterobacteriaceae*, methicillin-resistant *Staphylococcus aureus*, glycopeptide-resistant enterococci, and multidrug-resistant *Pseudomonas aeruginosa* (4-7). However, intravenous (IV) fosfomycin administration may lead to hypernatremia, particularly when high doses or prolonged treatment regimens are used, due to its high sodium content (8-11). In addition, IV fosfomycin has been frequently associated with hypokalemia, as reported in multiple studies (8-11).

Based on several clinical studies, including the multicenter ZEUS study, a daily dose of 12-18 g of fosfomycin has been recommended for the treatment of urinary tract infections (UTIs) (6,8,12,13). Notably, higher daily doses (>12 g) have been associated with a greater incidence of hypernatremia compared to lower doses (28.7% vs. 19.7%, p=0.06) (10). A European study reported that IV fosfomycin, commonly used to treat challenging infections, caused hypernatremia in 10.5% of patients (11). Furthermore, treatment was discontinued in six cases due to hypernatremia attributed to the high sodium content of fosfomycin (14 mmol sodium per gram) (11,14,15). Across multiple studies, the incidence of hypernatremia associated with IV fosfomycin has ranged from 6% to 24.3% (4,9,10,16,17). Review of medical records revealed that most cases were classified as severe (68%), although subsequent evaluations showed improvement or resolution in 44% of cases. Notably, in 72% of these cases, fosfomycin was the sole suspected causative agent (18).

In addition to hypernatremia, hypokalemia has also been documented as an adverse effect of IV fosfomycin, with reported frequencies ranging from 2.4% to 62.1% (8-11). The underlying mechanism is thought to involve increased potassium excretion in the distal renal tubules (4). Notably, hypokalemia may occur following short IV infusion durations (30-60 minutes), whereas extending infusion times to four hours has been shown to reduce its incidence (8,9). Interestingly, hypokalemia appeared to be less frequent among patients receiving higher daily doses (≥12 g) compared to those receiving lower doses (<12 g) (48.4% vs. 75%, p<0.001) (10). Importantly, no patients in these studies required treatment discontinuation due to hypokalemia (11).

IV fosfomycin has been used in Türkiye for specific clinical indications for approximately six years (17,19,20). Due to the limited data on its adverse effects, further research is needed to better understand the spectrum of potential complications, particularly EDs. This study aims to investigate the incidence and associated factors of EDs among hospitalized patients receiving IV fosfomycin.

Methods

Study Design and Participants

This study was a prospective, multicenter, observational cohort conducted across six centers involving patients who received IV fosfomycin between February 2023 and February 2024. The inclusion criteria consisted of individuals aged 18 years or older who had been hospitalized for more than 24 hours for any reason and received IV fosfomycin for more than 48 hours. Written informed consent was obtained from each patient or their legal guardian prior to study inclusion. Patients with missing key clinical or laboratory data were excluded from the

analysis. Thus, no imputation was performed, and all statistical analyses were conducted on complete cases. The study was reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology Guidelines (21).

Ethics Approval and Consent to Participate

The study received ethical approval from the Clinical Research Ethics Committee of Marmara University (decision no: 09.2023.22, date: 03.02.2023). Written informed consent was obtained from all participants. All procedures adhered to the ethical standards and the principles of the 1964 Helsinki Declaration and its later amendments.

Sample Size

To assess the adequacy of our sample size, we conducted a post-hoc calculation based on the findings of a previous study by Sürmelioğlu et al. (22), which reported a 33.9% incidence of hypokalemia in critically ill patients receiving IV fosfomycin. Assuming a 90% confidence level and an acceptable absolute margin of error of ±12%, the minimum required sample size was calculated as 43 patients. Since our study included 54 patients, it met this requirement, and the sample size could be considered sufficient under these parameters.

Data Collection

Fosfomycin treatment and the course of infection were monitored for clinical and microbiological outcomes and safety until discharge or death, when applicable. All data were (pseudo)-anonymized by the investigators at each study center and verified by a double-entry procedure. Recorded data included demographic characteristics, admission and definite diagnosis, body mass index, medical history and treatment indication, fosfomycin dose, duration and dosing schedule, pathogens isolated, susceptibility pattern and resistant status, diagnostic methods concerning infection, relevant concomitant diseases and risk factors, laboratory parameters, concomitant antimicrobial agents and duration of hospital stay. No intervention was performed.

Evaluation of the Relationship of EDs to IV Fosfomycin

The process for evaluating EDs was as follows:

- EDs were defined as the presence of at least two consecutive readings outside the usual range. In this study, the detection of hypernatremia and/or hypokalemia was also defined as ED.
- The resolution of EDs was ascertained when two consecutive normal values were observed.
- Information resources such as the drug package insert UpToDate® (Wolters Kluwer Health Inc., 2023), Micromedex® Drug Information (Merative™), and Sanford Guide to Antimicrobial Therapy were utilized to evaluate the appropriateness of IV fosfomycin infusion solutions, dosage, and potential side effects.
- The study utilized the Naranjo adverse drug reaction probability scale (NADRPS) to assess the correlation between EDs and patients receiving IV fosfomycin. NADRPS consists of 10 questions answered as "yes", "no" or "I don't know". Each answer is assigned different point values (-1,0, +1 or +2). Total scores range from -4 to +13: if the score is nine or higher, the reaction is considered definite; if it is 5 to 8, it is considered probable; if it is 1 to 4, it is possible; and if it is 0 or less, it is considered doubtful (23). While NADRPS provides a structured causality assessment tool, it is not fully optimized for multifactorial adverse effects like EDs in critically ill patients. Results should therefore be interpreted with this limitation in mind.

Hypernatremia is classified as mild (146-149 mmol/L), moderate (150-169 mmol/L) and severe (≥170 mmol/L) (24). Hypokalemia is classified as mild (3-3.4 mmol/L), moderate (2.5-3 mmol/L), and severe (<2.5 mmol/L) (25). Laboratory reference ranges of electrolytes were the same in all places where the study was conducted.

Definitions

Clinical success was defined as either clinical cure or clinical improvement. Microbiological success was defined as the eradication of the underlying pathogen. Clinical cure was defined as the resolution of signs and symptoms of infection and/or no additional antibiotic therapy necessary. Clinical improvement was defined as improvement of signs and symptoms of infection and/or administration of additional antibiotic therapy.

Statistical Analysis

Descriptive statistics, including mean, median, standard deviation, interquartile range (IQR), count, and percentages, were used to summarize continuous variables. For categorical variables, frequencies and percentages were given. The Kolmogorov-Smirnov test examined continuous variable normality and identified a non-parametric distribution. Mann-Whitney U tests were used for continuous variables to compare groups, whereas chi-square tests were used for categorical data. Statistical significance was determined using a 95% confidence interval (CI) and p-value <0.05. ED risk variables were evaluated, and odds ratios (OR) (95% CI, p-value) were provided. The full dataset was processed using IBM SPSS Statistics for Windows, Version 29.0 (Armonk, New York: IBM Corp.).

Results

A total of 60 patients were initially followed during the study period. However, 6 patients were excluded due to incomplete follow-up data or missing clinical information. Consequently, 54 patients who met the inclusion criteria and had complete data were enrolled in the final analysis (Figure 1). The median age (IQR) was 60 (35-73) years, and 68.5% of the patients were male. Most were admitted to the intensive care unit (ICU) (38.8%) or the infectious diseases department (25.9%). Demographic characteristics are summarized in Table 1.

Most culture samples were obtained from wound sites (40.7%). The predominant pathogens identified were *Acinetobacter baumannii (A. baumannii)* (38.9%) and *Klebsiella pneumoniae*

(*K. pneumoniae)* (27.8%). A total of 92.6% of patients received at least one additional antibiotic alongside IV fosfomycin. Common combinations included meropenem (25.9%) and meropenem with polymyxin E (16.7%). Culture results and antibiotic use are presented in Table 2. In 18 patients, the cultured pathogens could not be eradicated. These included *A. baumannii* (n=8), *K. pneumoniae* (n=3), *Proteus* species (n=3), and other organisms (n=4). Among these, ESBL plus carbapenem-resistant (CR) was identified in *A. baumannii* (7/8 patients) and *Proteus* spp. (2/3 patients). No resistance was found in 2 out of 3 non-eradicated *K. pneumoniae* isolates.

The median (IQR) IV fosfomycin dose was 12 g (12-18), with a mean treatment period of 13.2±7.2 days. The average daily dose in ICU patients (11.9±4.3 g) was higher than the dose used in other ward patients (10.3±4.5 g) (p=0.209). Hypernatremia developed in 10 patients (18.5%), while hypokalemia occurred in 28 patients (51.8%). After IV fosfomycin treatment, hypernatremia occurred in 2.8±2.4 days and hypokalemia at 2.7±2.0 days. Hypernatremia was observed at mild (6,60%) and moderate (4,40%) levels. Hypokalemia was observed at mild (20,71.4%), moderate (6,21.4%) and severe (2,7.1%) levels. While no patients were terminated IV fosfomycin treatment due to hypernatremia, two patients (7.1%) were stopped it due to hypokalemia, as seen in Table 3. For hypernatremia, the median Naranjo score was 4 (IQR: 3-4.5), indicating a possible relationship. For hypokalemia, the median Naranjo score was 4 (IQR: 4-5), corresponding to a possible-probable association.

Hypokalemia was considerably lower in those discharged versus those who died (38.4% vs. 69.4%, respectively, p=0.016). Patients with ESBL-positive infections had a greater risk of hypokalemia than those with negative (63.4% vs. 30.7%, respectively, p=0.04). The incidence of hypernatremia was significantly higher among patients with hypokalemia than among those without hypokalemia (90% vs. 46.1%, p=0.013). The rate of hypernatremia development in patients admitted to the ICU was substantially greater than in patients admitted to other wards (90% vs. 45.2%, respectively, p=0.002) (Table 4).

The incidence of EDs was found to be statistically significantly greater in patients who died (76% vs. 34.4%, p=0.002), patients with ESBL-positive infections (63% vs. 31.2%, p=0.032), and patients with positive fluid balance at the start of IV fosfomycin treatment (70.5% vs. 30.7%, p=0.03) than in other patients. The mortality rate was significantly higher among patients with EDs, with an OR of 6.25 (95% CI: 1.82-20, p=0.002), compared to those without EDs. Furthermore, the presence of ESBL (+) and positive fluid balance were associated with an increased risk of EDs, with respective OR of 3.77 (95% CI: 1.09-

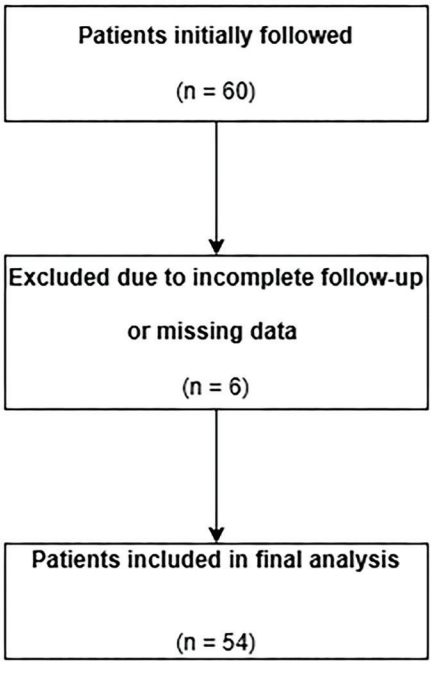

Figure 1. Study flowchart

Table 1. Socio-demographic characteristics of the patients

Variable	n=54
Age, median (IQR)	60 (35-73)
Sex, n (%)	
Male	37 (68.5)
Female	17 (31.5)
Body mass index, median (IQR)	25.37 (23.12-26.66)
Patient's hospitalization service, n (%)	
Intensive care unit	21 (38.8)
Infection diseases	14 (25.9)
Internal medicine service	6 (11.1)
Orthopedics	4 (7.4)
Other	9 (16.8)
Comorbidities*, n (%)	
Diabetes mellitus	19 (23.4)
Hypertension	12 (14.8)
Coronary artery disease	4 (4.9)
Dementia	4 (4.9)
Cerebrovascular accident	4 (4.9)
Chronic kidney disease	3 (3.7)
Atrial fibrillation	3 (3.7)
Heart failure	2 (2.4)
Other	30 (37)
Total length of stay (days), median (IQR)	29.5 (14.75 -49.25)
Discharge status, n (%)	
Discharged	29 (53.7)
Death	25 (46.3)
Renal status, n (%)	
Normal (eGFR >60 mL/min/m^2)	33 (61.1)
Decreased eGFR (eGFR <60 mL/min/m^2)	18 (33.3)
Hemodialysis	3 (5.6)

*: The patients had more than one comorbidity, eGFR: Estimated glomerular filtration rate, IQR: Interquartile range

Table 2. Distribution of clinical and microbiological characteristics of the patients

Variable	n=54
Culture sample location/site of infection, n (%)	
Deep tracheal aspirate	16 (29.6)
Urine	11 (20.4)
Blood	2 (3.7)
Wound	23 (40.7)
Catheter	3 (5.8)
Pathogens, n (%)	
Acinetobacter baumanii	21 (38.9)
Klebsiella pneumoniae	15 (27.8)
Pseudomonas aeruginosa	3 (5.6)
Acinetobacter baumanii + Klebsiella pneumoniae	3 (5.6)
Klebsiella pneumoniae + Pseudomonas aeruginosa	3 (5.6)
Proteus sp.	5 (9.3)
Proteus sp.*+ Klebsiella pneumoniae*	2 (3.7)
Corynebacterium striatum	1 (1.9)
Escherichia coli + Proteus sp.	1 (1.9)
Resistance status of pathogens*, n (%)	
ESBL, yes	38 (70.4)
CR, yes	35 (64.8)
ESBL + CR	30 (55.5)
None	11 (20.3)
Antibiotics used in combination with fosfomycin, n (%)	
Meropenem	14 (25.9)
Polymyxin E	5 (9.3)
Meropenem + polymyxin E	9 (16.7)
Tigecycline	3 (5.6)
Meropenem + tigecycline	2 (3.7)
Amikacin	1 (1.9)
Meropenem + amikacin	1 (1.9)
Tigecycline + polymyxin E	4 (7.4)
Piperacillin-tazobactam	1 (1.9)
Imipenem	2 (3.7)
Ceftazidime-avibactam	3 (3.7)
None	4 (7.4)
Other	5 (9.5)
Eradication status (microbiological success), n (%)	
Yes	36 (66.6)
Clinical efficacy status, n (%)	
Clinical cure	23 (42.5)
Clinical improvement	18 (33.3)
Failure	13 (24.2)

*: Patients have more than one pathogen and resistance mechanism, CR: Carbapenem-resistant enterobacterales, ESBL: Extended-spectrum beta-lactamases

13.10, p=0.032) and 5.40 (95% CI: 1.12-26.04, p=0.03) (Table 5). There is no significant difference in EDs between patients hospitalized in the ICU and those treated elsewhere (62.5% and 46.6%, respectively, p=0.246).

Although the IV fosfomycin dose and treatment time did not show any notable variation in the treatment of ESBL-positive bacteria, a significant disparity was observed in the usage of additional antibiotics. The rate of administering at least one

Table 3. Distribution of information regarding intravenous fosfomycin treatment

Variable	n=54
IV fosfomycin dose (g), median (IQR)	12 (12-18)
IV administration time (minute), median (IQR)	120 (60-120)
Total treatment time (days), mean ± SD	13.2±7.2
Has hypernatremia occurred? n (%)	
Yes	10 (18.5)
No	44 (41.5)
On what day after treatment did hypernatremia occur? mean (± SD)	2.8±2.4
Has hypernatremia been treated? n=10, (%)	
Yes	3 (30)
No	7 (70)
Has fosfomycin treatment been stopped due to hypernatremia? n=10, (%)	
Yes	0 (0)
No	10 (100)
Naranjo score for hypernatremia-fosfomycin, n=10, (%)	
Doubtful	1 (10)
Possible	7 (70)
Probable	2 (20)
Has hypokalemia occurred? n (%)	
Yes	28 (51.8)
No	26 (48.2)
On what day after treatment did hypokalemia occur? mean (± SD)	2.7±2.0
Has hypokalemia been treated? n=28, (%)	
Yes	13 (46.4)
No	15 (53.6)
Has fosfomycin treatment been stopped due to hypokalemia? n=28, (%)	
Yes	2 (7.1)
No	26 (92.9)
Naranjo score for hypokalemia- fosfomycin, n=28, (%)	
Doubtful	2 (7.2)
Possible	13 (46.5)
Probable	13 (46.4)

IQR: Interquartile range, IV: Intravenous, SD: Standard deviation

additional antibiotic was (64.8% vs. 27.7%, p=0.032) in ESBL-positive and ESBL-negative individuals, respectively.

There were no differences between patients' EDs and variables such as IV fosfomycin doses, administration time, treatment duration, hospital stay length, number of additional antibiotics, or baseline sodium and potassium levels (p>0.05). Furthermore, the daily sodium and potassium meq loads estimated across all treatments received by the patients did not alter their ED status (p>0.05).

Table 4. Statistical analysis of parameters associated with electrolyte disorders

Variable		p-value
	Hypokalemia (%)	
Discharge status		0.016
Discharged	38.4	
Death	69.4	
ESBL-positive		0.04
Yes	63.4	
No	30.7	
	Hypernatremia (%)	
Patient's hospitalization service		0.002
Intensive care unit	90	
Other	45.2	
Hypokalemia		0.013
Yes	90	
No	46.1	
	Total electrolyte disorders (%)	
Discharge status		0.002
Discharged	34.4	
Death	76	
ESBL-positive		0.03
Yes	63	
No	31.2	
Fluid balance at the start of IV fosfomycin		0.03
Positive	70.5	
Other	30.7	
Patients' hospitalization service		0.246
Intensive care unit	62.5	
Other	46.6	

ESBL: Extended-spectrum beta-lactamases, IV: Intravenous

Table 5. Factors associated with electrolyte disorders (odds ratios from logistic regression)

Risk factors	OR (95% CI)	p-value
Death	6.25 (1.82-20)	0.002
ESBL (+)	3.77 (1.09-13.10)	0.032
Positive fluid balance at the beginning of fosfomycin treatment	5.40 (1.12-26.04)	0.03

CI: Confidence interval, ESBL: Extended-spectrum beta-lactamases, OR: Odds ratio

Discussion

In this study, we addressed the prevalence and risk factors for EDs in patients receiving IV fosfomycin in a variety of medical settings, with a focus on ICUs. Additionally, we evaluated pathogen resistance profiles, the usage of additional antibiotics concomitantly with IV fosfomycin, and the efficiency of targeted organism eradication.

Resistance and Eradication Status of Targeted Organisms

Fosfomycin exhibits a notable attribute in its efficacy against ESBL-producing *Escherichia coli (E. coli)* and ESBL + CR *K. pneumoniae*, as demonstrated in numerous recent studies (26). Conversely, including IV fosfomycin as part of the combination regimen for treating *A. baumannii* showed a trend toward a more favorable microbiological response and reduced mortality (19,27,28). A study evaluating the efficacy and safety of IV fosfomycin in treating difficult-to-treat resistant Gram-negative infections, particularly UTIs (56.7%), identified *K. pneumoniae* (56.7%) and *E. coli* (23.3%) as the most prevalent target organisms. In most cases (76%), IV fosfomycin was used in combination with other antimicrobial agents. Clinical improvement was achieved in 73.3% of patients, and eradication of the initial infections occurred in 66.7% (29). In another study focusing on cases of CR *K. pneumoniae* and *E. coli*, a 91% success rate was attained in eradicating the bacteria (30). As observed in this study, the situation was similar to previous studies, suggesting that the effectiveness of fosfomycin in combination with other antimicrobial agents could be increased (4,11,14).

The current study used IV fosfomycin in conjunction with other antibiotics to treat wound infections, deep tracheal aspirates, and UTIs caused by *A. baumannii* and *K. pneumoniae*. Furthermore, roughly 80% of these pathogens possess at least one resistance mechanism, such as ESBL or CR. Therefore, more than 90% of patients received IV fosfomycin in addition to another antibiotic. This study supports previous studies on the effectiveness and safety of IV fosfomycin in combined regimens for treating antibiotic-resistant infections (11,17,19,28,29,31). Compared to other studies, this one found a somewhat lower eradication rate of *A. baumannii* when using a fosfomycin combination

regimen (19,27,28). This finding may reflect the inherent treatment challenges associated with multidrug-resistant *A. baumannii* infections. However, no microbiological resistance profiling was conducted to confirm specific mechanisms in this study. IV fosfomycin appeared to provide more successful results, especially in *E. coli* and *K. pneumoniae* cases. Meanwhile, variations in the target organisms, treatment dosages, hospitalization status (ICUs or other services), and existence of infections with various resistance mechanisms could account for differences in eradication and microbiological cure rates across studies (11,17,19,28,29,31).

IV Fosfomycin Dose and Duration of Administration

Studies recommend a daily dose of 12-24 g of IV fosfomycin, administered in 2 to 4 divided doses (6,10,13,32). It can also be administered via continuous infusion at daily doses ranging from 8 to 32 g (26,33). In a study focusing on CR *K. pneumoniae* and *E. coli* cases, daily IV fosfomycin doses of 16-24 g were used (30). Temoçin et al. (17) reported that the average daily IV fosfomycin dose was 13.11±4.4 g. The total daily dose was observed to be higher in ICU patients compared to those in general wards. Studies using IV fosfomycin in combination regimens for resistant pathogens employed doses similar to those in the current study (11,17). However, average IV fosfomycin doses varied across studies—either lower or higher than in this study—depending on factors such as pathogen resistance profile, infection site and severity, treatment duration, and whether patients were hospitalized in the ICU or other wards (6,10,14,19,29,30).

Similar to dosing, treatment durations with IV fosfomycin in this study are consistent with those reported in the literature (11,19). In a similar ICU-based study, Zirpe et al. (10) reported an average treatment duration as short as four days, which contrasts with established durations. However, the resistance mechanisms of the pathogens were not specified, as noted in the study's limitations. Likewise, Temoçin et al. (17) reported an average treatment duration of eight days. In their study, which included a population primarily with *K. pneumoniae* UTIs, the resistance status of the target organisms was not specified. This lack of data limits the ability to compare the impact of resistance mechanisms on treatment duration. Although the targeted pathogens were appropriate for IV fosfomycin treatment, resistance mechanisms may have contributed to shorter treatment durations. In the present study, the presence of resistant pathogens in most patients necessitated prolonged and high-dose IV fosfomycin regimens.

IV Fosfomycin-induced Hypernatremia-hypokalemia and Risk Factors

In previous studies investigating IV fosfomycin use, the incidence rates of hypernatremia (23.3-41.9%) and hypokalemia (28.57-43.3%) have varied, though they remain common findings (17,22,29,34). However, Michalopoulos et al. (6) reported no fosfomycin-associated side effects in their study. Despite potential side effects, IV fosfomycin has generally been considered a safe treatment option. Most studies have described its adverse effects as mild to moderate, non-serious, and reversible (35). These side effects rarely lead to discontinuation of therapy (29,31,36). Nevertheless, some cases have reported treatment cessation due to hypernatremia (11,15,18,37). In the present study, IV fosfomycin was discontinued in two patients due to non-severe hypokalemia. The variability in adverse event rates across studies may be due to differences in laboratory reference ranges, electrolyte monitoring frequency, and ICU patient populations (38).

Importantly, most previous studies did not use a formal causality assessment scale to evaluate the association between IV fosfomycin and adverse effects (6,10,11,17,22,29,34). For example, Putensen et al. (11) suspected a link between fosfomycin and adverse events in 22 patients (10.5%) and documented hypokalemia in five cases (2.4%). In contrast, our study used NADRPS, which revealed a strong association between EDs and IV fosfomycin. Although the Naranjo scale added structure to our assessment, it is important to acknowledge that EDs in ICU patients are often multifactorial. As such, the limitations of NADRPS in this complex setting should be considered. Moreover, although we recorded the timing of ED onset, we did not correlate this with pharmacokinetic variables such as drug serum levels or dosing intervals. Future studies using time-to-event analyses and dose-response models are warranted.

Multiple studies have identified dysnatremia as the most common ED among ICU patients (39-43). In our study, hypernatremia frequently co-occurred with hypokalemia. Putensen et al. (11) found this co-occurrence in only four patients. We also observed that hypernatremia was significantly more common among ICU patients than among those in general wards. EDs due to IV fosfomycin developed within approximately two days in our cohort, which was shorter than the four-day onset reported by Sürmelioğlu et al. (22). Stelfox et al. (40) reported a similar two-day onset in the ICU setting. These findings suggest that electrolyte monitoring should begin promptly after initiating IV fosfomycin therapy.

Most patients in our study were ICU patients, and mortality was 6.25 times higher among those who developed EDs. Multiple non-drug-related factors influence ED development in the ICU, many of which are highly prevalent (40-42). Previous studies have shown that EDs are independently associated with poor prognosis and increased mortality in critically ill patients (40,43). While the observed association between EDs and increased mortality (OR: 6.25) is clinically significant, this finding should be interpreted cautiously. The relationship may reflect underlying disease severity rather than a direct causal effect. Confounding by indication and severity of illness are likely contributing factors. In our cohort, the primary causes of death included septic shock, respiratory failure, and multiorgan dysfunction, consistent with severe underlying infections. While EDs were not the direct cause of death in any patient, they may have contributed to clinical deterioration in critically ill individuals. Given the multifactorial nature of EDs and mortality in ICU settings, distinguishing causality is challenging; however, the strong statistical association suggests that EDs may serve as markers of poor prognosis in this population (39,40,44).

Treatment of ESBL-producing pathogens with higher doses of IV fosfomycin, which contains significant sodium content, may further elevate the risk of hypokalemia and hypernatremia (11,20,22). Our data show that patients with ESBL-positive infections had significantly higher odds of developing hypokalemia (OR: 3.77; 95% CI: 1.09-13.10; p=0.032). This observation may reflect the increased severity of illness and higher antibiotic burden typically associated with ESBL-positive infections. Patients infected with ESBL-producing organisms are more likely to have prolonged hospital stays, receive combination antimicrobial therapies, and experience fluid-electrolyte imbalances due to their complex clinical course. Therefore, the observed association might be driven more by infection severity than by ESBL status alone. The rate of additional antibiotic utilization was seen to be markedly greater in the management of ESBL-positive pathogens as opposed to negative ones. Hypokalemia is thought to result primarily from increased renal potassium loss induced by IV fosfomycin, particularly when infused over less than four hours (9,11,22). Additionally, patients with positive fluid balance may be more prone to dilutional hypokalemia. A key finding of this study was that positive fluid balance increased the odds of EDs by 5.40. All patients in our cohort received fosfomycin via short-term infusions, which may explain the higher hypokalemia incidence compared to other studies (11,17,22,29,34). The underlying mechanism likely involves osmotic diuresis induced by high sodium content in fosfomycin formulations, leading to increased renal potassium excretion. Sodium-induced volume expansion may also enhance urinary potassium loss, especially with short-term infusions. Nevertheless, the exact pharmacokinetic dynamics remain to be clarified. Regardless of these mechanisms, EDs are consistently more prevalent in ICU patients than those in general wards. This can be attributed to multiple factors such as underlying organ dysfunction, use of nephrotoxic and diuretic medications, frequent fluid shifts, nutritional support, and the overall complexity of ICU care. In addition, polypharmacy and high-dose antimicrobial regimens—common in this setting—may further exacerbate EDs. These factors, combined with fosfomycin's sodium load and renal potassium excretion effects, likely contribute to the high baseline ED rates observed in ICU patients (39-41,43,45). A recent multicenter study from Türkiye also demonstrated the multifactorial nature of drug-induced EDs in ICUs and supports our findings (39). Furthermore, a significant association has been established between EDs and mortality in hospitalized patients (15,40-42).

Hypernatremia related to IV fosfomycin can often be managed by adjusting co-administered drugs, changing the diluent solution, and increasing maintenance fluids to improve fluid balance (17,18). Sürmelioğlu et al. (22) identified enteral nutrition and albumin supplementation as additional risk factors for fosfomycin-induced hypernatremia. While hypernatremia has been attributed to fosfomycin's high sodium content, the exact pathophysiological mechanism remains unclear (4,9-11,14-18,22). Shorr et al. (14) emphasized that prolonged or high-dose fosfomycin use may increase hypernatremia risk. Notably, our study found no direct association between the sodium load of IV fosfomycin and the development of hypernatremia. Neither the dose nor the duration of fosfomycin administration had a significant effect on ED incidence. This raises the possibility that factors other than sodium content may be involved in the development of hypernatremia associated with IV fosfomycin use. In our study, IV fosfomycin was administered as part of combination therapy in more than 90% of cases. The most common co-administered antibiotics were meropenem and polymyxin E. Although these agents are not typically associated with high rates of EDs, the cumulative effect of multiple nephrotoxic and electrolyte-altering agents—especially in critically ill patients—should not be underestimated. Clinicians should consider the overall risk profile of combination regimens when initiating fosfomycin-based therapies.

Based on our findings, we recommend initiating close electrolyte monitoring protocols during IV fosfomycin therapy, particularly within the first 48 hours. Prolonging infusion time and adjusting fluid composition may help mitigate EDs. Prospective studies comparing different infusion durations and evaluating multivariate risk prediction models would help refine clinical guidelines.

Study Limitations

This study has several limitations that should be acknowledged. First, the relatively limited clinical use of IV fosfomycin in Türkiye resulted in a modest sample size. Although the inclusion of 54 patients was deemed sufficient based on post-hoc calculations to estimate the prevalence of hypokalemia with acceptable confidence, the sample size was not adequate to support multivariable regression modeling. Therefore, all presented associations are unadjusted and potentially subject to residual confounding from factors such as age, comorbidities, renal function, and ICU admission.

Second, the study population was clinically heterogeneous, comprising patients from various departments including intensive care, internal medicine, infectious diseases, and orthopedics. Due to the limited sample size, stratified analyses by hospital ward or treatment indication could not be conducted, which restricts the generalizability of the findings across different patient subgroups. Furthermore, as this was not a randomized controlled trial, causal inferences should be made with caution.

Despite these limitations, the study has important strengths. It is one of the few prospective, multicenter investigations to evaluate EDs associated with IV fosfomycin. The use of NADRPS provided a structured approach to causality assessment, which is rarely implemented in studies of this nature. Additionally, by including patients from diverse clinical settings, the study offers a broad overview of fosfomycin use in real-world hospital practice, contributing meaningful data to the limited safety literature on this agent.

Conclusion

IV fosfomycin appears to be a generally safe and effective option for treating multidrug-resistant infections, particularly when

used in combination with other antibacterial agents. However, clinicians should be aware that EDs, especially hypokalemia and hypernatremia, are relatively common adverse effects. These disorders are more frequently observed in ICU patients and may be influenced by factors such as pathogen resistance profiles, positive fluid balance, and mortality-related complications. Awareness of these risks is critical to ensure safe prescribing practices. Close electrolyte monitoring and individualized fluid management strategies are recommended to minimize adverse outcomes during IV fosfomycin therapy.

Ethics

Ethics Committee Approval: The study received ethical approval from the Clinical Research Ethics Committee of Marmara University (decision no: 09.2023.22, date: 03.02.2023).

Informed Consent: Written informed consent was obtained from all participants.

Footnotes

Authorship Contributions

Concept: Y.E.A., C.Ç., N.A., Ö.F.Ö., M.S., Design: Y.E.A., C.Ç., N.A., Data Collection or Processing: Y.E.A., C.Ç., Ö.F.Ö., B.D., R.Ş., Ö.A., B.E., Z.Ü.G., Analysis or Interpretation: Y.E.A., C.Ç., N.A., Literature Search: Y.E.A., C.Ç., N.A., Writing: Y.E.A., C.Ç., N.A., M.S.

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Original Article

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Protective Factors Against Breast Cancer Development: A Retrospective Study on Breastfeeding and Fertility

Meme Kanseri Gelişimine Karşı Koruyucu Faktörler: Emzirme ve Doğurganlık Üzerine Retrospektif Bir Çalışma

Nursena ÇİFLİK[1], Rümeysa YEGİN[2], Aeisha AHMED[2], Nushaba ABBASOVA[2], Duygu GEDİK[1], Hüseyin TEPETAM[1], Şule KARABULUT GÜL[1]

[1]University of Health Sciences Türkiye, Kartal Dr. Lütfi Kırdar City Hospital, Department of Radiation Oncology, İstanbul, Türkiye
[2]University of Health Sciences Türkiye, Hamidiye Faculty of Medicine, İstanbul, Türkiye

ABSTRACT

Objective: Breast cancer (BC) is the most common type of cancer among women. Various risk and protective factors play a role in its development. This study evaluates the association between parity, breastfeeding, and age at BC diagnosis among women with BC.

Methods: Between January 2016 and December 2023, data from follow-up records of 1,014 patients diagnosed with BC and admitted to our hospital's radiation oncology clinic for radiotherapy treatment were analyzed. The collected data were statistically analyzed using Microsoft Access and SPSS 25.0.

Results: When patients with BC were grouped into those under and over the age of 55, a significant association was found between parity and later age at BC diagnosis (odds ratio: 2.02, 95% confidence interval: 1.29-3.16; p<0.002). When the number of live births was evaluated, having more than one live birth was associated with a later age at BC diagnosis (p<0.001). Regarding breastfeeding status, the proportion of patients diagnosed with BC under the age of 55 was 70.4% in the non-lactation group, whereas this rate was approximately 55.1% in the lactation group. This finding suggests that lactation may contribute to delaying the age of BC diagnosis (p<0.001).

ÖZ

Amaç: Meme kanseri (MK), kadınlar arasında en sık görülen kanser türüdür. Hastalığın gelişiminde birçok risk faktörü ve koruyucu faktör rol oynamaktadır. Bu çalışma, MK olan kadınlarda parite, emzirme ve MK tanı yaşı arasındaki ilişkiyi değerlendirmektedir.

Yöntemler: Ocak 2016 ve Aralık 2023 tarihleri arasında, hastanemiz radyasyon onkolojisi kliniğine MK tanısı ile radyoterapi tedavisi için başvuran 1.014 hastanın takip dosyalarındaki veriler incelenmiştir. Elde edilen veriler, Microsoft Access ve SPSS 25.0 programları kullanılarak istatistiksel analizlere tabi tutulmuştur.

Bulgular: MK tanısı alan hastalar, 55 yaş altı ve üstü olarak gruplandırıldığında, gebelik oranları karşılaştırılmış ve gebelik lehine anlamlı bir fark bulunmuştur (olasılık oranı: 2,02, %95 güven aralığı: 1,29-3,16; p<0,002). Gebelik sayıları değerlendirildiğinde, birden fazla çocuk sahibi olmanın MK tanısının daha ileri bir yaşta konulmasıyla ilişkili olduğu saptandı (p<0,001). Emzirme durumuna göre yapılan incelemede, laktasyon olmayan hasta grubunda 55 yaş altı MK görülme oranı %70,4 iken, laktasyon öyküsü olan grupta bu oran yaklaşık %55,1 olarak saptanmıştır. Bu bulgu, emzirmenin MK tanı yaşını geciktirici bir etkiye sahip olabileceğini göstermektedir (p<0,001).

Address for Correspondence: Assoc. Prof. Şule Karabulut Gül, University of Health Sciences Türkiye, Kartal Dr. Lütfi Kırdar City Hospital, Department of Radiation Oncology, İstanbul, Türkiye
E-mail: sulegul2003@yahoo.com
ORCID IDs of the authors: N.Ç.: 0009-0009-9972-5872, R.Y.: 0009-0001-9479-0298, A.A.: 0009-0009-3671-6952, N.A.: 0009-0002-4123-4906, D.G.: 0000-0001-6125-4969, H.T.: 0000-0002-6571-4114, Ş.K.G.: 0000-0003-4219-8900

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ABSTRACT

Conclusion: BC is a multifactorial disease with an increasing incidence. Our study demonstrates that parity and breastfeeding are significantly associated with the age at BC diagnosis. These findings should be interpreted as associations within a BC cohort rather than direct estimates of BC risk Future research will help to further explore these interactions in greater detail.

Keywords: Breast cancer, age at diagnosis, parity, breastfeeding

ÖZ

Sonuç: MK, birçok faktörün etkilediği kompleks bir hastalıktır ve görülme sıklığı giderek artmaktadır. Çalışmamız, gebelik sayısı ve emzirmenin, MK tanı yaşı ile anlamlı şekilde ilişkili olduğunu göstermektedir. Bu bulgular, MK riskini doğrudan yansıtmak yerine, MK tanısı almış hasta grubundaki ilişkileri göstermektedir. Gelecekteki araştırmalar, bu etkileşimlerin daha ayrıntılı bir şekilde incelenmesine katkı sağlayacaktır.

Anahtar Kelimeler: Meme kanseri, tanı yaşı, parite, laktasyon

Introduction

Breast cancer (BC) is the most common malignant tumor among women and the second most frequently diagnosed cancer worldwide (1,2). It is estimated that 2.3 million new cases occur annually, making it the fourth leading cause of cancer-related death globally (3).

Despite the increased availability of screening programs and advances in treatment, the incidence of BC continues to rise. This trend has been attributed to factors such as improved living standards, the use of hormone replacement therapy, and lower parity rates, particularly in developing countries (4,5).

Various reproductive (e.g., early menarche, nulliparity, hormone use, parity, and breastfeeding) and anthropometric (e.g., height, weight, waist circumference) factors have been identified as influencing the risk of BC development (6-9). Parity, defined as the number of live births, and breastfeeding, which is considered a significant protective factor, are of particular interest due to their hormonal impact on breast tissue. This study aims to highlight the significance of lactation and parity among known risk factors and to investigate their association with age at diagnosis among women diagnosed with BC.

Methods

This retrospective study included 1014 patients who were presented to our clinic between January 2016 and December 2023, were diagnosed with BC and received radiotherapy. Data were collected on patients' age at diagnosis, age at menarche and menopause, lactation history, smoking and alcohol use, hormone replacement therapy, comorbidities, and genetic background. These data were obtained from outpatient follow-up records.

Approved by Clinical Research Ethics Committee of University of Health Sciences Türkiye, Kartal Dr. Lütfi Kırdar City Hospital (approval no: 2024/010.99/2/38 date: 27.03.2024).

Statistical Analysis

Statistical analyses were conducted using Microsoft Access (Microsoft Corp., Redmond, WA, USA) for data management and SPSS version 25.0 (SPSS Inc., Chicago, IL, USA) for statistical testing. Odds ratios (OR) and 95% confidence intervals (CIs) were calculated to assess associations between reproductive factors and age at BC diagnosis. The chi-square test was used for categorical data analysis.

Parity was recorded based on the number of live births. Breastfeeding status was evaluated as a binary variable (yes/no), based on the presence of a history of lactation.

Results

The mean age of all patients diagnosed with BC (n=1.014) was 52 years, while the mean age at diagnosis among the postmenopausal group was 59 years. Table 1 summarizes the distribution of risk factors assessed in patients diagnosed with BC.

Parity and lactation status were compared between patients under and over the age of 55, as well as between premenopausal and postmenopausal groups, using chi-square analysis. Regarding breastfeeding, the proportion of patients under 55 who had no history of lactation was 70.4%, whereas this proportion was approximately 55.1 % in the group with a history of lactation (OR: 1.94, 95% CI: 1.35-2.80; p<0.001) (Table 2); additionally,

Table 1. Distribution of risk factors in patients diagnosed with breast cancer (n=1,014)

Risk factor	Category	n (%)
Age	≥55	429 (42.4)
	<55	585 (57.6)
Marital status	Single	121 (11.9)
	Married	860 (84.8)
	Widowed	33 (3.3)
Menopausal status	Premenopausal	436 (43.0)
	Postmenopausal	578 (57.0)
Lactation status	Yes	845 (83.3)
	No	169 (16.7)
Smoking	Yes	289 (28.5)
	No	725 (71.5)
Alcohol consumption	Yes	36 (3.6)
	No	978 (96.4)
Hormone replacement therapy	Yes	97 (9.6)
	No	917 (90.4)
Family history (breast cancer in family)	Yes	429 (42.3)
	No	585 (57.7)

Table 2. Analysis of reproductive risk factors in breast cancer patients aged <55 years (n=585) and ≥55 years (n=429)

Lactation			OR (95% CI)	p-value
No	119 (70.4)	50 (29.6)	1.00 Ref.	
Yes	466 (55.1)	379 (44.9)	1.94 (1.35-2.80)	<0.001
Nulliparous	77 (72.0)	30 (28.0)	1.00 Ref.	
Parous (≥1 live birth)	508 (56.0)	399 (44.0)	2.02 (1.29-3.16)	<0.002
Parity				
1-2	345 (70.0)	148 (30.0)	1.00 Ref.	
≥3	240 (46.1)	281 (53.9)	2.73 (2.13-3.50)	<0.001

Outcome: diagnosis age ≥55 (vs <55)
OR: Odds ratio, CI: Confidence interval

lactation status was associated with age at diagnosis when analyzed across menopausal status (p<0.001).

Among postmenopausal patients under 55 years of age, the proportion without lactation was 38.7%, compared to 24.9% among those who had breastfed, indicating a statistically significant difference (p<0.001).

When parity rates were compared between patients diagnosed with BC below and above the age of 55, parity was associated with a significantly later age at BC diagnosis (OR: 2.02, 95% CI: 1.29-3.16; p<0.002). Further analysis showed that having more than one live birth was associated with a later age at diagnosis (p<0.001).

Among patients with a history of three or more live births, 46.1% were diagnosed before the age of 55, whereas this proportion was 70% among those with two or fewer live births (OR: 2.73, 95% CI: 2.13-3.50; p<0.001).

Discussion

One limitation of this hospital-based study is that some responses were based on patient recall, which may have introduced variability in the data. However, as one of the major referral centers for BC cases on the Anatolian side of İstanbul, we believe the findings may be reflective of the broader population in Türkiye.

Previous studies have demonstrated that various factors, including hormones, age, genetic predisposition, and lifestyle, contribute to the incidence of BC (10,11). Age is considered one of the most important risk factors (12,13), with increasing incidence observed as age advances (14,15). McPherson et al. (16) reported that 2 out of every 1,000 women aged 50 were diagnosed with BC, while Vogel (17) found that women over 50 had a significantly higher risk of developing the disease.

Another study analyzed the association between age at diagnosis and relative survival, showing that women aged 45-49 had the best prognosis, with higher survival rates than younger patients (18). In urban areas of India, the highest incidence was observed among women aged 40-49, whereas in rural areas, it was found in the 65-69 age group (19). A study conducted in Northern India reported that 26% of diagnosed patients were under the age of 35 (20). Epidemiological data from the United States (US) have shown an increase in BC incidence among young women in recent years, accompanied by poorer long-term outcomes. These patients are also more likely to face treatment-related complications such as infertility, psychosocial distress, and chronic conditions, emphasizing the need for multidisciplinary and individualized treatment strategies in this population (21).

In our study, the proportion of patients under the age of 55 was relatively high and statistically significant. This may indicate a decreasing age at diagnosis due to improved screening programs or a shift in risk factors associated with developing countries.

In epidemiological studies, lactation is considered a protective factor against BC (22). Consistent with this literature, breastfeeding has been associated with a reduced risk of BC; however, in our cohort, breastfeeding history was associated with a later age at diagnosis rather than direct risk reduction. This finding supports the hypothesis that prolonged and gradual involution following lactation may influence breast tissue remodeling and carcinogenesis. During pregnancy, breast tissue proliferates in preparation for lactation. The filling of alveoli with milk and the subsequent weaning phase trigger breast tissue involution and remodeling. This process is characterized by denser stroma, altered collagen composition, increased inflammation and proliferation, and elevated expression of estrogen and progesterone receptors. When breastfeeding is prolonged and gradually discontinued, the breast undergoes what is referred to as "gradual involution", which may provide additional protection against carcinogenesis (23). These associations may be partly explained by hormonal mechanisms, including prolonged suppression of estrogen exposure during pregnancy and lactation, as well as long-term hormonal differentiation of breast tissue.

In a 2002 study by Collaborative Group on Hormonal Factors in BC, which included 50,302 women diagnosed with invasive BC and 96,973 controls from 30 countries, an inverse relationship was observed between breastfeeding duration and BC risk. The study demonstrated that each year of breastfeeding was associated with a 4.3% reduction in relative BC risk, for both localized and metastatic tumors (24).

A 2023 study by Chen et al. (25) showed that breastfeeding might reduce BC incidence by suppressing oncogene expression in progenitor cells, modulating the cellular microenvironment via calcium, secretory immunoglobulin A, and alpha-lactalbumin, and supporting normal involution processes. Similarly, Ye et al. (26) reported a protective association between breastfeeding and BC risk mediated through decreased breast tissue density. Furberg et al. (23) also found that even limited breastfeeding slightly reduced BC risk among both younger and older parous women. Consistent with these findings, our study demonstrated a significant association between breastfeeding history and earlier vs later age at diagnosis.

Parity is another reproductive factor associated with BC outcomes through hormonal mechanisms. Not only the number of live births but also the exclusivity and duration of breastfeeding contribute to breast tissue remodeling, potentially reducing carcinogenic transformations. Prolonged and exclusive breastfeeding appears to support involution and hormone regulation.

A large national cohort study from Norway investigated the relationship between parity and BC before age 55, finding that early age at first and last birth and high parity were associated with a reduced risk. The protective effect of high parity was most pronounced in women whose first birth occurred before the age of 20, while it was minimal in those who gave birth at or after age 30 (27). A population-based case-control study in Sweden also demonstrated a significant association between higher parity and reduced BC risk (28). Similarly, a Chinese case-control study showed a statistically significant trend of increasing BC risk with decreasing number of full-term pregnancies (29). In a US based population cohort of older women, having five or more live births was found to be protective compared to having only one or two (30).

Study Limitations

One of the potential study limitations is that, due to its retrospective design, there may be missing or inaccurate data in patient records, and bias may arise regarding the accuracy of self-reported information. Additionally, measurement errors may occur in variables such as menopause age and breastfeeding duration. Changes in healthcare policies and screening programs between 2016 and 2023 may have influenced the study results.

Conclusion

BC is a multifactorial disease with a rising incidence worldwide. This study demonstrates that higher parity and a history of breastfeeding are significantly associated with a later age at BC diagnosis. Although causal or risk-reducing effects cannot be inferred due to the retrospective design and the absence of a control group, these findings are consistent with existing epidemiological literature suggesting a potential protective role of reproductive factors. Further prospective, population-based studies are needed to clarify the complex biological mechanisms underlying these relationships.

Ethics

Ethics Committee Approval: Approved by Clinical Research Ethics Committee of University of Health Sciences Türkiye, Kartal Dr. Lütfi Kırdar City Hospital (approval no: 2024/010.99/2/38 date: 27.03.2024).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: H.T., Concept: D.G., Design: Ş.K.G., Data Collection or Processing: A.A., Analysis or Interpretation: N.A., Literature Search: R.Y., Writing: N.Ç.

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Original Article

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Comparison of 17-hydroxyprogesterone Levels in Infants with ELISA and LC-MS/MS Measurement Methods

İnfantlarda 17-hidroksiprogesteron Düzeyinin ELISA ve LC-MS/MS Ölçüm Yöntemleriyle Karşılaştırılması

Nazife DOĞAN, Alper GÜMÜŞ

University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital, Department of Medical Biochemistry, İstanbul, Türkiye

ABSTRACT

Objective: Although enzyme-linked immunosorbent assay (ELISA) is frequently used in the routine measurement of the steroid hormone 17-hydroxyprogesterone (17-OHP) level, there are studies on other methods. In our study, we compared the discordance of 17-OHP level in ELISA with liquid chromatography-tandem mass spectrometry (LC-MS/MS).

Methods: 17-OHP level was serum samples up to 5 months of age at University of Health Sciences Türkiye, Başakşehir Çam and Sakura Hospital between May 1, 2022 and September 10, 2022. One hundred and thirty four sera had 17-OHP level above the reference range measured by ELISA, and 17-OHP level was measured with LC-MS/MS. After examining 17-OHP level in these sera with 2 different measurement methods, the obtained data were statistically analyzed using the SPSS 20.0 software package.

Results: 17-OHP level was detected above the reference range in 134 out of 134 sera (100%) by ELISA. 17-OHP level in 106 (79.1%) of the sera was detected within the reference range by LC-MS/MS. In statistical analysis, comparison of 17-OHP level with 2 different measurement methods was performed by chi-square test. A significant difference ($p<0.0001$) was observed in the 2x2 table in the chi-square test.

Conclusion: ELISA is widely used as a cost-effective method in measuring 17-OHP level, a steroid hormone. Differences that may occur due to the metabolism of 17-OHP in infants may lead to a false increase in ELISA. Due to this increase in routine, a more expensive and sensitive method, LC-MS/MS can also be used. In our study, we emphasized the importance of confirming falsely increased 17-OHP levels measured by ELISA with LC-MS/MS in infants younger than 3 months.

Keywords: Immunoassay, chromatography, infant

ÖZ

Amaç: Steroid hormon olan 17-hidroksiprogesteronun (17-OHP) düzeyinin rutin ölçümünde enzim bağlantılı immünosorbent ölçümü (ELISA) sıklıkla kullanılsa da başka yöntemler üzerinde çalışmalar vardır. Çalışmamızda ELISA'daki 17-OHP'nin ölçüm belirsizliğini sıvı kromatografi kütle spektrometrisi (LC-MS/MS) ile karşılaştırdık.

Yöntemler: 17-OHP düzeyleri, 1 Mayıs 2022 ile 10 Eylül 2022 tarihleri arasında Sağlık Bilimleri Üniversitesi, Başakşehir Çam ve Sakura Hastanesi'nde 0-5 aylık infantların serumunda ölçüldü. 17-OHP düzeyi ELISA ile referans aralığının üzerinde saptanan 134 serumda17-OHP düzeyi LC-MS/MS ile ölçüldü. Bu serumlarda 17-OHP düzeyleri 2 farklı ölçüm yöntemi ile incelendikten sonra elde edilen verilerin SPSS 20.0 yazılım paketi kullanılarak istatistiksel analizi yapıldı.

Bulgular: 17-OHP düzeyini ELISA ile 134 serumun 134'ünde (%100) referans aralığının üzerinde tespit ettik. Aynı örneklerin 106'sında (%79,1) 17-OHP düzeyi LC-MS/MS ile referans aralığında tespit edildi. İstatistiksel analizde 17-OHP'nin 2 farklı ölçüm yöntemi ile karşılaştırılması ki-kare testi ile yapıldı. Ki-kare testinde 2x2 tablosundaki p-değeri için anlamlı bir fark ($p<0,0001$) gözlendi.

Sonuç: Steroid yapıdaki hormonlardan 17-OHP'nin düzeyinin ölçümünde ELISA maliyet-etkin bir yöntem olarak yaygın kullanılmaktadır. İnfantlarda 17-OHP'nin metabolizmasına bağlı oluşabilecek farklılıklar ELISA'da yalancı artışa yol açabilmektedir. Rutindeki bu artmış kullanım nedeniyle daha pahalı ve hassas LC-MS/MS yöntemi de kullanılabilir. Çalışmamızda 3 aydan küçük infantlarda ELISA ile yalancı artmış 17-OHP düzeylerinin LC-MS/MS ile doğrulanmasının önemini vurguladık.

Anahtar Kelimeler: İmmün ölçüm, kromatografi, infant

Address for Correspondence: Nazife Doğan MD, University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital, Department of Medical Biochemistry, İstanbul, Türkiye
E-mail: drnazifedogan@gmail.com
ORCID IDs of the authors: N.D.: 0009-0008-6737-0416, A.G.: 0000-0002-4453-6339

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Introduction

Steroid hormones play crucial roles in processes such as differentiation, development, growth, and various physiological functions in living organisms. These hormones are structurally characterized by the presence of a cyclopentanoperhydrophenanthrene ring. During circulation, steroid hormones bind with high affinity to specific transport proteins, whereas they bind more loosely to non-specific carriers such as albumin. Steroid hormones are synthesized in various tissues including the adrenal cortex, gonads, and placenta. The initial step in their biosynthesis involves the enzymatic conversion of cholesterol to pregnenolone (1).

In the zona fasciculata and zona reticularis of the adrenal cortex, 17 alpha-hydroxylase/17,20-lyase enzyme systems located in the endoplasmic reticulum convert pregnenolone to 17-hydroxypregnenolone. In the zona fasciculata, 3 beta-hydroxysteroid dehydrogenase (3β-HSD) catalyzes the conversion of 17-hydroxypregnenolone to 17-hydroxyprogesterone (17-OHP). This intermediate is subsequently converted into 11-deoxycortisol by the enzyme 21-hydroxylase (21-OH). Finally, 11 beta-hydroxylase, a mitochondrial enzyme, catalyzes the formation of cortisol from 11-deoxycortisol (1,2).

During fetal life and the early postnatal period, serum 17-OHP levels are elevated. These levels gradually decline in both sexes until puberty. 17-OHP secretion exhibits a diurnal rhythm, with peak levels occurring in the early morning hours. Additionally, ovarian secretion of 17-OHP increases during the luteal phase of the menstrual cycle. The most common pathological cause of elevated 17-OHP levels is 21-OH deficiency, which underlies most cases of congenital adrenal hyperplasia (CAH). Therefore, 17-OHP measurement is essential in the diagnosis and monitoring of CAH and other disorders involving mineralocorticoid and androgen synthesis (2,3) (Figure 1).

In cases of CAH, which is an autosomal recessive disease group, genetic 46,XX and complete androgen insensitivity 46,XY can be observed. With an incidence of approximately 1 in 15,000 live births and a carrier rate of 1 in 60, CAH is the most common cause of ambiguous external genitalia in neonates. 21-OH deficiency accounts for 90-95% of CAH cases (4). Depending on the degree of enzymatic deficiency, CAH is classified into classical and non-classical forms. The classical form includes the salt-wasting and simple virilizing types. The salt-wasting form may present with hypovolemia, shock, and death, whereas adrenal crisis is not typically observed in the simple virilizing type. In contrast, the non-classical form often presents with mild symptoms and may not be recognized until later in life. Accurate classification of CAH subtypes is crucial for prenatal diagnosis and therapeutic decision-making. In newborn screening (NBS) programs, 17-OHP levels are measured in heel-prick blood samples. This screening is particularly valuable for early diagnosis in salt-wasting males, non-symptomatic males, and severely virilized females who may be misidentified as male at birth (5).

Elevated 17-OHP levels are also observed in 11 beta-hydroxylase and 3β-HSD deficiencies (2,3). However, transient elevations of 17-OHP can occur in preterm infants, those with low birth weight, neonatal jaundice, neonatal stress, due to cross-reactivity with conjugated steroid metabolites, low T4 levels, or antenatal corticosteroid exposure. Accurate interpretation of these transient elevations is essential to prevent misdiagnosis and unnecessary treatment (6).

Measurement of 17-OHP level can be performed by radioimmunoassay (RIA) and high-performance liquid chromatography (HPLC) after extraction from serum or plasma. In liquid chromatography-tandem mass spectrometry (LC-MS/MS), extraction is performed with the addition of an internal standard such as d8-17-OHP. In enzyme-linked immunosorbent assay (ELISA), enzymes like alkaline phosphatase or horseradish

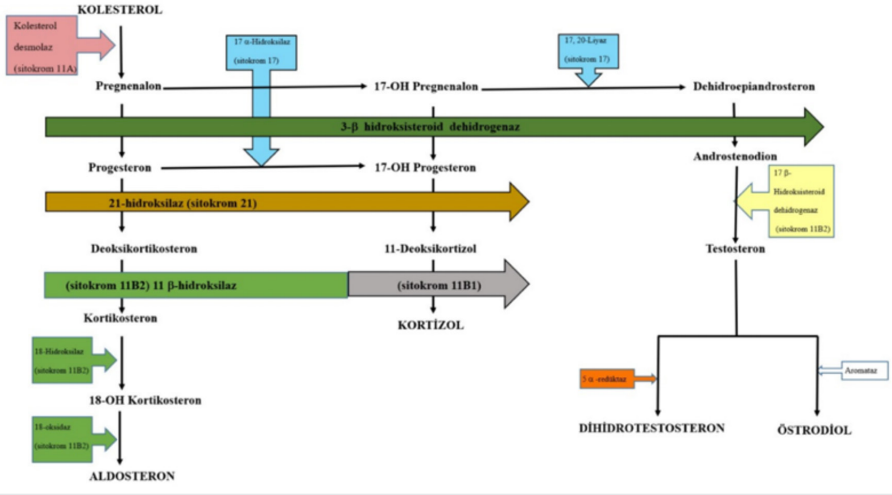


Figure 1. Adrenal cortical hormone biosynthesis pathway

OH: Hydroxy progesterone

peroxidase bind to specific antigen-antibody complexes and convert substrates into colored products, allowing quantification of 17-OHP in serum or plasma. Although immunoassays such as ELISA rely on highly specific antigen-antibody interactions, cross-reactivity with structurally similar compounds may still occur (7-10).

The reliability of 17-OHP measurements in biochemical laboratories is influenced by pre-analytical, analytical, and post-analytical factors. Variations in sample handling procedures and differences between analytical methods may affect measurement outcomes. A comprehensive interpretation that considers potential interferences along with the demographic and clinical context of the patient is essential. Final result approval should be conducted by a clinical biochemist as part of the post-analytical review process to ensure accurate reporting (11).

Methods

In our hospital, 17-OHP levels in serum were analyzed using an immunoassay method (Diameter kit, Alisei ELISA Analyzer) in a total of 1,013 patients between May 1, 2022, and September 10, 2022. Among these, 134 infants under the age of 5 months who had 17-OHP results exceeding the age-specific reference range were re-evaluated using a different method and analytical system: the LC-MS/MS method (Agilent 6460 Triple Quadrupole Mass Spectrometer).

The LC-MS/MS enables the separation and quantification of 17-OHP from complex biological matrices. The process begins with the extraction of 17-OHP from serum using an appropriate solvent system. In this study, d8-17-OHP was added as an internal standard to each sample prior to extraction in order to correct for variability during the analytical process and to ensure accurate quantification (12). Following extraction, the samples were liquid chromatographic system, where 17-OHP was separated based on its interaction with the stationary phase. The eluted analyte was then introduced into the tandem mass spectrometer, which provides enhanced sensitivity and specificity through a two-step process. In the first stage, precursor ions corresponding to 17-OHP were selected based on their mass-to-charge (m/z) ratio. In the second stage, these ions were fragmented into product ions, enabling precise identification based on their unique fragmentation patterns (12,13). Exclusion criteria included hemolyzed, lipemic, and clotted samples, which were omitted from further analysis. The data obtained were classified based on patient age and sex. Permission was obtained from the Ethics Committee of University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital with the subject (decision no: 14, date: 11.01.2023), and informed consent was also obtained from the patients' guardians.

Statistical Analysis

All statistical analyses were performed using SPSS version 20.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics, including mean, standard deviation, and standard error, were used to summarize the data. Group comparisons were assessed using either analysis of variance or the chi-square test, as appropriate. All statistical results were evaluated at a 95% confidence interval, and a $p<0.05$ was considered statistically significant.

Results

The distribution of the 134 infants under 5 months of age included in the study is presented according to gender (Graphic 1a) and age (Graphic 1b). In all 134 infants, serum 17-OHP levels measured by ELISA method were above the age-specific reference range. However, when the same samples were reanalyzed using LC-MS/MS method, 79.10% (n=106) were reported to be within the reference range and 20.90% (n=28) were reported to be above the reference range according to the data in Table 1.

In addition, Table 2 reported 17-OHP levels above the quantifiable upper limit (>16 ng/mL) in 16.41% (n=22) of infants when tested with ELISA. When these samples were studied with LC-MS/MS, 77.27% (n=17) (group 1) were reported within the reference range, and 22.73% (n=5) (group 2) were reported above the reference range. Table 2 shows the distribution of data according to age and gender in these two groups. A chi-square test was conducted to compare the two measurement methods (ELISA vs. LC-MS/MS) in a 2x2 contingency table. The comparison revealed a statistically significant difference between the two methods ($p<0.0001$).

Table 1. Distribution of the study according to gender and age when studied with the LC-MS/MS method

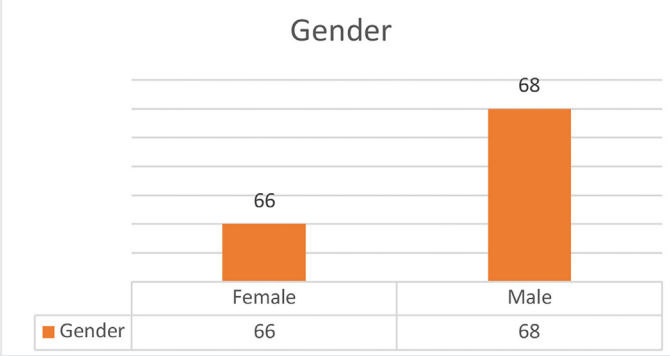
		Group 1		Group 2	
		Number (n)	Percentage (%)	Number (n)	Percentage (%)
Gender	Female	50	47.17	16	57.14
	Male	56	52.83	12	42.86
Age	<1 month	48	45.29	11	39.29
	1-2 months	37	34.9	11	39.29
	2-3 months	14	13.2	5	17.85
	3-4 months	5	4.72	1	3.57
	4-5 months	2	1.89	-	-

LC-MS/MS: Liquid chromatography-tandem mass spectrometry

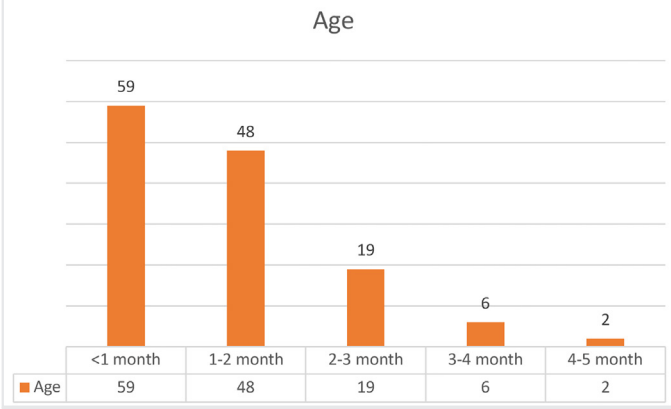
Table 2. Distribution of those higher than the upper limit (>16 ng/mL) by the ELISA method in the study according to gender and age when evaluated by the LC-MS/MS method

		Group 1		Group 2	
		Number (n)	Percentage (%)	Number (n)	Percentage (%)
Gender	Female	6	35.29	5	100
	Male	11	64.71	-	-
Age	<1 month	4	23.53	2	40
	1-2 months	11	64.71	3	60
	2-3 months	2	11.76		
	3-4 months	-			
	4-5 months	-			

LC-MS/MS: Liquid chromatography-tandem mass spectrometry, ELISA: Enzyme-linked immunosorbent assay



Graphic 1a. Distribution of the study by gender



Graphic 1b. Distribution of the study by age

Discussion

17-OHP is a 21-carbon steroid hormone that is produced as an intermediate during the biosynthesis of glucocorticoids and sex steroids. Physiologically, elevated serum 17-OHP levels are observed during fetal development and the early postnatal period. A slight postnatal increase in 17-OHP levels may occur in male infants between days 30 and 60. In both sexes, serum 17-OHP concentrations decline gradually until puberty, after which levels become comparable between males and females. Serum 17-OHP testing is commonly used for the diagnosis of CAH, particularly in cases of 21-OH or 11 beta-hydroxylase enzyme deficiencies. It also plays an important role in the diagnosis and monitoring of mineralocorticoid and androgen synthesis disorders (14). In circulation, approximately 55% of serum 17-OHP binds to albumin, 41% to corticosteroid-binding globulin, and a small proportion to sex hormone-binding globulin. In its protein-bound form, 17-OHP is considered biologically inactive (15).

In routine laboratory practice, 17-OHP level is measured using immunoassays such as ELISA and RIA, as well as the more advanced LC-MS/MS technique. Although immunoassays are convenient and widely used, they are subject to non-specific binding and cross-reactivity with structurally related steroid hormones, which can lead to false elevations inconsistent with the patient's clinical picture. As a result, the use of LC-MS/MS has become increasingly preferred for its superior specificity and accuracy in 17-OHP quantification (16). Although correlations have been reported between LC-MS/MS and immunoassay results in the measurement of steroid hormones like 17-OHP, methodological discrepancies may exist. Each technique has its own advantages and limitations, which must be considered in both clinical and research settings (17,18).

CAH is a rare but potentially life-threatening autosomal recessive endocrine disorder that affects both sexes equally. The disorder is categorized into classical and non-classical forms based on the severity of 21-OH deficiency. In its classical form, CAH is further subdivided into salt-wasting and simple virilizing types. The salt-wasting type, characterized by adrenal insufficiency, dehydration, hyponatremia, and shock, can be fatal if left undiagnosed in the neonatal period. In contrast, the non-classical type typically presents with milder symptoms that manifest later in life (19). In recognition of the critical importance of early diagnosis, the Ministry of Health has incorporated serum 17-OHP measurement into national NBS programs. CAH may present with adrenal crises, which are characterized by symptoms such as vomiting, diarrhea, dehydration, hyponatremia, hyperkalemia, and hypoglycemia. Approximately one-third of neonates with ambiguous genitalia are ultimately diagnosed with CAH. In affected female newborns, virilization and ambiguous genitalia are the predominant clinical features, whereas male newborns may present with hyperpigmentation, enlarged phallus, and scrotal enlargement (20).

In our study, serum 17-OHP levels measured by the ELISA method of infants whose gender (Graph 1a) and age (Graph 1b) data are given in were reported above the reference range. In newborns with ambiguous genitalia or salt-wasting symptoms, 17-OHP is commonly measured using ELISA as part of CAH screening protocols. In male infants, clinical suspicion of CAH is raised in the presence of scrotal hyperpigmentation, enlarged penis, and large scrotum. However, since these findings may be qualitatively interpreted based on the clinician's experience, early diagnosis and treatment may be delayed. In 21-OH deficiency (21-OHD) screening, when 17-OHP is reported by immunoassay, cross-reactivity to other steroids may cause false-positive results. A study from Japan evaluated false-positive results above the reference range of 17-OHP ELISA in preterm infants by LC-MS/MS (21). In the literature, in a study conducted on 328 preterm infants with immunoassay (ELISA) in NBS, 33 were false positives, which was confirmed by comparison with LC-MS/MS (22).

Female infants with classical CAH are typically diagnosed at birth due to abnormalities in external genitalia, which result from excess androgen exposure during intrauterine life. In contrast, male infants with classical salt-wasting CAH generally appear phenotypically normal at birth and are diagnosed between days 7 and 14 based on the development of clinical symptoms, including weight loss, vomiting, lethargy, hyponatremia, hyperkalemia, dehydration, and in some cases, shock. Less commonly, classical non-salt-wasting CAH cases are identified in children aged 2-4 years, often during investigation for virilization. These cases may be missed in NBS programs due to the absence of salt-wasting symptoms in the neonatal period (23). In our laboratory, the upper detection limit for serum 17-OHP using the Diameter kit (Alisei ELISA Analyzer) was 16 ng/mL. A noteworthy finding is that according to the data obtained from our study, more 17-OHP was detected in male infants above the upper reading value measured by ELISA than in female infants in Table 2. However, when the same male infant samples in Table 2 were reanalyzed by LC-MS/MS, it was observed that 17-OHP level was measured within the normal reference range. When the same samples of 6 female infants whose 17-OHP level measured by ELISA and found above the reference range were examined by LC-MS/MS, 5 female infants (n=5) were detected having 17-OHP above the reference range. According to the data obtained from our study, CAH with high 17-OHP level was reported more in female infants. This situation emphasizes the importance of confirmatory tests and method selection to prevent misdiagnosis and unnecessary treatment, especially in borderline or discordant cases.

Serum 17-OHP measurement remains a widely used diagnostic and monitoring tool in the detection and management of CAH, especially during the newborn period. In our study, the same serum samples from infants under 5 months of age with 17-OHP levels exceeding the upper limit measured by ELISA were also reanalyzed using the LC-MS/MS method. Importantly, elevated 17-OHP levels were confirmed by LC-MS/MS primarily in infants younger than 2 months. This finding emphasizes the importance of age-specific interpretation of 17-OHP levels and suggests that biochemical confirmation using LC-MS/MS is especially valuable in the early neonatal period to reduce the risk of false-positive results and avoid unnecessary interventions.

Study Limitations

In the late 1990s, in the reports of immunological analyses of steroid hormones such as 17-OHP, many analytical problems were evaluated with gas chromatography-mass spectrometry (MS) and techniques such as LC-MS/MS were more suitable for the analysis of steroid hormones in body fluids. In this technique, steroid hormones that can be visualized structurally with analytical selectivity can be measured with the multiple reaction monitoring mode of MS. In the literature, LC-MS/MS is considered a reliable reference method for the evaluation of less selective immunoassay techniques (ELISA, RIA, etc.) (13-15). This study has several potential limitations. A key methodological consideration is the inherent differences between the LC-MS/MS and ELISA techniques, each of which presents distinct advantages and disadvantages. The LC-MS/MS method operates on the principle of separating biological components based on their differential binding affinities to the stationary phase, allowing for high-resolution characterization of trace compounds, steroid hormones such as 17-OHP, toxins, metabolites, and proteins. The advantages of LC-MS/MS include its ability to:

- Use very small sample volumes
- Achieve high selectivity for structurally similar molecules
- Provide high reproducibility and low detection limits
- Simultaneously quantify multiple analytes

However, this method also presents limitations. The complexity of the instrumentation requires specialized training for both operation and data interpretation. Additionally, the high initial equipment cost, ongoing maintenance expenses, and sample preparation steps—especially for protein analysis—can be challenging. When analyzing proteins, HPLC is often used prior to MS, and this process typically involves enzymatic digestion of peptides to enhance chromatographic resolution. However, such enzymatic pretreatment may affect MS sensitivity and reproducibility (17,18). Another limitation of this study is its single-center design. Due to sample volume constraints in infants under 5 months of age, some patients had to be excluded from the analysis because of insufficient sample availability.

Since 17-OHP levels can be increased in premature infants due to cross-reactivity in immunoassay (ELISA), second-tier markers are recommended for this limitation. In CAH, the enzyme 11 beta-hydroxylase catalyzes the conversion of 17-OHP to 21-deoxycortisol (21-DF). In 21-OHD, 21-DF increases due to the increased presence of elevated 17-OHP. Although 21-DF is a specific biochemical marker for 21-OHD, it is used as a useful second-tier marker for CAH due to the long analysis time (24).

Conclusion

The ELISA method, on the other hand, is widely used in routine practice due to its low cost, practical application, and suitability for high-throughput screening. Despite its widespread use, ELISA is subject to non-specific interactions and cross-reactivity with structurally related steroids, which may result in false elevations of 17-OHP levels. These limitations have raised concerns regarding the clinical reliability of ELISA, especially in the measurement of steroid hormones like 17-OHP. In our study, we evaluated the discrepancies in serum 17-OHP levels measured by ELISA compared to LC-MS/MS in infants up to 5 months of age. We emphasized that the use of LC-MS/MS to confirm false positive elevations detected by ELISA may be important, especially in infants younger than 3 months, where physiological variations are common and the risk of misdiagnosis is higher. Although LC-MS/MS is more costly, it offers superior sensitivity and specificity.

Based on our findings, we propose that ELISA may remain a practical first-line method for measuring serum 17-OHP levels in children older than 3 months and adults, with LC-MS/MS reserved for confirming results that are clinically incongruent. This approach may offer a cost-effective yet clinically reliable strategy for routine laboratory use.

Ethics

Ethics Committee Approval: Permission was obtained from the Ethics Committee of University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital with the subject (decision no: 14, date: 11.01.2023).

Informed Consent: Informed consent was also obtained from the patients' guardians.

Footnotes

Authorship Contributions

Surgical and Medical Practices: N.D., A.G., Concept: N.D., A.G., Design: N.D., A.G., Data Collection or Processing: N.D., Analysis or Interpretation: N.D., A.G., Literature Search: N.D., A.G., Writing: N.D., A.G.

Conflict of Interest: No conflict of interest was declared by the authors.

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Original Article

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The Effects of Medications Used in the Treatment of Rheumatological Diseases on Pregnancy and Fertilization: A Single-center Experience

Romatolojik Hastalıkların Tedavisinde Kullanılan İlaçların Gebelik ve Fertilizasyon Üzerine Olan Etkileri: Tek Merkez Deneyimi

Beliz KARATAŞ[1], Neşe ÇABUK ÇELİK[2], Burak KARAKAŞ[3], İlker YALÇIN[4], Gizem PİRE[5], Hatice Şeyma EREN[6], Merve ŞENOL KUZU[7], Merve YILDIRIM[8], Burcu Nur ÖZDAMAR[9], Muhammed Faruk AŞKIN[10], Ali ŞAHİN[11]

[1]Binali Yıldırım University Mengücek Gazi Training and Research Hospital, Erzincan, Türkiye
[2]University of Health Sciences Türkiye, Sincan Training and Research Hospital, Ankara, Türkiye
[3]Gebze Fatih State Hospital, Clinic of Internal Medicine, Division of Rheumatology, Kocaeli, Türkiye
[4]Sivas Sample Hospital, Sivas, Türkiye
[5]Hitit University Çorum Erol Olçok Training and Research Hospital, Çorum, Türkiye
[6]Cumhuriyet University Faculty of Medicine Hospital, Department of Internal Medicine, Division of Rheumatology, Sivas, Türkiye
[7]Kelkit State Hospital, Gümüşhane, Türkiye
[8]Cumhuriyet University Faculty of Medicine Hospital, Department of Internal Medicine, Sivas, Türkiye
[9]Gebze Fatih State Hospital, Clinic of Internal Medicine, Kocaeli, Türkiye
[10]Kastamonu Training and Research Hospital, Kastamonu, Türkiye
[11]Cumhuriyet University Faculty of Medicine Hospital, Division of Rheumatology, Sivas, Türkiye

ABSTRACT

Objective: Considering that the group of rheumatological patients generally consists of women in their reproductive period due to hormonal effects, we aimed to investigate the effects of the treatments given to prevent joint and organ damage caused by these diseases on pregnancy and fertilization.

Methods: This study included 1,000 female patients who were followed up due to rheumatological diseases at the rheumatology

ÖZ

Amaç: Romatolojik hasta grubunun hormonal etkiler nedeniyle genellikle üreme çağındaki kadınlardan oluştuğu düşünüldüğünde, bu hastalıkların neden olduğu eklem ve organ hasarlarını önlemek için verilen tedavilerin gebelik ve döllenme üzerine etkilerini araştırmayı amaçladık.

Yöntemler: Bu çalışmaya Ocak 2014-2021 tarihleri arasında hastanemiz iç hastalıkları anabilim dalı romatoloji kliniğinde

Address for Correspondence: Beliz Karataş MD, Binali Yıldırım University Mengücek Gazi Training and Research Hospital, Erzincan, Türkiye
E-mail: dr_lizim@hotmail.com
ORCID IDs of the authors: B.K.: 0000-0003-1894-8062, N.Ç.Ç.: 0000-0002-9045-7105, B.K.: 0000-0003-3624-4958, İ.Y.: 0000-0001-8018-5364, G.P.: 0000-0003-4009-688X, H.Ş.E.: 0000-0003-3430-9287, M.Ş.K.: 0009-0009-6189-2552, M.Y.: 0009-0003-3602-9665, B.N.Ö.: 0009-0006-5434-357X, M.F.A.: 0000-0003-0115-1567, A.Ş.: 0000-0002-6953-4276

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ABSTRACT

department of the internal medicine department of our hospital between January 2014 and January 2021. The patients' ages, rheumatological disease diagnoses, pregnancy status, abortion status, curettage status, medications used, medications used during pregnancy, pregnancy complications, infertility data were retrospectively analyzed.

Results: The number of patients who became pregnant after diagnosis increased with the use of colchicine and anakinra, while it decreased with the use of methotrexate and leflunomide. It was observed that the number of abortions before diagnosis increased in the presence of antiphospholipid antibody syndrome (APS) and systemic lupus erythematosus. It was determined that the number of patients giving live births decreased in the presence of an APS diagnosis. It was determined that the number of patients who had live births with the use of colchicine and hydroxychloroquine during pregnancy increased.

Conclusion: It should be considered that women of reproductive age with rheumatic diseases may desire pregnancy and may present to the clinic with either planned or unplanned pregnancies during their follow-ups, and accordingly, efforts should be made to avoid medications that could cause infertility as much as possible.

Keywords: Antiphospholipid antibody syndrome, colchicine, pregnancy

ÖZ

romatolojik hastalıklar nedeniyle takip edilen 1.000 kadın hasta dahil edildi. Hastaların yaşları, romatolojik hastalık tanıları, gebelik durumları, düşük durumları, küretaj durumları, kullanılan ilaçlar, gebelikte kullanılan ilaçlar, gebelik komplikasyonları, infertilite verileri retrospektif olarak analiz edildi.

Bulgular: Tanı sonrası gebe kalan hasta sayısı kolşisin ve anakinra kullanımı ile artarken, leflunomid kullanımı ile azaldı. Metotreksat kullanımı ile tanı sonrası gebelik sayısı azalmıştır. Antifosfolipid antikor sendromu (AFAS) ve sistemik lupus eritematozus varlığında tanı öncesi düşük sayısının arttığı görüldü. AFAS tanısı varlığında canlı doğum yapan hasta sayısının azaldığı belirlendi. Gebelikte kolşisin ve hidroksiklorokin kullanımı ile canlı doğum yapan hasta sayısının arttığı belirlendi.

Sonuç: Üreme çağındaki romatizmal hastalığı olan kadınların gebelik isteğinde bulunabilecekleri ve takipleri sırasında planlı veya plansız gebeliklerle kliniğe başvurabilecekleri göz önünde bulundurulmalı ve buna göre kısırlığa neden olabilecek ilaçlardan mümkün olduğunca uzak durulmalıdır.

Anahtar Kelimeler: Antifosfolipid antikor sendromu, kolşisin, gebelik

Introduction

The birth of a healthy baby is related to how the mother and/or expectant mother experience their reproductive cycle, pregnancy, and childbirth process. The dominance of immune-mediated pathophysiology in rheumatological diseases also affects the fertilization and pregnancy periods. Considering that the group of rheumatological patients often consists of women in their reproductive period due to the influence of hormones, the effects of joint and organ damage caused by these diseases, as well as the impact of treatments given to prevent them on pregnancy and fertilization, should be taken into account (1).

For example, in systemic lupus erythematosus (SLE), it has been noted that women with active lupus nephritis experience life-threatening pregnancy complications such as eclampsia more frequently, and in antiphospholipid antibody syndrome (APS), recurrent abortions occur (2). In a patient with Sjogren's syndrome, it has been reported that anti-Ro/SSA and anti-La/SSB antibodies (anti-SSA/SSB) can cause neonatal heart block in the fetus during pregnancy (3). In a pregnant woman diagnosed with ankylosing spondylitis (AS), in addition to the growth of the uterus, the change in the structure of the pelvic bones and ligaments can increase inflammatory back and hip pain, and the patient's mobility can be severely impaired. Additionally, this condition can also affect the management of childbirth (4). In cases of Familial Mediterranean fever (FMF), infertility due to amyloidosis can develop (5). These examples can be further increased. When these are considered, it is difficult for mothers and/or expectant mothers with rheumatological diseases to avoid using medication before or during pregnancy. Not all medications are safe (3). Drugs that inhibit DNA synthesis, such as methotrexate and leflunomide, are teratogenic; it is recommended to discontinue them before pregnancy (6). It is also known that cyclophosphamide treatment leads to infertility. Although most of the data on drug safety are obtained from case reports, small series, and observational studies, certain drugs are still used during pregnancy due to the dangerous consequences of uncontrolled systemic inflammatory disease and the patients' vulnerability to postpartum disease flare-ups (3).

Therefore, knowing the effects of rheumatological diseases and the medications used in their treatment on pregnancy and fertilization will be guiding for patient management and medication choices.

Methods

Ethics Statement

In this study, 1,000 female patients with rheumatological diseases, either outpatient or inpatient, who were followed up in the rheumatology department of the internal medicine department of our hospital between January 2014 and January 2021, were included. The inclusion criteria for the study were determined as being anatomically and physiologically female patients in the reproductive period from birth, aged 18-45, having at least one rheumatological disease, and using at least one rheumatological medication. The breastfeeding status of the patients included in the study was disregarded. Ethics approval for the study was obtained from the Sivas Cumhuriyet University Non-

Interventional Clinical Research Ethics Committee (decision no: 2021-10/16, date: 20.10.2021). Informed consent was obtained in writing from the patients.

The patients' ages, rheumatological disease diagnoses, disease durations, pregnancy status and numbers before and after diagnosis, abortion status and numbers before and after diagnosis, curettage status and numbers, live birth status and numbers, comorbid conditions, medications used, medications used during pregnancy, pregnancy complications (eclampsia and pre-eclampsia), pregnancy-related hypertension and thyroid diseases, gestational diabetes mellitus status, organ damage status related to rheumatological diseases, and infertility data were analyzed retrospectively. Conditions where hypertension (systolic 140 mm/Hg, diastolic 90 mm/Hg and above) was detected during pregnancy and accompanied by proteinuria (300 mg/24 hours and above) were classified as pre-eclampsia; if convulsions accompanied the condition in the last trimester of pregnancy, it was classified as eclampsia (7). In our study, patients who had never achieved pregnancy despite 12 months of regular and unprotected sexual intercourse, those who had previously achieved pregnancy but had not been able to conceive despite regular unprotected intercourse in the last year, those who experienced recurrent abortions despite achieving pregnancy, and those who had never had a live birth due to stillbirth were included under the definition of infertility (8). Cases where a live fetus was born after completing the 28th week of pregnancy were recorded as live births (9). Pregnancies terminated voluntarily before the 20th week of gestation or for medical reasons after the 20th week of gestation were classified as curettage (10). The event of the complete or partial expulsion of an embryo or fetus weighing less than 500 grams and its appendages outside the uterine cavity within the first 20 weeks of pregnancy was classified as an abortion (miscarriage) (11). The drugs used were evaluated independently of the dose. The patient was examined based on whether they took the medication, even if it was not at an effective dose. The use of medication during pregnancy was recorded as the period from the first trimester of pregnancy until the birth resulting in either a live or stillbirth, or until an abortion occurred.

Statistical Analysis

Data were processed in SPSS version 23, Pearson chi-square, Mann-Whitney U test, Wilcoxon test were performed. In our study, there was no control group because the patients were compared within themselves. Since we evaluated the patients within themselves, the comorbid conditions, lifestyle changes, and other factors affecting pregnancy, such as the course of the disease, were the same. This also allowed us to understand the effectiveness of the medications.

The reason for not having a control group is that we only conducted research on patients with rheumatological diseases, so there were no cases that did not use medication. Even if we did not give it, there was a history of medication use from another center.

Results

Demographic Data

In our study, the median age of the patients was 37 years (min 19-max 45). Two hundred twenty-four patients (22.4%) had FMF, 197 patients (19.7%) had rheumatoid arthritis (RA), 274 patients (27.4%) had AS, 59 patients (5.9%) had psoriatic arthritis, 1 patient (0.1%) had sarcoidosis, 1 patient (0.1%) had mastitis, 1 patient (0.1%) had polymyositis, 7 patients (0.7%) had vasculitis, 169 patients (16.9%) had Behçet's disease, 3 patients (0.3%) had Still's disease, 2 patients (0.2%) had gout, 146 patients (14.6%) had fibromyalgia, 105 patients (10.5%) had SLE, 60 patients (6%) had Sjogren's syndrome, 37 patients (3.7%) had systemic sclerosis and Raynaud's phenomenon, and 29 patients (2.9%) had APS. 127 patients (12.7%) used sulfasalazine, 426 patients (42.6%) used colchicine, 340 patients (34%) used hydroxychloroquine (HCQ), 144 patients (14.4%) used methotrexate, 54 patients (5.4%) used leflunomide, 259 patients (25.9%) used corticosteroid preparations, 103 patients (10.3%) used azathioprine, 14 patients (1.4%) used mycophenolate mofetil, 127 patients (12.7%) used duloxetine, 757 patients (75.7%) used non-steroidal anti-inflammatory drugs (NSAIDs), 58 patients (5.8%) used infliximab, 88 patients (8.8%) used adalimumab, 8 patients (0.8%) used tocilizumab, 3 patients (0.3%) used tofacitinib, 42 patients (4.2%) used etanercept, 18 patients (1.8%) used rituximab, 53 patients (5.3%) used certolizumab, 3 patients (0.3%) used abatacept, 12 patients (1.2%) used secukinumab, 2 patients (0.2%) used ustekinumab, 10 patients (1%) used cyclophosphamide, 19 patients (1.9%) used golimumab, 16 patients (1.6%) used anakinra, and 8 patients (0.8%) used canakinumab. Two hundred patients (20%) used colchicine during pregnancy, 174 patients (17.4%) used HCQ during pregnancy, 2 patients (0.2%) used methotrexate during pregnancy, 13 patients (1.3%) used sulfasalazine during pregnancy, 27 patients (2.7%) used steroid preparations during pregnancy, 55 patients (5.5%) used azathioprine during pregnancy, 279 patients (27.9%) used NSAIDs during pregnancy, 31 patients (3.1%) used adalimumab during pregnancy, 14 patients (1.4%) used etanercept during pregnancy, 38 patients (3.8%) used certolizumab during pregnancy, and 17 patients (1.7%) used anakinra during pregnancy (Table 1).

Seven hundred twenty patients (72%) had experienced pregnancy before diagnosis; the median number of pregnancies was 2 (min 1-max 11). Five hundred seventeen patients (51.7%) had pregnancies after diagnosis; the median number of pregnancies was 1 (min 1-max 6). Eighty eight patients had abortus before diagnosis; the median abortus was 2 (min 1-max 7). Thirty nine patients had abortus after diagnosis; the median abortus was 1 (min 1-max 4). Nine hundred fifty seven patients had live births; the median birth was 2 (min 1-max 5). Sixty nine patients underwent curettage; the median number of curettages was 1 (min 1-max 3). Forty three patients (4.3%) were unable to have children (Table 2).

The relationship between patients' pregnancy, abortion, curettage, live birth status and numbers before and after diagnosis,

Table 1. Demographic characteristics of patients

Age (year), Mean±*SD, (min-max)	37±6.16 (19-45)
Methotrexate using, (n %)	144 (14.4%)
Duloxetine using, (n %)	127 (12.7%)
Hydroxychloroquine using, (n %)	340 (34%)
Sulfasalazine using, (n %)	127 (12.7%)
Colchicine using, (n %)	426 (42.6%)
**NSAID using, (n %)	757 (75.7%)
Leflunomide using, (n %)	54 (5.4%)
Glucocorticoid using, (n %)	259 (25.9%)
Azathioprine using, (n %)	103 (10.3%)
***MMF using, (n %)	14 (1.4%)
Adalimumab using, (n %)	88 (8.8%)
Infliximab using, (n %)	58 (5.8%)
Certolizumab using, (n %)	53 (5.3%)
Golimumab using, (n %)	19 (1.9%)
Etanercept using, (n %)	42 (4.2%)
Secukinumab using, (n %)	12 (1.2%)
Tocilizumab using, (n %)	8 (0.8%)
Tofacitinib using, (n %)	3 (0.3%)
Rituximab using, (n %)	18 (1.8%)
Abatacept using, (n %)	3 (0.3%)
Ustekinumab using, (n %)	2 (0.2%)
Canakinumab using, (n %)	8 (0.8%)
Anakinra using, (n %)	16 (1.6%)
Cyclophosphamide using, (n %)	10 (1%)
‡FMF, (n %)	224 (22.4%)
Behcet's disease, (n %)	169 (16.9%)
‡‡RA, (n %)	197 (19.7%)
¶AS, (n %)	274 (27.4%)
¶¶SLE, (n %)	105 (10.5%)
†PSA, (n %)	59 (5.9%)
Sjogren syndrome, (n %)	60 (6%)
††APS, (n %)	29 (2.9%)
Fibromyalgia, (n %)	146 (14.6%)
Vasculitis (large vessel and small vessel), (n %)	7 (0.7%)
Systemic sclerosis, (n %)	37 (3.7%)
Gout, (n %)	2 (0.2%)
Mastitis, (n %)	1 (0.1%)
Still's disease, (n %)	3 (0.3%)
Sarcoidosis, (n %)	1 (0.1%)
Myositis, (n %)	1 (0.1%)
Using sulfasalazine during pregnancy, (n %)	13 (1.3%)
Using colchicine during pregnancy, (n %)	200 (20%)
Using hydroxychloroquine during pregnancy, (n %)	174 (17.4%)
Using methotrexate during pregnancy, (n %)	2 (0.2%)
Glucocorticoids during pregnancy using, (n %)	27 (2.7%)
Using azathioprine during pregnancy, (n %)	55 (5.5%)
Using **NSAIDs during pregnancy, (n %)	279 (27.9%)
Using etanercept during pregnancy, (n %)	14 (1.4%)
Using adalimumab during pregnancy, (n %)	31 (3.1%)
Using certolizumab during pregnancy, (n %)	38 (3.8%)
Using anakinra during pregnancy, (n %)	17 (1.7%)

*: Standard deviation, **: Non-steroidal anti-inflammatory drugs, ***: Mycophenolate mofetil, ‡: Familial Mediterranean fever, ‡‡: Rheumatoid arthritis, ¶: Ankylosing spondylitis, ¶¶: Systemic lupus erythematosus, †: Psoriatic arthritis, ††: Antiphospholipid antibody syndrome

and their rheumatological diseases and medications used. It was determined that the number of pregnancies in patients decreased after the use of colchicine, HCQ, sulfasalazine, methotrexate, leflunomide, glucocorticoids, NSAIDs, adalimumab, infliximab, golimumab, and anakinra (Table 3). The abortions in the cases were observed after discontinuation of colchicine, HCQ, acetylsalicylic acid, and low molecular weight heparin (Table 4). The number of patients who became pregnant after diagnosis increased by 0.76 times [95% confidence interval (CI): 0.66-0.89] with the use of colchicine, and by 0.153 times (95% CI: 0.035-0.66) with the use of anakinra; it decreased by 1.82 times (95% CI: 1.06-3.11) with the use of leflunomide. It was observed that the number of pregnancies after diagnosis decreased with the use of methotrexate. In patients with APS and SLE, the number of pregnancies after diagnosis was lower compared to before diagnosis. It was observed that the number of abortions before diagnosis increased in the presence of APS and SLE diagnoses. The likelihood of developing eclampsia among pregnancy complications was found to be 0.016 times higher in APS cases (95% CI: 0.005-0.051) and 0.087 times higher in SLE cases (95% CI: 0.061-0.122). It was determined that the number of curettages increased in the presence of an APS diagnosis, while the number of patients giving live births decreased by 3.56 times (95% CI: 1.29-9.78). Among those using methotrexate, the number of patients undergoing curettage was found to have increased by 0.63 times (95% CI: 0.39-0.99). In all cases using colchicine, an increase in the number of live births was recorded with the use of colchicine during pregnancy. It was determined that the number of patients who had live births with the use of HCQ during pregnancy increased by 0.39 times (95% CI: 0.13-0.99) (Table 5).

Data on Medication Use During Pregnancy

The average dose of colchicine used during pregnancy was 1.37 mg/day, 1 g/day for sulfasalazine, 400 mg/day for HCQ, 6 mg/day for prednisolone, and 130 mg/day for azathioprine. The average dose of adalimumab used during pregnancy was 40 mg/2 weeks, 50 mg/week for etanercept, 100 mg/day for anakinra, and 200 mg/2 weeks for certolizumab pegol. The average duration of colchicine used during pregnancy was 18.5 years (222 months), 2.5 years (30 months) for sulfasalazine, 6 years (72 months) for HCQ, 3.5 months for prednisolone, and 2 years (24 months) for azathioprine. The average duration of adalimumab used during

Table 2. Pregnancy, abortus, curettage and live birth status of the patients and the number of pregnancies, abortus and curettages

	Pregnant before diagnosis	Getting pregnant after diagnosis	Abortus before diagnosis	Abortus after diagnosis	Live birth	Curettage	Never having a pregnancy (infertility)
Number of patients	720	517	88	39	957	69	43
n (%)	72%	51.7%	8.8%	3.9%	95.7%	6.9%	4.3%
Median (min-max)	2 (1-11)	1 (1-6)	2 (1-7)	1 (1-4)	2 (1-5)	1 (1-3)	0

Table 3. Difference between the number of pregnancies of patients before and after the medication

	Number of pregnancies after medication-number of pregnancies before medication z-score	p-value*
Colchicine	-3.74	≤0.001
Hydroxychloroquine	-6.97	≤0.001
Sulfasalazine	-3.43	≤0.001
Methotrexate	-5.09	≤0.001
Leflunomide	-3.56	≤0.001
Glucocorticoid	-4.93	≤0.001
**NSAID	-8.5	≤0.001
Adalimumab	-2.6	≤0.001
Infliximab	-2.24	≤0.001
Golimumab	-2.77	≤0.001
Anakinra	-2.39	≤0.001

*:<0.05 significant, **: Non-steroidal anti-inflammatory drugs

Table 4. Difference between the number of abortus of patients before and after the medication

	Post-medication abortus counts-pre medication abortus counts z-score	p-value*
Colchicine	-14.2	≤0.001
Hydroxychloroquine	-12.1	≤0.001
Acetylsalicylic acid	-10.8	≤0.001
****LMWH**	-2	≤0.001

*: 0.05 and below is significant, **: Low molecular weight heparin

pregnancy was 1.5 years (18 months), 2 years (24 months) for etanercept, 10 months for anakinra, and 6 months for certolizumab pegol (Table 6).

Since the patients informed us of their desire for pregnancy, all biological agents except adalimumab, etanercept, certolizumab, and anakinra were discontinued 3 months prior. For leflunomide, this period was 2 years, and for methotrexate, it was 6 months. NSAIDs were discontinued in the 32nd week of pregnancy.

Data on Infertility

We had 10 cases who were treated with cyclophosphamide due to vital organ involvement, and all of these patients were in the infertility group. Four patients had SLE-related nephritis and central nervous system involvement, 2 patients had Behçet's disease with pulmonary artery involvement, 2 patients had anti-neutrophil cytoplasmic antibody-negative small vessel vasculitis (Henoch-Schonlein purpura with gastrointestinal and renal involvement), and 2 patients had catastrophic antiphospholipid syndrome. SLE cases received a total of 6 doses of 500 mg intravenous (IV) cyclophosphamide every 2 weeks, while the vasculitis cases received IV cyclophosphamide at a dose of 15 mg/kg (between 500-1000 mg) once a month for 6 months. Patients were informed about the matter, consent was obtained, and the option of egg preservation was offered.

Discussion

In this article, where we investigate the impact of pregnancy and fertility on medication use and preferences in rheumatological diseases, we should mention the colchicine used by women of childbearing age who are frequently monitored in our clinic, due to our country being in the FMF belt and our city of Sivas being one of the cities where FMF is most commonly seen (12).

Colchicine is widely used in the treatment of rheumatological diseases, especially FMF. There are studies in the literature regarding the effects of colchicine on fertilization and pregnancy. As an example, in the review by Both et al. (13), who examined 83 articles, it was concluded that colchicine did not have an adverse effect on reproductive functions; on the contrary, it was found that untreated FMF could lead to infertility due to amyloid accumulation in the testes and ovaries. In addition, it was reported that no serious complications developed with the use of colchicine during pregnancy. In the meta-analysis conducted by Indraratna et al. (14) in Australia, it was shown that the use of colchicine during pregnancy was not associated with an increased risk of abortus, and due to the high likelihood of recurrence of FMF, which could lead to teratogenicity and systemic amyloidosis during pregnancy if left untreated, colchicine should not be discontinued. Additionally, among pregnant women diagnosed with FMF, those who used the medication were compared to those who did not; it was found that the incidence of abortus was significantly lower in those who used the medication. However, although the incidence of preterm birth and low birth weight was found to be increased in pregnant women with FMF who used colchicine, this situation was attributed to the disease itself. In our study, the number of pregnancies and fertilization status before and after colchicine treatment were evaluated in patients diagnosed with rheumatological diseases who were using colchicine. A significant increase was observed in the number of

Table 5. The relationship between medications and diseases and pregnancy, live birth, abortion and curettage

Chi-square	Colchicine use *Rate of increase 95% confidence interval, **p-value	Anakinra use *Rate of increase confidence interval, **p-value	Leflunomide use ***Rate of decrease (relative risk) confidence interval , **p value	Mann-Whitney U test	Methotrexate use *z-score, **p-value
Number of patients who became pregnant after diagnosis	***0.768 (0.66-0.89) **p<0.000**	***0.153 (0.035-0.66) **p<0.004**	******1.82 (1.06-3.11) **p≤0.035**	**Number of pregnancies after diagnosis**	***z=-1.813 **p≤0.05**
Wilcoxon	**ǂAPS **p-value**		**††SLE **p-value**		
Number of pregnancies after medication - number of pregnancies before medication (z-score)	**z=-3.20 **p≤0.001**		**z=-3.24 **p≤0.001**		
Mann-Whitney U test	**ǂAPS *z-score, **p-value**		**††SLE *z-score, **p-value**		
Number of abortus before diagnosis	***z=14.5 **p<0.000**		***z=12.9 **p≤0.000**		
Chi-square	**ǂAPS *Rate of increase 95% confidence interval **p-value**		**††SLE *Rate of increase 95% confidence interval **p-value**		
Number of patients developing eclampsia complications during pregnancy	*** 0.016 (0.005-0.051) **p≤0.001**		***0.087 (0.061-0.122) **p≤0.001**		
Mann-Whitney U test	**ǂAPS, *z-score, **p-value**				
Number of curettage	***Z:-3.74 **p≤0.001**				
Chi-square	**ǂAPS, ***Rate of decrease (relative risk), **p-value**				
Number of patients giving live birth	*****3.56, **p≤0.001**				
Chi-square	**Methotrexate use, * Rate of increase confidence interval, **p-value**				
Number of patients who had curettage	***0.63 (0.39-0.99), **p≤0.001**				
Mann-Whitney U	**Use of colchicine during pregnancy in all cases using colchicine**				
Number of live births	****p-value: 0.047**				
Cox regression	**Hydroxychloroquine use in pregnancy *Rate of increase confidence interval, **p-value**				
Number of patients giving live birth	***0.39 (0.13-0.99), **p≤0.05**				

*: Rate of increase confidence interval, **: 0.05 and below is significant, ***Rate of decrease (relative risk) confidence interval ††: Systemic lupus erythematosus, ǂǂ: Antiphospholipid antibody syndrome

patients who became pregnant after treatment. However, in cases using colchicine, the number of pregnancies after colchicine use was lower than the number of pregnancies before colchicine use. The reason for this may be that the cases, after becoming aware of their disease and considering the challenging process, had a desire to experience fewer pregnancies, or it may be due to our recommendation to the patients to postpone pregnancy until FMF remission is expected. However, among the cases using colchicine, there was a significant difference in the number of live births between those who used colchicine during pregnancy and those who did not; the number was higher in the pregnant women who used colchicine. Again, a significant decrease in the number of abortions was observed in cases using colchicine. These results were indicative of colchicine's positive effect on fertilization and supported the necessity of continuing treatment in pregnant women diagnosed with FMF.

Among the studies in the literature on the use of anakinra and canakinumab during pregnancy, which are the main biological agents used in the treatment of FMF, the study conducted by Youngstein et al. (15) with 31 pregnant women with autoinflammatory diseases from seven countries stands out. In this study, due to autoinflammatory diseases such as FMF,

Table 6. Doses and durations of medications used by patients during pregnancy

	Doses (mean)	Total usage period (mean) (months)
Colchicine	1.37 mg/day	222
Hydroxychloroquine	400 mg/day	72
Sulfasalazine	1 g/day	30
Prednisolone	6 mg/day	3.5
Azathioprine	130 mg/day	24
Adalimumab	40 mg/2 weeks	18
Etanercept	50 mg/week	24
Certolizumab pegol	200 mg/2 weeks	6
Anakinra	100 mg/day	10

adult-onset Still's disease, and tumor necrosis factor receptor-associated periodic syndrome, no serious infections were observed in either the mother or the fetus during pregnancy or after childbirth in pregnant women using either anakinra or canakinumab. In addition, although unilateral renal agenesis and ectopic neurohypophysis were detected in the fetus of a pregnant woman who used anakinra, the other pregnancies resulted in the birth of healthy fetuses without any complications. However, in terms of anakinra, this is the second case of renal agenesis in the literature. Therefore, they reported that this should be taken into consideration and that this patient had used a high dose of anakinra. In pregnancies exposed to canakinumab, no complications were noted. Nevertheless, Youngstein et al. (15) preferred anakinra over canakinumab for use during pregnancy due to its greater evidence and shorter half-life. They argued that canakinumab should not be used from the 22nd week of pregnancy onwards due to concerns that it could lead to infections in newborns. They emphasized that in pregnant women with autoinflammatory diseases, the cessation of interleukin-1 (IL-1) inhibitors would lead to increased chronic inflammation, resulting in a rise in pregnancy complications, and that infertility could develop before pregnancy due to the effects of cytokines and amyloidosis (15). In a review prepared by Brien et al. (16) in Canada, 69 pregnancies in which anakinra was used were examined, and live births occurred without any complications in 63.8% of them. In contrast, 17.4% resulted in premature birth, while the others experienced vaginal bleeding, hypertension, and oligohydramnios. In one case, stillbirth occurred. While 90.9% of the 11 pregnancies using canakinumab resulted in term births, gestational diabetes mellitus was reported in only one case. Brien et al. (16) noted that the rate of preterm births among these cases was lower than reported in the literature, and they did not attribute this solely to the existing condition. However, they reported that the mechanisms explaining the causation of premature birth by IL-1 inhibitors were open to research. In our study, an increase in the number of patients who became pregnant with the use of anakinra was detected; this was interpreted as increased fertilization due to decreased inflammation. Despite this, similar to colchicine, the number of pregnancies after anakinra in patients using anakinra was lower than the number of pregnancies before the use of the drug. In our study, it was found that only one out of 17 pregnant women using anakinra experienced a abortus in the first trimester. It was observed that this patient with FMF was in remission during pregnancy. However, the fetal anomaly was not known. In addition, it was determined that 4 cases had preterm births due to eclampsia, and these cases were found to have proteinuria and hypertension due to FMF renal involvement. In one case, gestational hypertension was found. Although these data were supportive of the literature, they were not statistically significant. The reason for this may be the small number of patients using anakinra during pregnancy. We did not have any patients using canakinumab during pregnancy. Our recommendation of planned pregnancy for female patients using canakinumab during the reproductive period and our transition to anakinra for patients who wished to become pregnant contributed to the occurrence of this situation.

If we examine methotrexate and leflunomide, which are among the most commonly used drugs in the treatment of RA, the review by Janssen and Genta (17) suggests that methotrexate does not have a negative effect on fertilization, but due to its embryotoxic effects, contraception is recommended. The effects of methotrexate on the fetus are described as craniofacial malformations, anencephaly, limb defects, hydrocephalus, and meningomyelocele (17). In the review by Bilgen et al. (6), it is stated that methotrexate should be discontinued 3 months before conception. In Germany, Weber-Schoendorfer et al. (18) observed an increase in spontaneous abortions in a study conducted with 65 pregnant women who were exposed to leflunomide. Therefore, they emphasized that in female patients using leflunomide, the drug plasma concentration should be below 0.02 mg/L before pregnancy; for this, pregnancy should be postponed until 2 years after stopping leflunomide, and in cases where this period is not met, drug elimination with cholestyramine should be performed. In our study, a decrease in the number of pregnancies among patients using methotrexate and leflunomide was observed. The reason for this may be the long duration of 2 years that women using leflunomide need to wait before becoming pregnant. In our study, there were 2 patients who used methotrexate during pregnancy. While one patient experienced a spontaneous abortus, it was learned that the other patient underwent a curettage. Besides this, it was found that the incidence of curettage increased in pregnant women who had a break of less than 3 months from methotrexate before becoming pregnant. We did not have any patients using leflunomide during pregnancy. The reason for this was seen as the interruption of the medication due to the desire for pregnancy among patients using leflunomide during the reproductive period.

Among the drugs used in the treatment of rheumatological diseases, cyclophosphamide stands out as an agent proven to cause infertility. In the literature, as noted by Mok (19), the use of cyclophosphamide was associated with premature ovarian insufficiency. In addition, Gajjar et al. (20) pointed out that due to the determination of oocyte count during fetal life, the use of cyclophosphamide in women at higher doses and older ages

might lead to irreversible infertility. In our study, there were 10 patients who used cyclophosphamide, and all of these patients were infertile.

Among rheumatic diseases, the conditions where pregnancy complications (for both the mother and fetus) are most frequently encountered are SLE and APS (2). It is known that recurrent abortus are included in the diagnostic criteria for APS (21). In women with SLE (with or without APS), the rates of prematurity, pre-eclampsia and eclampsia, hemolysis, elevated liver enzyme levels, low platelet count (hemolysis, elevated liver enzymes, low platelet count syndrome), maternal hypertension, and nephritis are increasing (2). In accordance with the literature, our study found that in patients diagnosed with APS and SLE, there was a decrease in the number of pregnancies, along with an increase in the rates of eclampsia, abortus and curettages in pregnancies before the diagnosis. In addition, we found that the number of patients with a primary diagnosis of APS who had live births decreased. However, in these cases, lower numbers of abortions were observed in pregnancies that developed after the diagnosis. With the thought that the agents used in treatment might be the reason for this difference, we specifically focused on HCQ. The discontinuation of HCQ treatment in pregnant women diagnosed with SLE and APS is associated with an increased risk of SLE flares during pregnancy. It was suggested that HCQ had a beneficial effect on maternal disease activity during pregnancy (2). In the review published by Abarientos et al. (22), it was argued that the use of HCQ during pregnancy was not associated with the risks of spontaneous abortions, congenital defects, fetal death, prematurity, and decreased live birth rates. However, in a cohort study conducted by Huybrechts et al. (23) in England, which investigated 2,045 pregnant women exposed to HCQ, it was reported that exposure to the drug in the first trimester caused a slight increase in malformations, including cleft palate, cleft lip, pulmonary hypoplasia, and urinary tract anomalies, independent of the presence of underlying rheumatological diseases or concurrent steroid use. Nevertheless, they concluded that in pregnant women diagnosed with SLE and RA, the benefits of treatment would outweigh these outcomes, the drug's half-life would be more than a month even if discontinued, and due to the risk of encountering pre-eclampsia, heart defects, fetal distress, and fetal deaths associated with increased disease activity, HCQ treatment should not be altered. In our study, it was observed that the use of HCQ before pregnancy was associated with a decrease in the number of pregnancies and the number of abortions among patients. The reason for the decrease in the number of pregnancies may be that the patients avoided becoming pregnant due to medication use or that we recommended delaying pregnancy to the patients to wait for SLE remission. In our study, it was found that the use of HCQ during pregnancy reduced spontaneous abortions and increased the number of patients who had live births.

In conclusion, we observed that the number of patients who became pregnant increased after the use of colchicine and anakinra in those diagnosed with rheumatological diseases, the number of patients who became pregnant decreased with the use of leflunomide, and the number of pregnancies decreased after the use of methotrexate. We found that the number of abortions and curettages before diagnosis increased in patients with diagnoses of APS and SLE, while the number of live births decreased.

Study Limitations

The positive aspects of our study are that there are more reviews than research articles in the literature on this topic, and we are among the few who have conducted such articles; however, the weaknesses may include not recording postnatal fetal anomalies and not examining the pathological diagnoses involved in the etiology of abortions. Although it was a single-center study, we avoided practices that could be considered biases, such as excluding patients who had abortus or underwent curettage from the study.

Conclusion

It should be considered that women of reproductive age with rheumatic diseases may desire pregnancy and may present to the clinic with either planned or unplanned pregnancies during their follow-ups, and accordingly, efforts should be made to avoid medications that could potentially cause infertility as much as possible. Patients should be thoroughly informed about the effects of their disease and the medications they are using.

Ethics

Ethics Committee Approval: Ethics approval for the study was obtained from the Sivas Cumhuriyet University Non-Interventional Clinical Research Ethics Committee (approval no: 2021-10/16, date: 20.10.2021).

Informed Consent: Informed consent was obtained in writing from the patients.

Footnotes

Authorship Contributions

Surgical and Medical Practices: B.K., Concept: B.K., B.N.Ö., M.F.A., Design: B.K., İ.Y., A.Ş., Data Collection or Processing: B.K., N.Ç.Ç., Bu.K., İ.Y., G.P., H.Ş.E., M.Ş.K., M.Y., B.N.Ö., M.F.A., Analysis or Interpretation: B.K., M.F.A., A.Ş., Literature Search: B.K., G.P., H.Ş.E., Writing: B.K., Bu.K., M.F.A.

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Original Article

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The Importance of Patient-reported Outcome Measures in Dialysis Care: Perspectives of Kidney Healthcare Providers in Türkiye

Diyaliz Bakımında Hasta Bildirimli Sonuç Ölçütlerinin Önemi: Türkiye'deki Böbrek Sağlığı Hizmet Sunucularının Görüşleri

Edanur KURBAN[1], Meltem GÜRSU[2], Ömer Celal ELÇİOĞLU[2], Canan SAYAN[2], Ayşegül YABACI TAK[3], Rümeyza KAZANCIOĞLU[2]

[1]Bezmialem Vakıf University Faculty of Medicine, İstanbul, Türkiye
[2]Bezmialem Vakıf University Faculty of Medicine, Division of Nephrology, İstanbul, Türkiye
[3]Bezmialem Vakıf University Faculty of Medicine, Department of Biostatistics and Medical Informatics, İstanbul, Türkiye

ABSTRACT

Objective: Patient-reported outcome measures (PROMs) are essential for monitoring patient health and personalized treatments. The effective use of PROMs in clinical practice can improve outcomes by increasing patient engagement. Educating both clinicians and patients on PROMs and conducting regular monitoring is crucial. This study aims to investigate the significance of PROMs for kidney healthcare providers (KHPs).

Methods: An online survey was prepared to assess KHPs' attitudes toward dialysis modalities and PROMs. The survey was distributed across Türkiye between March 25 and June 15, 2023. Data were analyzed using the Shapiro-Wilk test and Pearson's chi-squared test.

Results: A total of 102 doctors and 42 nurses (82 females, 62 males, mean age 45±8.6 years) participated. Among respondents, 57.7% believed that interaction between dialysis patients in the center significantly helped patients manage their disease. Additionally, 66% agreed that coming to the clinic three times a week is burdensome for most patients. Furthermore, 75.1% of KHPs encouraged patients to consider home dialysis due to its flexibility. KHPs believed that peritoneal dialysis (70.1%)

ÖZ

Amaç: Hasta bildirimli sonuç ölçütleri (PROM), hastaların sağlık durumlarını izlemek ve tedavilerini kişiselleştirmek için önemli araçlardır. PROM'ların klinik uygulamada etkin kullanımı, hasta katılımını artırarak tedavi sonuçlarını iyileştirebilir. PROM'lar konusunda hem klinisyenlerin hem de hastaların eğitimi ve düzenli izleme yapılması büyük önem taşımaktadır. Bu çalışma, böbrek sağlığı hizmet sunucuları (BSHS) için PROM'ların önemini araştırmayı amaçlamaktadır.

Yöntemler: BSHS'lerin diyaliz modaliteleri ve PROM'lara yönelik tutumlarını değerlendirmek amacıyla bir çevrim içi anket hazırlandı. Anket, 25 Mart-15 Haziran 2023 tarihleri arasında Türkiye genelinde dağıtıldı. Veriler Shapiro-Wilk testi ve Pearson'ın ki-kare testi ile analiz edildi.

Bulgular: Ankete 102 doktor ve 42 hemşire (82 kadın, 62 erkek, ortalama yaş 45±8,6 yıl) katıldı. Katılımcıların %57,7'si, merkezdeki diyaliz hastaları arasındaki etkileşimin, hastaların hastalıklarını yönetmelerine önemli ölçüde katkı sağladığını düşündü. Ayrıca, %66'sı hastaların haftada üç kez kliniğe gelmeyi külfetli bulduğunu belirtti. Katılımcıların %75,1'i ise hastalara zaman esnekliği

Address for Correspondence: Prof. Dr. Ömer Celal Elçioğlu, Bezmialem Vakıf University Faculty of Medicine, Division of Nephrology, İstanbul, Türkiye
E-mail: o.c.elcioglu@gmail.com
ORCID IDs of the authors: E.K.: 0009-0000-7589-2777, M.G.: 0000-0003-3972-2521, Ö.C.E.: 0000-0001-5943-0302, C.S.: 0009-0009-4282-8408, A.Y.T.: 0000-0002-5813-3397, R.K.: 0000-0003-1217-588X

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ABSTRACT

and home hemodialysis (79.8%) provide a better quality of life compared to center hemodialysis. Educational videos were the most preferred educational method for dialysis modalities (58.3%), followed by applied continuing education (48.2%) and dialysis rotations (41.7%).

Conclusion: Integrating PROMs into clinical practice and linking them with actionable interventions can enhance patient well-being and health outcomes. It is crucial to educate KHPs on PROMs and encourage consistent use by clinicians to optimize treatment outcomes.

Keywords: Dialysis modalities, kidney healthcare providers, PROMs

ÖZ

sunduğu için ev diyalizini düşünmelerini önerdi. BSHS'lerin %70,1'i periton diyalizinin, %79,8'i ise ev hemodiyalizinin, merkezdeki hemodiyalize kıyasla hastalar için daha iyi bir yaşam kalitesi sunduğuna inanıyordu. Diyaliz modalitelerine yönelik eğitimde en çok tercih edilen yöntem eğitim videolarıydı (%58,3); bunu uygulamalı sürekli eğitim (%48,2) ve diyaliz rotasyonları (%41,7) izledi.

Sonuç: PROM'ların klinik uygulamaya entegrasyonu ve bunların eyleme geçirilebilir müdahalelerle ilişkilendirilmesi, hastaların refahını ve sağlık sonuçlarını iyileştirebilir. BSHS'lerin PROM'lar konusunda eğitilmesi ve klinisyenlerin PROM'ları tutarlı bir şekilde kullanmaya teşvik edilmesi büyük önem taşımaktadır.

Anahtar Kelimeler: Diyaliz modaliteleri, böbrek sağlığı hizmet sunucuları, PROMs

Introduction

Chronic kidney disease (CKD) is a major global health issue, affecting millions and placing a significant burden on healthcare systems (1). As CKD progresses to end-stage kidney disease (ESKD), kidney replacement therapy—including dialysis or transplantation—is required for survival (2). Hemodialysis and peritoneal dialysis are the primary modalities, crucial for managing ESKD (3). However, dialysis often brings physical, emotional, and social challenges that negatively affect patients' quality of life (4).

Patient-reported outcome measures (PROMs) are essential tools for capturing patients' subjective experiences, including symptoms, functional status, and quality of life (5,6). With the growing focus on patient-centered care, PROMs have gained recognition in nephrology for guiding shared decision-making (7). Their systematic use enables healthcare providers to personalize treatment, improve outcomes, and enhance patient satisfaction (8), while also fostering better communication and patient engagement in care (9).

Despite the potential benefits of PROMs in kidney healthcare, their systematic integration into clinical practice remains limited, and there is a need for further research to explore the attitudes, perceptions, and practices of kidney healthcare providers (KHPs) regarding the use of PROMs (10). Understanding KHPs' perspectives on PROMs is essential for identifying barriers to their implementation and developing strategies to overcome these barriers effectively (11). In this context, it is crucial to consider the unique healthcare landscape of Türkiye, including the distribution of healthcare resources, cultural factors influencing patient-provider interactions, and the accessibility of different dialysis modalities. By examining the perspectives of KHPs in Türkiye, this study aims to contribute to the broader understanding of PROMs utilization in kidney healthcare and inform strategies for promoting patient-centered care and improving outcomes for individuals with CKD.

Methods

Study Design

This study used a cross-sectional design to investigate the significance of PROMs among KHPs in Türkiye. Data were collected through an online survey administered via Google Forms, a secure and widely-used online questionnaire platform. The survey consisted of 16 questions developed by the research team, grounded in a review of current literature, established PROMs frameworks, and expert opinions from nephrology and dialysis care professionals. The questionnaire included multiple-choice, Likert scale, and ranking items aimed at assessing participants' demographics, preferences regarding dialysis modalities, perceived challenges and facilitators for home dialysis, and attitudes toward PROMs. A Turkish version of the complete questionnaire is provided as Supplementary File 1.

Ethics Committee Information

Ethics approval was obtained from Bezmialem Vakıf University with the Ethics Committee (decision no: 2023/59, date: 22.03.2023).

Study Population

Nephrologists, pediatricians, dialysis-certified internal medicine physicians, and dialysis-certified practitioners in Türkiye were identified as the groups to be included in the study. Recruitment efforts were conducted through professional networks, healthcare organizations, and relevant associations specializing in nephrology and dialysis care. Of all participants, 56.9% were female and 43.1% were male. The professional distribution of participants is presented in Table 1.

Data Collection

The survey was administered electronically using a secure online platform. Data collection occurred between March 25 and June 15, 2023. Participants were provided with a link to the survey along with instructions for completion.

Consent

Ethics committee approval included a waiver of written informed consent; participation was voluntary and completion of the anonymous online survey implied consent. The questionnaire included a variety of question types designed to gather comprehensive insights from participants. Demographic questions, such as gender, profession, and years of experience, were used to characterize the participant profile. Closed-ended Likert scale questions (e.g., ranging from "strongly disagree" to "strongly agree") were employed to assess healthcare providers' attitudes toward PROMs and dialysis modalities. Additionally, multiple-choice questions were used to explore preferences regarding educational methods and perceived patient needs. These questions aimed to collect data on participants' clinical experiences, perceptions of PROMs, preferences for dialysis options, and their views on effective educational strategies, ultimately supporting subgroup analysis and broader interpretation.

Statistical Analysis

Descriptive statistics were used to summarize the demographic characteristics of the study participants and the distribution of responses to survey questions. Continuous variables were reported as means with standard deviations, while categorical variables were summarized using frequencies and percentages. The Shapiro-Wilk test was employed to assess the normality of data distribution, and Pearson's chi-squared test was utilized to analyze associations between categorical variables. Statistical significance was set at $p<0.05$.

The full survey questionnaire used in this study is provided as Supplementary File 1 (available online).

Results

A total of 102 physicians and 42 nurses completed the survey (82 females, 62 males; mean age: 45±8.6 years). Participants work in the Marmara Region (54.2%), Central Anatolia Region (16%), Aegean Region (9.7%), Mediterranean Region (8.3%), Southeastern Anatolia Region (5.6%), Black Sea Region (3.5%), and Eastern Anatolia Region (2.8%). The respondents included 87 nephrologists (60.4%), 42 nurses (29.2%), 12 pediatric nephrologists (8.3%), 2 dialysis-certified internal medicine physicians (1.4%), and 1 dialysis-certified general practitioner (0.7%).

Table 1. Profession distribution of participants

Profession	Number of participants	Percentage (%)
Nephrologist	87	60.4
Pediatric nephrologist	12	8.3
Dialysis-certified internist	2	1.4
Dialysis-certified general practitioner	1	0.7
Nurse	42	29.2
Total	144	100.0

Participants' years of experience in the nephrology were as follows: 10-20 years (43.1%), more than 20 years (25%), less than 5 years (16.7%), 5-10 years (15.3%).

Figure 1 presents responses to four key statements regarding dialysis modalities and patient experience. The interaction between dialysis patients at the center was seen as a positive influence on disease management by most providers, with 39.6% agreeing and 18.1% strongly agreeing. In contrast, opinions were mixed on whether in-center dialysis is less stressful than home dialysis, with 25% disagreeing and 31.3% responding as "unsure". A strong majority (75.1%) of respondents encouraged home dialysis, citing the flexibility it offers; 43.8% agreed and 31.3% strongly agreed. Regarding patient mobility, 36.8% agreed and 20.1% strongly agreed that being able to travel is extremely important for dialysis patients.

Figure 2 illustrates KHPs' preferences for the most effective educational methods regarding dialysis modalities. Education videos were most preferred (58.3%), followed by applied continuing education (48.2%) and dialysis rotations (41.7%). Online continuing education was also favored (41.7%), reflecting a need for flexible learning methods. Conference speeches (31.9%) were moderately preferred, while journal articles (8.3%) and brochures (8.3%) were least favored. Only 2.0% reported no need for further education on dialysis modalities.

Discussion

The findings of this study reveal that KHPs in Türkiye acknowledge the importance of PROMs in improving kidney healthcare. By focusing on patient-reported experiences, KHPs can deliver more individualized care and foster better communication and engagement with patients (12,13).

A notable finding was that 45.8% of KHPs expressed a preference for home dialysis over in-center dialysis. This preference is largely attributed to the flexibility home dialysis offers, which improves treatment adherence, quality of life, and patient autonomy (14). Facilities that support home dialysis typically offer structured training programs, including simulation-based sessions, home visits by specialized nurses, and 24/7 remote support lines to ensure patient safety and compliance (15,16).

However, the availability and scope of home dialysis training for KHPs vary widely. While no comprehensive national education program currently exists, findings from our survey indicate that only a minority of KHPs (18.7%) reported receiving structured training specifically on home dialysis modalities. According to the 2023 report of the Turkish Society of Nephrology, only 22 centers in Türkiye currently provide home hemodialysis services, and these programs are highly variable in terms of staffing, patient load, and training capacity (17). This suggests that less than 10% of dialysis centers in Türkiye offer active home hemodialysis programs.

These findings highlight the need for broader national policy and interdisciplinary training initiatives to expand home dialysis accessibility. Integrating PROMs with structured clinical training

and individualized care planning may help drive the transition toward more patient-centered and resource-efficient renal care models (18,19).

The study highlights a significant trend among healthcare professionals: most support referring patients to the dialysis modality they believe will provide the best clinical outcomes, even when patients are unsure about this. This raises important questions about patient-centered treatment and shared decision making in healthcare. It suggests that some healthcare providers prioritize perceived treatment effectiveness over patients' preferences. However, this approach also raises concerns about respecting patients' autonomy and involving them in decisions about their care. It has been reported that a significant proportion of kidney healthcare professionals prioritize what they perceive as the most effective treatment option, potentially overlooking patient preferences. This underscores the balance between clinical effectiveness and patient-centered care, highlighting that decisions made without consideration of patient preferences may affect the alignment between clinical effectiveness and patient preference (12,13).

Peer support among patients receiving dialysis has been shown to improve emotional well-being and self-management. Patients in centers that encourage peer interaction often report lower anxiety and depression levels. Promoting such support systems

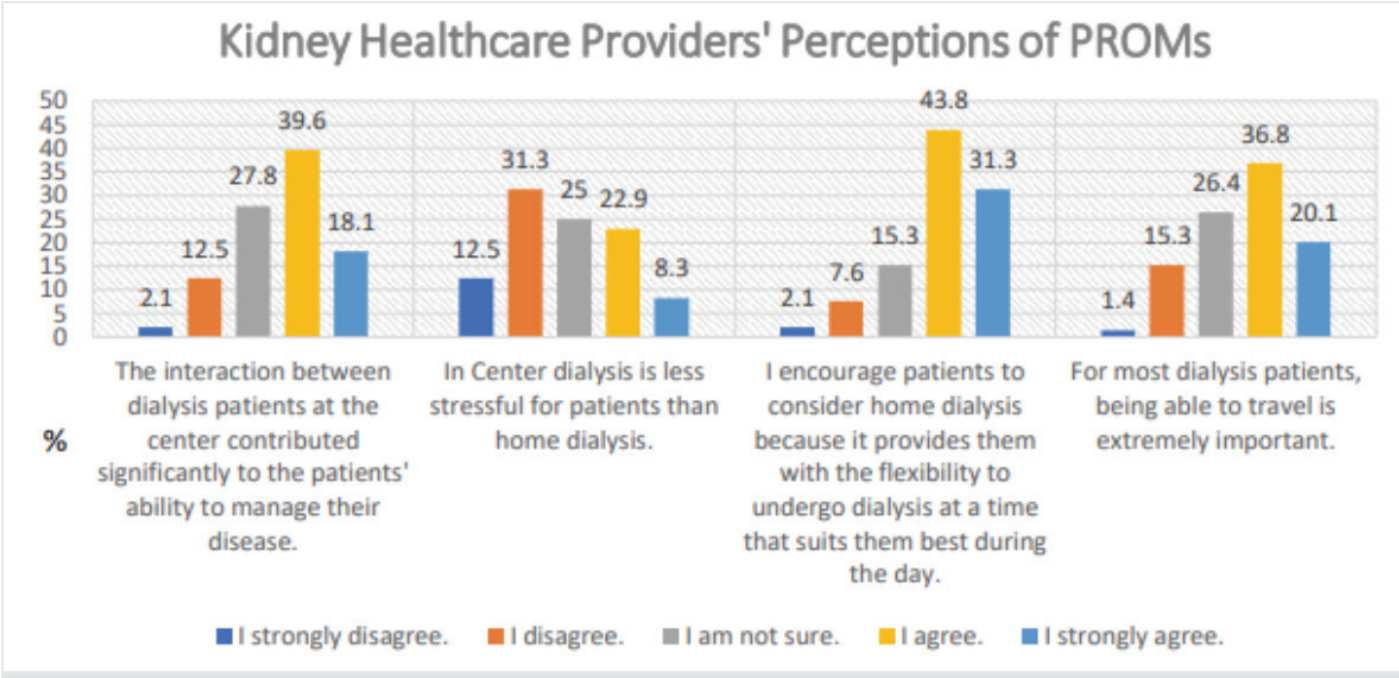

Figure 1. Evaluation of patient perspectives on dialysis modalities by kidney healthcare providers
PROMs: Patient-reported outcome measures

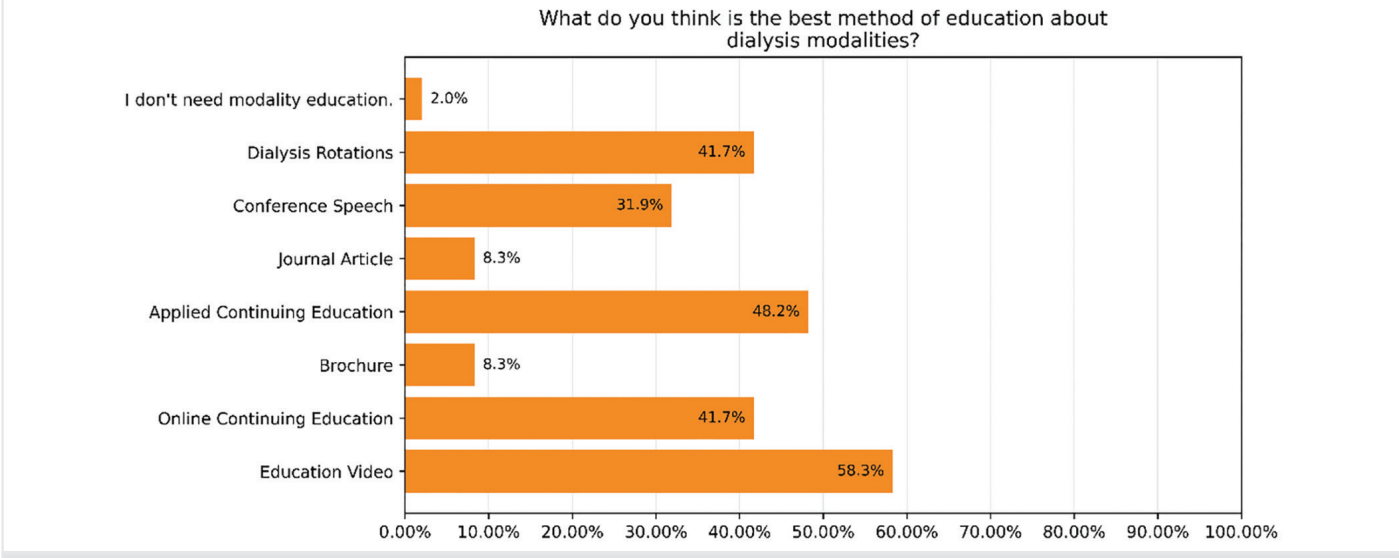

Figure 2. Dialysis modality training preferences of kidney healthcare providers

in dialysis centers could lead to improved emotional and clinical outcomes (14,15).

Many patients undergoing hemodialysis find the thrice-weekly schedule burdensome, impacting work-life balance and overall well-being. Flexible care models, such as home dialysis and telehealth, may reduce this burden. Some KHPs reported using video consultations and remote monitoring during the coronavirus disease 2019 pandemic, demonstrating the potential of these modalities in maintaining continuity of care. Shared decision-making also plays a role in enhancing treatment satisfaction and adherence (16,17).

Training for KHPs is critical to ensure high standards of care. Simulation-based education has proven particularly effective in developing technical and decision-making skills. Studies have shown that such training reduces errors and improves clinical preparedness (18,19). These hands-on approaches also promote interprofessional collaboration and empathy, both essential for patient-centered nephrology practice.

Workshops using case-based learning and role-play enhance communication skills and empathy. These formats enable providers to better understand patient perspectives and deliver more individualized care (20). However, integrating PROMs into clinical nephrology still faces challenges such as resource constraints and limited training. Overcoming these barriers will require support from policymakers, healthcare institutions, and advocacy groups.

Emotional well-being is a critical yet often overlooked aspect of dialysis care. Long-term dialysis patients frequently experience anxiety, depression, and social isolation. Greater control through home dialysis and strong peer/provider support can mitigate these effects. Regular emotional assessment via PROMs may help identify needs early and support holistic care (6).

Study Limitations

This study has several limitations. First, the sample may not be fully representative, as it consisted of voluntary participants. The perspectives of non-responders or those holding differing views may be underrepresented. Second, the use of an online survey may introduce bias, particularly social desirability bias. Third, the cross-sectional design limits the ability to assess changes in attitudes over time. Lastly, while the study explores preferences for home dialysis, it does not include specific data on the availability or readiness of centers to support such modalities, which could impact the feasibility of broader implementation.

Conclusion

This study highlights the value of PROMs in kidney care from the perspective of KHPs in Türkiye. PROMs enhance communication, guide shared decision-making, and support more personalized treatment. While home dialysis modalities are generally favored for their flexibility and quality-of-life benefits, the integration of PROMs and patient-centered care practices remains limited. Expanding education and structured training for KHPs, combined with system-level support, is essential to improve implementation. Future efforts should focus on addressing practical and systemic barriers to PROMs integration and supporting initiatives that prioritize patient perspectives and needs.

Ethics

Ethics Committee Approval: Ethics approval was obtained from Bezmialem Vakıf University with the Ethics Committee (decision no: 2023/59, date: 22.03.2023).

Informed Consent: Written informed consent was waived by the ethics committee; participation was voluntary and completion of the anonymous online survey implied consent.

Footnotes

Authorship Contributions

Concept: E.K., M.G., R.K., Design: E.K., M.G., Ö.C.E., R.K., Data Collection or Processing: E.K., C.S., Analysis or Interpretation: E.K., M.G., Ö.C.E., C.S., A.Y.T., Literature Search: E.K., M.G., A.Y.T., R.K., Writing: E.K., Ö.C.E., R.K.

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Virtual Orthognathic Surgery: A Retrospective 3D Analysis of Surgical Planning vs. Postoperative Outcomes

Sanal Ortognatik Cerrahi: Cerrahi Planlama ve Postoperatif Sonuçların Retrospektif 3B Analizi

Taha PERGEL[1], Emine Fulya AKKOYUN[1], Tuğba KUŞLU[2], Esra Saliha YÖRÜK[3]

[1]Bezmialem Vakıf University Faculty of Dentistry, Department of Oral and Maxillofacial Surgery, İstanbul, Türkiye
[2]Private Practice, İstanbul, Türkiye
[3]Bezmialem Vakıf University, Institute of Health Sciences, Department of Oral and Maxillofacial Surgery, İstanbul, Türkiye

ABSTRACT

Objective: Orthognathic surgery addresses facial deformities by improving both function and aesthetics, with its success relying heavily on accurate planning. This study aimed to assess the long-term accuracy of virtual surgical planning (VSP) by comparing three-dimensional (3D) preoperative virtual models with actual postoperative outcomes and identifying regions prone to deviation.

Methods: A retrospective study was conducted and approved by the Ethics Committee of Bezmialem Vakıf University. Patients who underwent bimaxillary surgery for Class II or III malocclusion and had postoperative computed tomography scans ≥6 months later were included. VSP was performed using NemoFab software. Standardized Le Fort I and bilateral sagittal split ramus osteotomies were conducted. The preoperative virtual planning model and the postoperative surgical model were aligned using surface-based registration in 3-matic and analyzed in Mimics. Linear and directional (sagittal, coronal, axial) deviations were measured at cephalometric landmarks, and 3D color-coded deviation maps were generated with a ±2 mm threshold. Distance differences between 15 cephalometric points on preoperative planning and postoperative models were statistically analyzed using a one-sample t-test.

Results: Forty-two patients (aged between 18 and 40) were included. The mean deviation was 2.19±0.82 mm. Significant deviations (>2 mm) were observed at anterior nasal spine (ANS)

ÖZ

Amaç: Ortognatik cerrahi, işlev ve estetiği iyileştirerek yüz deformitelerini düzeltmeyi amaçlar ve başarısı büyük ölçüde doğru cerrahi planlamaya bağlıdır. Bu çalışmanın amacı, sanal cerrahi planlamanın (SCP) uzun dönem doğruluğunu değerlendirmek ve sapmalara en yatkın anatomik bölgeleri belirlemektir.

Yöntemler: Bezmialem Vakıf Üniversitesi Etik Kurulu onayıyla yürütülen retrospektif çalışmaya, Sınıf II veya III maloklüzyon nedeniyle bimaksiller cerrahi geçiren ve ameliyattan en az 6 ay sonra postoperatif bilgisayarlı tomografi görüntüleri alınmış hastalar dahil edildi. SCP NemoFab yazılımı ile yapıldı. Tüm hastalara standart Le Fort I ve bilateral sagittal split ramus osteotomisi uygulandı. Preoperatif ve postoperatif üç boyutlu (3B) modeller 3-matic yazılımında yüzey tabanlı çakıştırma yöntemiyle hizalanarak Mimics yazılımında analiz edildi. Seçilen sefalometrik referans noktalar arasında doğrusal ve yönsel (sagittal, koronal, aksiyel) sapmalar ölçüldü. ±2 mm eşik değeri kullanılarak renk kodlu 3B sapma haritaları oluşturuldu. Preoperatif planlama ve postoperatif sonuç modellerinde belirlenen 15 sefalometrik nokta arasındaki mesafe farkları, tek örneklem t-testi ile istatistiksel olarak karşılaştırıldı.

Bulgular: Çalışmaya 18-40 yaş arası 42 hasta dahil edildi. Ortalama toplam sapma 2,19±0,82 mm olarak bulundu. Ön nazal spina (ANS) ve arka nazal spina (PNS) noktalarındaki sapmalar ile maksiller ortalama sapma anlamlı şekilde 2 mm'nin üzerindeyken,

Address for Correspondence: Asst. Prof. Emine Fulya Akkoyun, Bezmialem Vakıf University Faculty of Dentistry, Department of Oral and Maxillofacial Surgery, İstanbul, Türkiye
E-mail: efulyaakkoyun@hotmail.com
ORCID IDs of the authors: T.P.: 0000-0001-8154-8606, E.F.A.: 0000-0003-4154-2503, T.K.: 0000-0003-1701-2684, E.S.Y.: 0009-0006-4655-8730

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ABSTRACT

and posterior nasal spine (PNS) points, and for maxillary mean deviation, while mean deviations in axial, coronal and sagittal planes were significantly below 2 mm. No significant differences were observed based on sex, skeletal class, or surgical sequence. Most discrepancies occurred in the anterior maxilla, chin, and posterior mandible. Preoperative asymmetry and pogonion deviation were not predictive of discrepancies. Intraclass correlation coefficient values >0.90 confirmed measurement reliability.

Conclusion: VSP shows high overall accuracy; however, ANS and PNS remain prone to deviation, warranting further investigation in larger studies.

Keywords: Orthognathic surgery, virtual surgical planning, computer-assisted surgery, surgical outcome evaluation

ÖZ

aksiyel, koronal ve sagittal planlardaki ortalama sapmalar anlamlı şekilde 2 mm'nin altında bulundu. Cinsiyet, iskelet sınıfı ve cerrahi sıralama ile sapma arasında anlamlı fark saptanmadı. En belirgin sapmalar ön maksilla, çene ucu ve posterior mandibula bölgelerinde gözlendi. Preoperatif asimetri ve pogonion sapması, postoperatif sapmalarla ilişkili değildi. Tekrarlanan ölçümlerde sınıf içi korelasyon katsayısı değerlerinin >0,90 olması, analizlerin güvenilirliğini destekledi.

Sonuç: SCP genel olarak yüksek doğruluk sunmaktadır; ancak ANS ve PNS gibi belirli bölgeler sapmalara daha yatkındır ve bu bulguların daha geniş örneklemli çalışmalarla araştırılması gerekmektedir.

Anahtar Kelimeler: Ortognatik cerrahi, sanal cerrahi planlama, bilgisayar destekli cerrahi, cerrahi sonuç değerlendirmesi

Introduction

The primary goal of orthognathic surgery is to correct facial deformities and improve both functional and aesthetic concerns. Its success depends not only on surgical techniques but also on precise and detailed treatment planning (1). With advancements in modern technology, orthognathic surgery planning has evolved into a three-dimensional (3D) virtual process. Using 3D imaging and digitally reconstructed models, surgeons can anticipate potential intraoperative challenges and predict postoperative outcomes more accurately (2-4). Virtual surgical planning (VSP) allows for a highly accurate visualization of the jawbones and surrounding anatomical structures, reducing the risk of complications such as unfavorable fractures, nerve injuries, or malunions during surgery. Furthermore, VSP aids in determining whether additional procedures are necessary, allowing patients to be informed in advance. A linear difference of 2 mm or less and an angular difference of 4 degrees or less between the VSP and the actual postoperative outcome are widely regarded as acceptable thresholds for clinical accuracy. At the same time, exceeding these values are typically considered to be clinically significant (5-8).

Several studies have compared orthognathic surgery outcomes with VSP (2,7,9). However, few have clearly identified the specific anatomical regions where discrepancies occur between the virtual plan and the postoperative outcome. This study aims to evaluate the long-term accuracy of VSP by comparing 3D models representing the preoperative virtual plans and actual postoperative jaw positions, and to identify specific anatomical regions where deviations commonly occur between planned and actual outcomes.

Methods

Study Design/Sample

A retrospective study was designed and approved by the Ethics Committee of Bezmialem Vakıf University (decision no: 2023/202, date: 14.07.2023). Informed consent was waived due to the retrospective design. Patients aged 18 to 40 years who underwent bimaxillary orthognathic surgery for Class II or III dentofacial deformities and had a postoperative computed tomography (CT) scan taken at least six months after surgery between 2020 and 2023 were included in the study. VSP was performed using the NemoFab software (Nemotec, Madrid, Spain; 2020), and surgical splints were used during the procedure. All patients underwent Le Fort I osteotomy and bilateral sagittal split ramus osteotomy, performed by the same surgical team using a standardized technique.

Additional inclusion criteria were:

- Presence of a sufficient number of teeth to ensure preoperative and postoperative occlusal stability
- At least two occlusal contact points on both sides (tripod contact)
- Rigid fixation in all segments
- Adherence to a standardized protocol for preoperative and postoperative CT imaging

Patients were excluded if they:

- Underwent single-jaw surgery or genioplasty in addition to bimaxillary orthognathic surgery
- Had facial deformities due to trauma, cleft lip and palate
- Underwent orthognathic surgery using the model surgery technique
- Had a history of temporomandibular joint disorders or autoimmune diseases
- Lacked VSP records via NemoFab software

Tomographic Data Collection and 3D Model Analysis

3D models obtained from the preoperative VSP of patients meeting the inclusion criteria, representing the predicted postoperative positions of the jaws were generated and exported in standard tessellation language (STL) format. Subsequently, postoperative CT scans obtained at the 6-month follow-up for these patients were recorded in digital imaging

and communications in medicine format. These data were imported into Mimics Innovation Suite software (Materialise, Belgium, v.21.0). Postoperative 3D craniofacial models were reconstructed and exported in STL format. Both preoperative and postoperative 3D models were then imported into 3-matic software (Materialise, Belgium, v.13.0). At least 10 distinct and identical anatomical landmarks on skull were selected on both the preoperative and postoperative models, and the surface-based registration method was used. The registered models were then transferred back to Mimics software, where cephalometric landmarks were identified. The selected cephalometric landmarks included:

- Maxillary and mandibular dental midlines
- Anterior nasal spine (ANS) and posterior nasal spine (PNS)
- Cusps of the right and left upper and lower canines
- Mesiobuccal cusps of the right and left upper and lower first molars
- Pogonion, A point, and B point

The linear distances between corresponding points on the preoperative and postoperative models were measured and recorded. Additionally, the 3D coordinates of each landmark were determined, and distance differences in the sagittal, coronal, and axial directions were calculated separately (Figure 1). Preoperative mandibular asymmetry, maxillary and mandibular midline deviations, and pogonion deviation were measured. The presence of preoperative mandibular asymmetry was recorded. The "create part comparison analysis" function in 3-matic software was used to visualize the discrepancies between the aligned models. 3D color-coded deviation maps were generated to represent the degree of surface deviations. A ±2 mm (5) threshold was set to define the range of deviations for the color mapping. The maxillomandibular complex was divided into six regions: chin, right or left posterior mandible, anterior maxilla, and right or left posterior maxilla. The most significant discrepancy region was identified and noted for each model (Figure 2). A single observer performed all measurements. To assess intra-observer reliability, 20% of all measurements were randomly selected and repeated by the same observer after a minimum two-week interval. Intraclass correlation coefficients (ICC) were calculated for each cephalometric point and deviation measurement to evaluate the repeatability of the measurements.

Variables

The primary outcome variables included location of discrepancies, total, maxillary, and mandibular deviation amounts, as well as deviations at cephalometric points between the planned and actual postoperative measurements. Patient characteristics were recorded as potential influencing factors: age, sex, skeletal malocclusion type (Class II or Class III), surgical sequencing (maxilla-first or mandible-first approach). Patients were divided into two groups based on whether their deviation amounts were less than or greater than 2 mm (5).

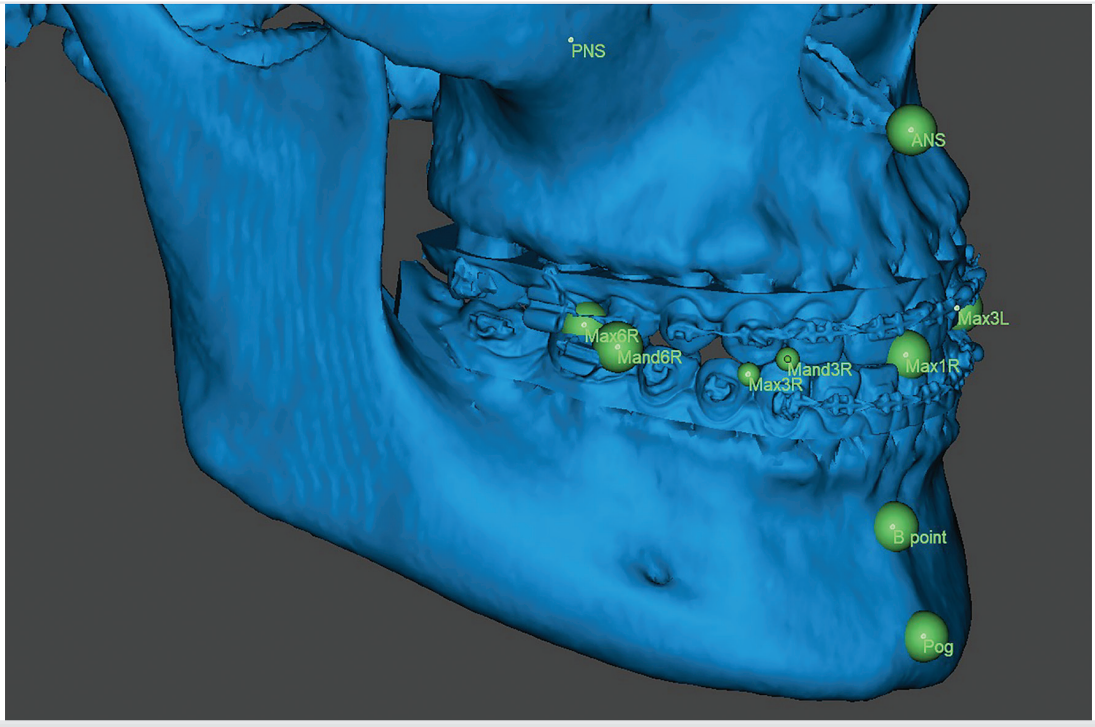

Figure 1. Three-dimensional representation of the cephalometric landmarks marked on both the preoperative (planned) and postoperative virtual models. The 3D coordinates of each landmark were identified, and distance differences between the planned and postoperative positions were measured separately in the sagittal, coronal, and axial planes

ANS: Anterior nasal spine, PNS: Posterior nasal spine, 3D: Three-dimensional

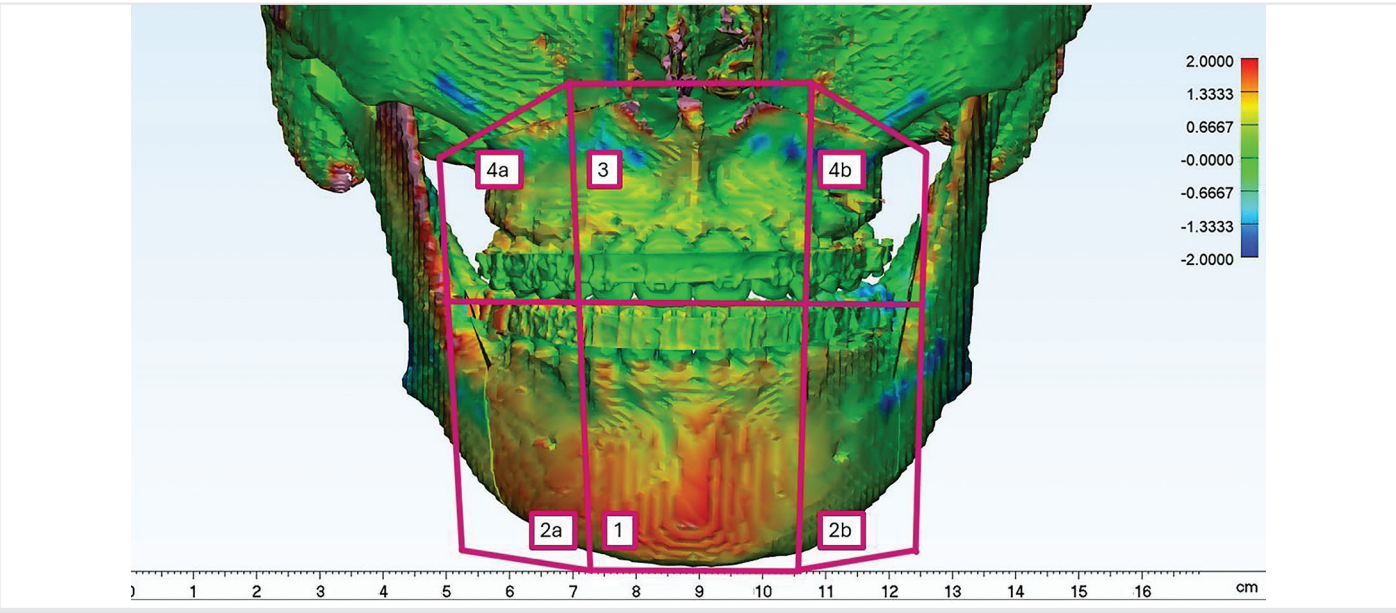

Figure 2. Color-coded 3D deviation maps generated using the "create part comparison analysis" function in 3-matic software to visualize surface discrepancies between the aligned preoperative and postoperative models. A ±2 mm threshold was applied to define the range of deviations for color mapping. The maxillomandibular complex was divided into six regions: (1) chin, right (2a) or left (2b) posterior mandible, (3) anterior maxilla, and right (4a) or left (4b) posterior maxilla

3D: Three-dimensional

Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics software (IBM Corporation, New York, USA, v.26). Descriptive statistics were calculated, including means, minimum and maximum values, medians, standard deviations (SD), and variances. The distance differences between the 15 cephalometric points identified on both the preoperative virtual planning and postoperative surgical outcome models were statistically compared using a one-sample t-test. The analysis was based on a 2 mm deviation threshold, which is considered clinically acceptable according to the literature (5). This test determined the regions where deviations were statistically significant. The normality of the data was assessed using the Shapiro-Wilk test. Independent samples t-tests and Wilcoxon signed-rank tests were conducted to compare differences in sex, skeletal malocclusion type, and surgical sequencing. Additionally, the relationship between sex, skeletal malocclusion type, surgical sequencing (maxilla-first or mandible-first), and the presence of deviations was analyzed using crosstabulations. All tests were two-sided, and a p-value of <0.05 was considered statistically significant.

Results

Forty-two patients were included in the study (26 females, 16 males), with a mean age of 23.07±3.40 years (mean ± SD). Among them, nine patients had Class II skeletal malocclusion, while 33 had Class III skeletal malocclusion. Surgeries were performed using a maxilla-first approach in 24 patients and a mandible-first approach in 18 patients.

The total mean deviation was 2.19±0.82 mm. In half of the patients, the mean total deviation was below 2 mm, whereas in the other half, it exceeded 2 mm. The total mean deviation was 1.55±0.24 mm in patients without clinically significant deviation (≤2 mm), whereas it was 2.84±0.66 mm in those with deviations greater than 2 mm. Descriptive statistics for deviations at each cephalometric point, as well as maxillary, mandibular, and total deviation values, along with deviations in the coronal, sagittal, and axial planes, are presented in Table 1.

According to the results of the one-sample t-test, deviations of the ANS and PNS points were statistically significantly higher than the test value of 2 mm (p=0.030 and 0.007, respectively). Additionally, the maxillary mean deviation (p=0.030) was significantly higher than the test value. In contrast, total mean deviations in three directions (coronal, sagittal, and axial) ($p<0.001$), were significantly lower than the test value. However, maxillary, mandibular, and total deviation amounts, as well as mean deviations in three directions, showed no statistically significant differences between sex, skeletal malocclusion type, or maxilla/mandible-first categories ($p>0.05$). Cross tabulations examining the relationship between sex, skeletal malocclusion type, maxilla/mandible-first categories, and the presence of deviation are presented in Table 2. No statistically significant relationship was found between any of these variables and the presence of deviation ($p>0.05$).

Evaluation of the 3D color-coded deviation maps revealed that the most prominent discrepancies were observed in the anterior maxilla in 17 patients, in the chin region in 12 patients, posterior mandible in 11 patients, and the posterior maxilla in 2 patients.

Table 1. Summary of descriptive measures and statistical test results

	Mean	SD	Median	Min	Max	Range	Variance	p-value*
Age (year)	23.07	3.4	23	18	33	15	11.53	-
Maxillary advancement (mm)	4.76	1.74	5	2	8	6	3.02	-
Point A (mm)	2.1	1.29	2.12	0.17	5.71	5.54	1.68	0.634
Point B (mm)	2.07	1.48	2.08	0.24	7.45	7.21	2.18	0.744
ANS (mm)	2.6	1.75	2.37	0.09	6.47	6.38	3.05	0.030
PNS (mm)	2.92	2.09	2.65	0.01	10.68	10.67	4.37	0.007
Pogonion (mm)	2.45	2.05	1.95	0.06	10.62	10.56	4.21	0.164
Right upper canine (mm)	2.23	1.24	1.96	0.27	5.91	5.64	1.53	0.239
Right upper first molar (mm)	2.23	1.56	1.82	0.15	6.74	6.59	2.42	0.336
Left upper canine (mm)	2.15	1.62	1.59	0.03	6.9	6.87	2.63	0.565
Left upper first molar (mm)	2.11	1.43	1.87	0.22	5.77	5.55	2.04	0.630
Upper midline (mm)	2.14	1.88	1.42	0.05	7.54	7.49	3.52	0.625
Right lower canine (mm)	2.08	1.24	1.72	0.56	5.1	4.54	1.53	0.671
Right lower first molar (mm)	1.97	1.22	1.81	0.06	5.98	5.92	1.49	0.860
Left lower canine (mm)	1.82	1.23	1.49	0.25	5.12	4.87	1.51	0.565
Left lower first molar (mm)	2.17	1.05	2.11	0.25	4.18	3.93	1.1	0.292
Lower midline (mm)	1.87	1.39	1.43	0.01	5.89	5.88	1.93	0.539
Axial mean deviation (mm)	1.07	0.57	0.94	0.21	2.94	2.73	0.32	<0.001
Coronal mean deviation (mm)	1.64	0.6	1.42	0.73	3.05	2.32	0.36	<0.001
Sagittal mean deviation (mm)	0.07	0.08	0.05	0	0.41	0.4	0.01	<0.001
Maxillary mean deviation (mm)	2.31	0.89	2.14	0.99	4.47	3.48	0.8	0.030
Mandibular mean deviation (mm)	2.06	0.9	2.16	0.66	4.28	3.62	0.82	0.659
Total mean deviation (mm)	2.19	0.82	2.02	1.23	4.38	3.15	0.67	0.131

*: One-sample t-test, SD: Standard deviation, ANS: Anterior nasal spine, PNS: Posterior nasal spine

Table 2. Chi-square analysis of deviation presence by sex, skeletal malocclusion type, and surgical sequence

		Patients with deviation <2 mm (n)	Patients with deviation ≥2 mm (n)	p-value*
Sex	**Female**	14	12	0.376
	Male	7	9	
Skeletal malocclusion type	**Class II**	5	4	0.500
	Class III	16	17	
Surgical sequence	**Mandible-first**	6	12	0.059
	Maxilla-first	15	9	

*: Chi-square tests

There was no statistically significant relationship between the presence of preoperative mandibular asymmetry and the presence of postoperative deviation (p=0.710). Additionally, no significant difference was found between the amount of preoperative pogonion deviation from the midline and the presence of postoperative deviation (p=0.300). ICC values for repeated measurements exceeded 0.90 for all evaluated variables, supporting the robustness and reliability of the 3D analysis.

Discussion

Virtual planning techniques and 3D-printed surgical splints are now widely adopted in orthognathic procedures (10-12). VSP enables comprehensive visualization of the dental arches in relation to surrounding skeletal structures within a single 3D model. Compared to traditional planning methods, this digital approach offers multiple advantages. It allows for detailed diagnostic analysis within a 3D environment and enables surgeons to simulate various surgical scenarios to determine the most optimal outcome. It also supports assessing and correcting centric relation in the temporomandibular joint and is a practical educational resource. In computer-assisted surgical simulation systems, the finalized virtual plan can be accurately translated to the clinical setting through surgical splints, which are produced using computer-aided design and computer-aided

manufacturing technologies directly from the digital model (13). Presurgical plans do not always match the actual surgical results. Although surgical notes can be helpful, surgeons may differ in estimating the amount of movement. Additionally, these notes often lack the precision needed to evaluate the accuracy of virtual surgery properly. Postoperative models provide the most reliable way to measure the actual surgical changes. The present study aims to assess the long-term accuracy of VSP by comparing 3D models representing the preoperative virtual plans and actual postoperative jaw positions, and to identify specific anatomical regions where deviations commonly occur between planned and exact outcomes.

In this study, the total mean deviation was 2.19±0.82 mm. Although this value is slightly above the commonly accepted clinical threshold of 2 mm, the difference was not statistically significant. This may indicate that the minor postoperative changes resulting from factors such as soft tissue adaptation or bone remodeling are clinically negligible and may not significantly affect surgical outcomes. Neither preoperative mandibular asymmetry nor the degree of pogonion deviation from the midline showed a statistically significant association with postoperative discrepancies. This suggests that while preoperative asymmetry is an important clinical consideration, it may not be a reliable predictor of surgical inaccuracy when modern virtual planning and execution protocols are used.

A notable portion of the maxillary discrepancy may be attributed to deviations at the ANS and PNS points, both of which were statistically significant. These landmarks are particularly susceptible to intraoperative manipulation, such as dissection or trimming with burs, and may also undergo greater postoperative remodeling. Additionally, the maxillary mean deviation ($p=0.030$), along with mean deviations in three directions (coronal, sagittal, and axial) ($p<0.001$), were significantly higher than the test value. It is possible that intraoperative factors—such as splint seating, fixation technique, or maxillary positioning errors—play a more prominent role in the development of anterior maxillary deviation, as also supported by the overrepresentation of ANS deviation. These findings highlight the importance of carefully evaluating maxillary positioning during surgery, particularly in the anterior region, and suggest that even minor technical imprecisions can result in clinically perceptible deviations.

There appears to be a clear gap in the literature concerning the use of well-validated assessment methods. Notably, a lack of consensus is observed across studies regarding the criteria and approaches used for evaluation and validation. Han et al. (14) and Baan et al. (1) applied voxel-based registration using the cranial region as the reference, which contributed positively to the accuracy of their outcomes. Hsu et al. (5) and Hernández-Alfaro and Guijarro-Martínez (15) proposed a reliable superimposition technique using surface best-fit registration, while Zinser et al. (16) utilized point-based registration, a method more susceptible to human-induced error. The authors adopted the surface-based registration technique in this study to align the preoperative and postoperative models.

Xia et al. (17) utilized a hybrid approach combining surface best-fit alignment with reference point-based assessment. The reference point discrepancies were quantified as both linear and angular deviations across all three spatial dimensions. In a sample of five patients, the mean linear discrepancy was reported as 0.12 mm, with a SD of 0.19 mm (16,17). Hernández-Alfaro and Guijarro-Martínez captured the intraoperative dentition position within the intermediate splint using an intraoral scanner. These scanned surfaces were then compared to the preoperative virtual plans through Mathworks (Natick, MA) software, which generated color-coded deviation maps. The authors reported the mean and SD of the surface distance discrepancies (15). Multiple authors have suggested that a discrepancy of up to 2 mm between the virtual surgical plan and the actual postoperative outcome can be considered an acceptable threshold for surgical accuracy (5,10,13,17,18). Thus, the 2 mm success criterion should be considered the surgical goal. According to the results of this study, the ANS and PNS points were statistically significantly higher than the test value of 2 mm ($p=0.030$ and 0.007, respectively). However, maxillary, mandibular, and total deviation amounts, and deviations in three directions, showed no statistically significant differences between sex, skeletal malocclusion type, or maxilla/mandible-first categories ($p>0.05$). ANS and PNS landmarks are particularly susceptible to intraoperative manipulation, such as dissection or trimming with burs, and may also undergo greater postoperative remodeling. Minor bony reductions performed either for the dissection of nasal muscles from the ANS or to preserve the nasal tip may account for the observed changes at the ANS point. Regarding the PNS, bone reduction extending from the ANS to the PNS is often performed to allow proper repositioning of the nasal septum along the midline without deviation. Changes in muscle orientation and traction forces due to superior or inferior repositioning of the maxilla are also believed to play a role in this remodeling process. Although these alterations are not clinically significant, they are potential explanations for the observed changes.

Perez and Ellis (19) argue that errors inadvertently created by performing mandibular surgery last would potentially be eliminated and not translated to the occlusion if the maxilla was positioned last instead. For instance, a 1 mm malposition of the mandible performed after maxillary surgery would create a malocclusion; however, the same malposition performed first would not. The maxilla would instead be malpositioned this slight amount to accommodate the appropriate occlusion. Slight malpositions (i.e., 1 mm or less), even in the incisor area, are not usually clinical problems. However, a 1-mm malocclusion could be a problem. However, Bozok et al. (20) reported that the absolute mean difference of the B point and the pogonion in the maxilla-first group was statistically significantly higher than in the mandible-first group. Several studies have focused on evaluating the accuracy of maxillary positioning following orthognathic surgery. However, limited attention has been given to the predictability of VSP in cases where mandibular surgery is performed first. This has led to ongoing discussions about whether the surgical sequence influences the accuracy of VSP, and whether additional measures—such as more rigid fixation—may

be necessary when a mandible-first approach is used. Our study found no statistically significant difference between patients who underwent mandible-first and maxilla-first approaches.

Study Limitations

One of the key limitations of this study is the relatively small sample size (n=42), which may reduce the ability to detect subtle but potentially meaningful differences, particularly in subgroup analyses. Additionally, using ANS and PNS as maxillary landmarks may have overestimated surgical discrepancies, as these points are prone to intraoperative reduction and postoperative remodeling. Excluding them led to a notable decrease in measured maxillary deviation, underscoring the importance of landmark selection in accuracy assessment. Furthermore, since cutting guides were not used, deviations may also have resulted from differences between the osteotomy planes defined during virtual planning and those performed intraoperatively by the surgeon. Larger-scale studies are needed to draw more definitive conclusion.

Conclusion

Taken together, the findings suggest that while VSP ensures a high degree of accuracy overall, specific anatomical landmarks—such as the ANS and PNS—remain susceptible to deviation. Moreover, clinically meaningful discrepancies may arise independently of traditionally assumed predictors such as skeletal classification or surgical sequencing. These results highlight the need for further research with larger, statistically powered sample sizes.

Ethics

Ethics Committee Approval: The retrospective study was designed and approved by the Ethics Committee of Bezmialem Vakıf University (decision no: 2023/202; date: 14.07.2023).

Informed Consent: Informed consent was waived due to the retrospective design.

Footnotes

Authorship Contributions

Surgical and Medical Practices: T.P., E.F.A., T.K., Concept: T.P., E.F.A., T.K., Design: T.P., E.F.A., T.K., Data Collection or Processing: T.P., E.F.A., T.K., E.S.Y., Analysis or Interpretation: T.P., E.F.A., E.S.Y., Literature Search: T.P., E.F.A., E.S.Y., Writing: T.P., E.F.A.

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Original Article

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Sexual Problems of Women with Kidney Transplant: A Qualitative Study

Böbrek Nakli Olan Kadınların Cinsel Sorunları: Nitel Bir Çalışma

Naile AKINCI[1], Yeliz YILDIRIM VARIŞOĞLU[2], Bayram DOĞAN[3]

[1]Fenerbahçe University Faculty of Health Sciences, Department of Nursing, İstanbul, Türkiye
[2]İstanbul University Faculty of Nursing, Department of Nursing, İstanbul, Türkiye
[3]Bezmialem Vakıf University Faculty of Medicine, Department of Urology, İstanbul, Türkiye

ABSTRACT

Objective: This qualitative study aimed to explore the experiences, perspectives, and challenges faced by women who underwent kidney transplantation, particularly regarding the impact of transplantation on their own and their partner's sexual lives.

Methods: The study was conducted with 15 women who had received kidney transplants at a private hospital in İstanbul. Data were gathered using a two-part semi-structured interview form developed by the researcher based on a review of the relevant literature. The data obtained from the interviews were analyzed using content analysis. Data analysis was carried out concurrently with data collection. This study adhered to the consolidated criteria for reporting qualitative research.

Results: Based on a thematic analysis of the interviews, four main themes emerged: concerns about reproductive health, including subthemes of fear of infertility and anxiety about pregnancy; disease-associated sexual reluctance, including subthemes of reduced sexual interest, fatigue, weakness, sleep disturbances, and depression; perception of femininity and body image, including subthemes of feelings of incompleteness and inadequacy; concerns about the spouse/partner, including subthemes of fears about being unable to meet the sexual needs of the spouse/partner and feelings of guilt related to their partner's sexual dissatisfaction.

Conclusion: In conclusion, sexual dysfunction continues to persist among women even after kidney transplantation due to various physical and psychological factors. To support patients in

ÖZ

Amaç: Bu nitel çalışma, böbrek nakli yapılan kadınlarda, naklin kendi ve partnerlerinin cinsel yaşamları üzerindeki etkisine ilişkin deneyimlerini, bakış açılarını ve karşılaştıkları zorlukları araştırmayı amaçlamaktadır.

Yöntemler: Çalışma, İstanbul'daki özel bir hastanede böbrek nakli olan 15 kadınla yürütüldü. Veriler, araştırmacı tarafından ilgili literatürün incelenmesine dayanarak geliştirilen iki aşamalı yarı yapılandırılmış görüşme formu kullanılarak toplandı. Görüşmelerden elde edilen veriler içerik analizi kullanılarak analiz edildi. Veri analizi veri toplama ile eş zamanlı olarak gerçekleştirildi. Bu çalışma, nitel araştırma raporlama için konsolidasyon kriterlerine uymuştur.

Bulgular: Görüşmelerin tematik analizi sonucunda dört ana tema ortaya çıktı: anne olamama korkusu ve gebelik kaygısı alt temalarını içeren üreme sağlığı ile ilgili endişeler; cinsel ilginin azalması, yorgunluk, halsizlik, uyku bozuklukları ve depresyon alt temalarını içeren hastalıkla ilişkili cinsel isteksizlik teması; eksiklik ve yetersizlik duyguları alt temalarını içeren kadınlık algısı ve beden imajı; eşin/partnerin cinsel ihtiyaçlarını karşılayamama korkusu ve partnerinin cinsel tatminsizliği ile ilgili suçluluk duyguları alt temalarını içeren eş/partner ile ilgili endişeler.

Sonuç: Sonuç olarak, çeşitli fiziksel ve psikolojik faktörler nedeniyle böbrek naklinden sonra bile kadınlarda cinsel işlev bozukluğu devam etmektedir. Hastaların genel refahlarının bir parçası olarak sağlıklı bir cinsel yaşam sürdürmelerini desteklemek için, cinsel

Address for Correspondence: Asst. Prof. Naile Akıncı, Fenerbahçe University Faculty of Health Sciences, Department of Nursing, İstanbul, Türkiye
E-mail: naileaksit@gmail.com
ORCID IDs of the authors: N.A.: 0000-0002-7328-8610, Y.Y.V.: 0000-0002-6350-7218, B.D.: 0000-0002-3007-8525

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ABSTRACT

maintaining a healthy sexual life as part of their overall well-being, sexual health should be routinely assessed by a multidisciplinary team, including transplant surgeons, surgical and obstetric/gynecology nurses, and psychologists.

Keywords: Kidney transplantation, sexual dysfunction, qualitative study

ÖZ

sağlık, nakil cerrahları, cerrahi ve obstetrik/jinekoloji hemşireleri ve psikologlar dahil olmak üzere multidisipliner bir ekip tarafından rutin olarak değerlendirilmelidir.

Anahtar Kelimeler: Böbrek nakli, cinsel işlev bozukluğu, nitel çalışma

Introduction

Sexuality is the whole of the characteristics of living beings as a requirement of masculinity and femininity, as well as the most basic natural condition for the production necessary for the continuity of living life (1).

The sexual problems experienced by patients after organ transplantation can be seen as a result of psychological and physiological factors. Sexual dysfunction is an important problem before and after kidney transplantation (2). It is claimed that kidney transplantation reduces morbidity and mortality in most patients with end-stage renal disease, improves the quality of life, and restores sexual function and fertility (3). However, according to studies performed after kidney transplantation, it has been reported that sexual dysfunction is more common especially in women (4,5). Similarly, it has been reported that sexual dysfunction is common in women after kidney transplantation in the Turkish population, and its incidence is in a wide range such as 46-93.9% (6-8). On the other hand, among the treatment options for end-stage renal disease, the most effective option for restoring the health and sexual functions of patients is kidney transplantation (9-11). Although sexual dysfunction is common after kidney transplantation, its etiology is assumed to be multifactorial. Disorders associated with symptoms such as decreased sexual desire, inability to reach orgasm, vaginal dryness, menstrual irregularities, infertility, and dyspareunia can be observed (12). Also, the integration of a new organ into the body may mean adjustment of body image, which can hurt intimacy and sexual behavior (13). Although it is known that the quality of life in women increases and hypoactive sexual disorder improves after kidney transplantation, it is known that body image and femininity perceptions related to surgical scars, fear of losing the new organ, and problems experienced in adapting to living with the organ will also affect sexual functions.

On the other hand, besides the emotional and social dimensions, an unplanned pregnancy shortly after a kidney transplant may expose both the mother and the fetus to significant risks, and women are advised to seek contraception counseling. Almost all women who have a transplant after discharge are in frequent contact with a team of doctors and nurses. However, it is reported that sexuality is often overlooked (14,15).

This study was designed qualitatively to understand the sexual problems of women with kidney transplantation and the emotions they experienced during the disease process. In this way, it is thought that the implications for the clinical management of sexuality, which are ignored with the revealing of the sexual problems experienced by women after kidney transplantation, will guide future studies on the subject.

Methods

Study Design

This qualitative study aimed to identify experiences, views, and problems of women who had kidney transplants regarding the effects of kidney transplants on their and their partner's sexual life. This study was conducted by using constructivist content analysis to understand the sexual problems of kidney transplant women and their emotions during the disease process. In this way, it is thought that the implications of the clinical management of sexuality, which is ignored in surgical clinics, will guide future studies on the subject. This study adhered to the consolidated criteria for reporting qualitative research.

Participants

The target population of this study consisted of women who had undergone kidney transplantation in the urology department of a private hospital between June 2021 and December 2021. Although qualitative studies typically involve small sample sizes, ranging from 5 to 25 participants, it is widely accepted that sampling may cease once data saturation is achieved that is, when no new themes or insights emerge (16,17).

Accordingly, 15 female patients who met the inclusion criteria and voluntarily agreed to participate were selected through criterion sampling. The inclusion criteria were as follows:

- Having undergone kidney transplantation at least six months prior to the study,
- Being aged 18 years or older,
- Being oriented to person, place, and time,
- Being able to communicate in Turkish, and
- Voluntarily consenting to participate in the study.

Data Collection

Interviews were conducted individually in a quiet, private room. Each interview lasted approximately 30-40 minutes. Since the participants did not consent to audio recording, the researcher documented the interviews through detailed handwritten notes.

Data Collection Tools

Data were gathered using a two-part semi-structured interview form developed by the researcher based on a review of the relevant literature. The first part of the form included demographic and clinical questions regarding the participants' characteristics, such as age, income status, reason for transplantation, and date of transplantation. The second part comprised open-ended questions aimed at exploring the effects of kidney transplantation on their sexual lives. Example questions included:

- "How was your sexual life before your illness?"
- "What changes have occurred in your sexual life after the operation?"
- "How has your spouse been affected by the changes in your body following the transplantation?"

Data Analysis

The data obtained from the interviews were analyzed using content analysis. Data analysis was carried out concurrently with data collection, following the method outlined by Graneheim and Lundman (18). This process involved transcribing each interview immediately after completion, reading the full transcription to gain an overall understanding of the content, identifying basic codes, grouping similar initial codes into broader sub-themes, and ultimately deriving overarching themes from these sub-themes (18).

Initially, the first three interviews were independently coded by each researcher. The codes were then compared, and any discrepancies were resolved through consensus. After reaching agreement on the coding of the first three interviews, the remaining interviews were coded and analyzed accordingly. Data saturation was achieved after 15 interviews.

The main themes identified were: concerns about reproductive health, disease-associated sexual reluctance, perception of femininity and body image, concerns about the spouse/partner. These themes were discussed in detail in the findings and discussion sections.

Ethical Considerations

Interviews were conducted after the necessary institutional and ethics committee approvals were obtained from the Clinical Research Ethics Committee of İstanbul Medipol University (decision no: 391, date: 28.05.2020). Before each interview, participants were informed about the purpose and nature of the study. They were assured that all written information would be securely stored by the researchers, that confidentiality would be maintained, and that their responses would be used solely for scientific purposes. Written and verbal informed consent was obtained from all participants.

Results

Of the 15 participants, the mean age was 43±4.28 years. More than half of the women had completed higher education (8 out of 15, 53.3%), indicating that the sample largely consisted of women with an advanced educational background. In addition, two-thirds of the participants were married (10 out of 15, 66.7%), suggesting that the majority were living with a spouse or partner at the time of data collection.

Four main themes were generated based on the thematic analysis of the interviews with participants about their sex lives after kidney transplantation. Themes and relevant subthemes are presented in Table 1.

Theme 1: Concerns About Reproductive Health

One participant had the fear of not being able to get pregnant and the anxiety of not being able to become a mother both before and after the transplant surgery.

"….When I met my husband, I was a dialysis patient. During that time, I did not agree to marry him because I thought that I would not be able to get pregnant and become a mother. We loved each other very much. That's why I didn't agree to get married to him because I wished him to become a father and live through a healthy process. However, my husband did not give up. We finally got married. Although we went through a very difficult pregnancy and the postpartum period, he did not cheat on me or he did not leave me" (P1).

Table 1. Themes and sub-themes

Themes	Sub-themes
Concerns about reproductive health	Fear of not being able to become a mother Fears about pregnancy
Disease-associated sexual reluctance	Low sexual interest Fatigue, weakness Depression Sleeping problems
Perception of femininity/body image	Feelings of incompleteness Feeling of inadequacy Concerns of not deserving love from the spouse/partner Concerns of not being liked
Concerns about the spouse/partner	Concerns about not deserving a healthy spouse/partner Concerns about inadequacy to meet the sexual needs of the spouse/partner Feeling guilty about the sexual problems with the spouse/partner

Theme 2: Disease-associated Sexual Reluctance

Almost all participants reported that they experienced sexual reluctance because of the fatigue and weakness that they felt before receiving the transplant. While some participants felt better after receiving the transplant, others had lowered sexual interest and desire.

"…I was feeling very tired and weak during the treatment I received before transplantation. I didn't feel like doing anything. I'm feeling a little better now. However, I can't say that I wish to have sex that much. I force myself to make love only because my husband wishes to have sex" (P1).

Another woman declared:

"...My husband and I couldn't have a normal sexual relationship because I felt fatigued and weak all the time before the transplantation. The fatigue continued for a while after the transplant. To tell you the truth, I have sex only to make my husband happy. I, personally, do not feel to have sex that much" (P12).

One of the women experiencing sexual desire because of the fatigue and weakness explained her feelings as such:

"...I'm feeling better now and I don't feel fatigued. However, I've been dealing with the disease for years. If I were not married, I would never think of having sex" (P13).

Theme 3: Perception of Femininity/Body Image

The examination of the participants' statements revealed that they felt incomplete or imperfect as a woman.

"…My husband is a healthy person. I wouldn't wish him to marry an imperfect woman like myself and go through problems throughout his life. My husband is a very good person. He stands by me despite all my inadequacies. As a woman, I could not do anything for my husband during the treatment process. I got pregnant after the treatment and stayed in the hospital for months after giving birth. At those times, I couldn't take care of my baby or my husband. My husband went through quite difficult times. I sometimes ask myself what I have done to deserve him. My husband continues to support me in every way despite all issues…" (P10).

Another woman declared:

"…I had no sexual desire before and during the treatment. I'm feeling better now, but my husband says he's afraid something will happen. I think he does not want to be with me or he does not like me as a woman anymore" (P4).

Most of the women also stated that they were not wanted by their husbands, they were not desired and they did not feel like women (P2, P4, P8, P9-15).

"…I'm incomplete now. Needless to say, my husband does not like me…I don't know, I haven't felt like a woman for a long time" (P8).

"…I don't feel like a woman… I am ashamed of my husband" (P9).

Theme 4: Concerns About the Spouse/Partner

Based on the statements of the participants, it was determined that most of them felt guilty because they neglected their spouses/partners during the disease and treatment processes. The thoughts that they deserved to be cheated on, abandoned, or neglected by their spouses/partners revealed the concerns of the participants about their spouses/partners.

"…After giving birth, I stayed in the hospital for months. I could not be with my baby and my husband. I'm feeling better after the transplant. Nevertheless, I cannot resent my husband if, one day, he says that there is someone else in his life... I've exhausted him" (P1).

"…My husband is a healthy man and deserves to be with a healthy woman. Sometimes I feel sorry for him. The treatment process that I went through was exhausting not only for me but for him as well. After all, how long a man could stand? He could have cheated on me…" (P3).

Another woman declared:

"...During the treatment process, my husband and I have been separated for long periods, I neglected him a lot. As a woman, I know that I cannot satisfy him" (P5).

"…I feel that my husband does not wish to be intimate with me, I mean sexually, after the treatment. I had the same feeling before I received treatment, too. Maybe he doesn't want to be with me anymore. I agree with him. Who could wait for a woman for such a long time?" (P6).

Concerns about the spouse may also be related to the patriarchal structure of society. In Turkish culture, many women are still married at the request of their families, and their husbands' sexual satisfaction is more important to their traditions. In the studies conducted in Turkish society on women's sexual satisfaction, it has been determined that women have a sense of pleasing their spouses more than themselves, and their sexual satisfaction is dependent on their spouse's happiness. Some participants described experiences indicating that their marriages were shaped by family expectations or limited personal choice. Arranged marriages that continue in Turkish society also negatively affect sexual satisfaction and perception of sexuality. Women's concerns about their spouses are usually because they feel incomplete and unhealthy, and they think that their spouses deserve to be with a healthy women more. This situation may also reflect the culture, regardless of the disease. In other words, women's sexual satisfaction or satisfaction is related to how satisfied they are with their spouses.

Discussion

In this study, it was found that women experienced favorable changes in their sex lives after kidney transplant but sexual reluctance, perception of femininity, concerns about the spouse/partner, and reproductive health concerns that were present previously continued after transplantation. In the literature, it has been reported that women's sexuality improves after kidney transplantation (19). In a study comparing pre-transplant and

post-transplant sexual problems and sexual function in female kidney transplant patients, it was observed that sexual function significantly improved after transplantation (2). A study on women examined participants in three groups as those on hemodialysis, those in the post-transplant period, and those in the control group. That study reported sexual dysfunction rates as 89.7%, 73.9%, and 56.7% in the study groups, respectively. Total female sexual function index scores in the hemodialysis group were significantly lower compared to the scores obtained by women in the post-transplant and control groups ($p<0.05$). Beck Depression Inventory (BDI) scores in the hemodialysis and control groups were 23.24 and 14.17, respectively. There was a significant difference between the two groups ($p<0.05$). The BDI score was 16.65 in the post-transplant group and it was not statistically significantly different. Female sexual dysfunction should be evaluated routinely in patients with chronic kidney failure (20). Özdemir et al. (8) conducted a study on kidney transplant patients in the Turkish population. That study reported sexual dysfunction rates as 56.9% in men and 93.9% in women after transplantation. Sağduyu et al. (9) reported that 80% of kidney transplant patients had problems with sexual function and sexual dysfunction often continued after transplantation.

A study investigating sexual functioning and sexual self-esteem in women, who received pancreas and kidney transplants, reported that 39% of women were found to have normal sexual functioning. Contrary to the literature, only about one-third of women reported that transplantation improved their sexuality (21). The results of this study support the findings reported by previous studies. It can be suggested that sexuality is favorably affected by the improvement of physical symptoms such as fatigue and weakness in women after transplantation. However, in the post-transplant period, women should be evaluated for the perception of femininity, the presence of a sexual desire disorder, and concerns about the spouse/partner. This situation indicates that physiological recovery alone is not sufficient for a complete improvement in sexual life, and that psychosocial and cultural factors also play a decisive role. In particular, gender roles, women's body image, and communication patterns with their partners can significantly influence the sustainability of sexual well-being after transplantation.

Sexual dysfunction is a common problem in case of chronic kidney disease and persists in 50% of patients. A study investigating women's sexual anxiety and quality of life four years after kidney transplantation reported that the highest sexual anxiety scores were observed in the domain of discussing sexuality (mean=2.70) and concerns about sexual pleasure (mean=2.45) with healthcare professionals. There was a significant and inverse correlation between the quality of life and high anxiety levels about the implications of sexual activity on health, quality of sexual intercourse, sexual pleasure, sexual dysfunction, and pessimistic beliefs about treatment. The major problem that women might encounter before and after transplantation is about receiving healthcare services for sexual health, especially when sexuality is neglected in the post-transplant period (1). Therefore, the lack of knowledge and communication skills among healthcare professionals leads to the unmet sexual health needs of female patients. This creates a significant gap in quality of life, despite medical success.

As a part of a research project, a survey was conducted on all types of care providers for kidney patients. It was found out that not all transplant surgeons (73.9%) discussed sexual health with patients and felt responsible for performing such a discussion before and after kidney transplantation, and the patients' level of information was inadequate (39.1%) (22). Surgeons can guide patients toward undergoing an evaluation of sexual health and receiving relevant counseling after kidney transplantation to avoid the persistence of unmet needs. This finding highlights the importance of a multidisciplinary approach. The active involvement of not only surgeons but also nurses, psychologists, and reproductive health specialists can contribute to the improvement of sexual health in female patients.

Ten percent of the world's population suffers from chronic kidney disease. Kidney transplantation improves the quality of life of patients. Sexual dysfunction is common after kidney transplantation. The etiology of sexual dysfunction after kidney transplantation is assumed to be multifactorial. It affects sexual satisfaction and health-related issues unfavorably. Integration of a new organ into the body can mean that the individual should adapt to a new body image. Perceived body image changes can eventually have negative implications on intimacy and sexual behavior. Healthcare professionals need to be trained to optimize the general health and sexual satisfaction of patients with chronic kidney disease and kidney transplants (13). Moreover, expanding psychosocial support services and patient education programs would not only address the physiological effects of organ transplantation but also facilitate the social and emotional adjustment process of individuals.

In a study conducted in a hemodialysis unit at Assiut University Hospitals in Egypt, it was reported that more than half of hemodialysis patients had sexual dysfunction and poor quality of life. In that study, a positive correlation was found between sexual dysfunction and poor quality of life in women undergoing hemodialysis (23). Sexual function and quality of life should be routinely screened in women with chronic kidney disease or kidney transplants. Such patients should receive support from a multidisciplinary team when needed. In conclusion, although kidney transplantation provides physiological benefits, persistent problems remain in the domain of sexual health. Therefore, integrating sexuality into routine medical follow-up should be considered a critical necessity for both individual and public health.

Study Limitations

Limitations include the small number of participants, which may limit the transferability of the findings, and the potential memory (recall) bias. Additionally, since the participants did not consent to audio recording, interviews were documented through handwritten notes, which may have reduced the richness

of verbatim data and increased the risk of missing nuances.

Recommendations for Future Research

Future research should aim to address these limitations by conducting multicenter, longitudinal studies with larger and more diverse populations to better understand the long-term trajectory of sexual health post-transplantation. It is essential to develop and validate culturally sensitive instruments for assessing sexual function and related concerns.

Moreover, intervention-based studies examining the effectiveness of targeted counseling programs, psychological therapies, and partner-inclusive approaches could provide valuable insights into best practices for managing sexual dysfunction. Finally, greater emphasis should be placed on training healthcare professionals to initiate discussions on sexual health routinely and empathetically in transplant care settings.

Clinical Implications

Optimal management should include, routine assessment of sexual function post to kidney transplant and screening for sexual dysfunction during follow-up.

Conclusion

This study underscores the complex interplay between physical recovery and psychosocial adaptation in women following kidney transplantation. Although transplantation leads to significant improvements in physical health and partially enhances sexual functioning, persistent concerns related to body image, sexual desire, partner relationships, and femininity continue to affect patients' sexual well-being.

These findings highlight the necessity of integrating routine sexual health assessments and counseling into the pre- and post-transplant care process. Healthcare professionals must be trained to recognize and address the multifactorial nature of sexual dysfunction in kidney transplant recipients, considering both physiological and psychological dimensions.

Future care models should adopt a multidisciplinary, patient-centered approach to optimize not only the medical outcomes but also the emotional, relational, and sexual health of female transplant patients. By doing so, healthcare systems can contribute to a more comprehensive improvement in the quality of life for women living with a kidney transplant.

Ethics

Ethics Committee Approval: Interviews were conducted after the necessary institutional and ethics committee approvals were obtained from the Clinical Research Ethics Committee of İstanbul Medipol University (decision no: 391, date: 28.05.2020).

Informed Consent: Written and verbal informed consent was obtained from all participants.

Footnotes

Authorship Contributions

Surgical and Medical Practices: N.A., Y.Y.V., B.D., Concept: N.A., Design: N.A., Data Collection or Processing: N.A., Y.Y.V., B.D., Analysis or Interpretation: N.A., Y.Y.V., Literature Search: N.A., Y.Y.V., B.D., Writing: N.A., Y.Y.V.

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Original Article

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Prognostic Significance of Lymphocyte Percentage and IL-6 Level in Patients Undergoing Radiotherapy for Advanced Lung Cancer

Radyoterapi Yapılan İleri Akciğer Kanseri Hastalarında Lenfosit Oranı ve IL-6 Düzeyinin Prognostik Önemi

Kimia ÇEPNİ, Tuğçe DURSUN UÇAR, Tuğçe Hilal UÇGUN, Huriye Senay KIZILTAN

University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital, Department of Radiation Oncology, İstanbul, Türkiye

ABSTRACT

Objective: Although most patients with locally advanced lung cancer show a moderate response to chemoradiotherapy, the results are not satisfactory. In lung cancer, lymphocyte percentages and interleukin-6 (IL-6) cytokine levels have been reported to be significantly correlated with survival rates. In this study, we investigated the effects of lymphocyte percentages and IL-6 levels on overall survival and progression-free survival.

Methods: One hundred forty-two patients diagnosed with lung cancer and treated with radiotherapy were included in the study. Patients were examined according to gender, age, clinical stage, Eastern Cooperative Oncology Group performance status, pathology and pre-radiotherapy lymphocyte percentages and IL-6 cytokine levels. The results were also analyzed according to radiotherapy dose, treatment sites and response rates.

Results: When comparing patients with lymphocyte percentage >15% to those with lymphocyte percentage ≤15%, median overall survival was 18 months and 7 months, progression-free survival was 17 and 5 months, respectively, and median overall survival and progression-free survival were significantly higher in those with lymphocyte percentage >15% (p=0.007 and p=0.006). When comparing patients with IL-6 ≤7 pg/mL to those with >7 pg/mL, median overall survival was 14 and 7 months, progression-free survival was 9 and 4 months, and median overall survival and

ÖZ

Amaç: İlerlemiş akciğer kanseri hastalarının çoğunda, kemoradyoterapiyle orta düzeyde bir cevap alınsa da sonuçlar yüz güldürücü değildir. Akciğer kanserinde, lenfosit yüzdeleri ve interlökin-6 (IL-6) sitokin düzeylerinin yaşam oranları ile anlamlı düzeyde korelasyon gösterdiği bildirilmiştir. Bu çalışmada, lenfosit yüzdeleri ve IL-6 düzeylerinin genel sağkalım ve progresyonsuz sağkalım üzerine etkisini araştırdık.

Yöntemler: Çalışmaya akciğer kanseri tanısı almış ve radyoterapi görmüş 142 hasta dahil edildi. Hastalar cinsiyet, yaş, klinik evre, Eastern Cooperative Oncology Group performans durumu, patoloji ve radyoterapi öncesi lenfosit yüzdeleri ve IL-6 sitokin seviyelerine göre incelendi. Sonuçlar ayrıca radyoterapi dozu, tedavi bölgeleri ve yanıt oranlarına göre analiz edildi.

Bulgular: Lenfosit yüzdesi >%15 olan hastalar lenfosit yüzdesi ≤%15 olan hastalarla karşılaştırıldığında, medyan genel sağ kalım sırasıyla 18 ay ve 7 ay, progresyonsuz sağ kalım sırasıyla 17 ve 5 ay olarak bulundu ve medyan genel sağ kalım ve progresyonsuz sağ kalım lenfosit yüzdesi >%15 olanlarda anlamlı şekilde daha yüksekti (p=0,007 ve p=0,006). IL-6 ≤7 pg/mL olan hastalar >7 pg/mL olan hastalarla karşılaştırıldığında, medyan genel sağ kalım 14 ve 7 ay, progresyonsuz sağ kalım 9 ve 4 ay idi ve medyan genel sağ kalım ve progresyonsuz sağ kalım IL-6 ≤7 pg/mL olan hastalarda anlamlı derecede daha yüksekti (p=0,011 ve p=0,01).

Address for Correspondence: Kimia Çepni MD, University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital, Department of Radiation Oncology, İstanbul, Türkiye
E-mail: kimiagh@gmail.com
ORCID IDs of the authors: K.Ç.: 0000-0001-7467-6917, T.D.U.: 0009-0003-1884-1334, T.H.U.: 0000-0001-5842-4971, H.S.K.: 0000-0002-9930-7197

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ABSTRACT

progression-free survival was significantly higher in patients with IL-6 ≤7 pg/mL (p=0.011 and p=0.01).

Conclusion: In advanced lung cancer patients, lymphocyte counts and IL-6 levels before radiotherapy are important prognostic biomarkers, and these tests can be used in patient follow-up and to develop different treatment strategies.

Keywords: IL-6 in cancer, lymphocyte in cancer, inflammation in cancer, radiation in hematotoxicity

ÖZ

Sonuç: İlerlemiş akciğer kanseri hastalarında, radyoterapi öncesi lenfosit sayımı ve IL-6 düzeyleri önemli prognostik biyobelirteçlerdir ve bu testler hasta takibinde ve farklı tedavi stratejileri geliştirmek için kullanılabilir.

Anahtar Kelimeler: Kanserde IL-6, kanserde lenfosit, kanserde inflamasyon, hematotoksisitede radyasyon

Introduction

Lung cancer (LC) is divided into two main histopathologic groups: small cell LC (SCLC) and non-SCLC (NSCLC). SCLC is a malign neuroendocrine neoplasm that constitutes 15-20% of all LCs. NSCLC occurs in 80-85% of cases. NSCLC has different histopathologic subtypes such as squamous cell, adeno and large cell carncer. Adenocancer and squamous cell cancer are the most common subtypes of NSCLC and exhibit different genetic pathways, control mechanisms and prognostic features. These differences have important clinical implications in terms of disease pathogenesis, treatment response and patient prognosis (1).

In addition, clinical studies in NSCLC have revealed that adenocarcinoma and squamous cell carcinoma respond differently to chemotherapy, agents targeting kinase mutations, and immune checkpoint inhibitors (2). Accordingly, these two histopathological subtypes of LC are considered to be different diseases at the molecular, pathological and clinical levels (3). Despite all advances in diagnosis and therapies of LC, overall survival (OS) rates are still not not enough yet (4,5).

Prognostic factors affecting survival are known to be factors such as histopathology, tumor stage and markers, poor performance, weight loss in a short time, increasing acute phase reactans, such as interleukin-6 (IL-6), ferritin, C-reactive protein (CRP) and D-dimer levels (6,7).

Surgery in the early stage and radiotherapy (RT) in inoperative patients are important accepted treatments in LC. Although a moderate response is obtained with chemotherapy, RT or chemoradiotherapy with or without immunotherapy (IT) in most patients with LC, the results are not satisfactory (8).

Lymphocytes and neutrophils play important roles in inflammation in tumors (6,9,10). The distruption of normal ratio between neutrophils and lymphocytes causes imbalance between apoptotic and cytotoxic effects, and may contribute to development of hypoxia in tumor and metastases (11).

Since RT has a cytotoxic effect especially on hematopoietic cells, the number of lymphocytes decreases very early because they are more sensitive to radiation. Once lymphopenia develops, it may take a long time to recover (12). In addition, there is information in the literature that radiation increases immunity at certain doses (13). It has been shown that immunity can be increased and survival rates can be improved with low-volume, high-dose, few-fractionated RT, as in stereotactic radiosurgery (14).

To increase the effect of treatments, targeted treatments and IT are increasingly preferred in addition to chemotherapy. Various methods such as increasing lymphocyte rates have been tried in IT in order to increase the effectiveness of treatment in LC and improve survival rates (15).

In various cancers, high pre-treatment "neutrophil-to-lymphocyte ratio" (NLR) determined with peripheral blood tests has been reported to be an independent, inexpensive, and easily applicable prognostic biomarker associated with poor survival, especially in breast and gastrointestinal cancers (16-18). In addition, the prognostic impact of NLR on LC has been shown in many studies.

In LC, inflammatory markers such as CRP, "platelet-to-lymphocyte ratio", NLR and "lymphocyte-to-monocyte ratio" has been shown to significantly associate with prognosis (19-21).

"Absolute lymphocyte counts" (ALC) below <500 cells/mL are reported to negatively affect cancer treatment responses (22). Although new immunological and histological biomarkers such as "epidermal growth factor receptor" and "intercellular adhesion molecule-1" have been identified, the measurement of these markers is costly and often time-consuming (23).

There is still no reliable prognostic factor that can be easily determined and is closely related to clinical outcomes determined by meta-analyses in patients with LC. In this study, we aimed to investigate the effects of factors such as pre-RT lymphocyte percentages and IL-6 levels on prognosis of advanced LC patients.

Methods

Study Design and Participants

This study was an observational retrospective cohort study and 142 patients who were diagnosed with LC and received RT between 2020 and 2024 were included in the study. Patients were examined according to gender, age, clinical stage, Eastern Cooperative Oncology Group (ECOG) performance status, pathology and pre-RT lymphocyte percentages, and levels of IL-6 cytokine and other inflammatory markers such as D-dimer.

Results were also analyzed according to RT dose, treatment sites and response rates.

Inclusion Criteria

Patients aged 18 years and over, diagnosed with LC and received RT and/or chemotherapy were included.

Exclusion Criteria

Patients with serious infection, those treated in the intensive care unit, and those who received IT were excluded from the study.

Ethical Approval

Ethical approval was obtained from the University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital Ethics Committee (decision no: 149, date: 07.05.2025). Informed consents were obtained from patients.

Statistical Analysis

Statistical analyses of this study were performed with R software with version 4.2.0. Variables were analyzed for normality using Kolmogorov-Smirnov and Shapiro-Wilk tests together with Q-Q plots and histograms. Median and mean ± standard deviation values were used for continuous variables. Categorical variables were expressed as frequency (percentage). Mann-Whitney U and Kruskal-Wallis tests were applied for independent continuous variables. Wilcoxon signed-rank test was used for dependent variables. Spearman correlation test was used to analyze the relationships between continuous variables. Log-rank with Kaplan-Meier analysis were performed for "OS" and "progression-free survival" (PFS). Factors affecting the risk of recurrence were analyzed with univariate Cox regression analysis. Variables found to be significant in univariate Cox analysis were re-evaluated with multivariate Cox regression analysis. Model fit odds ratio was evaluated using Akaike information criterion and fit values. $P<0.05$ was defined as significant.

Results

Patient Characteristics

One hundred forty two patients were included in this study. Patients' median age was 59 years (18-89). The rate of stage IV disease was 76.05% (n=108). Performance scoring of ECOG was greater than 2 in 122 patients (85.91%). Characteristics of the patients are shown in Table 1.

Laboratory Tests

Pre-RT median lymphocyte percentage was 12% and median level of inflammatory cytokine IL-6 was 12 pg/mL (Table 2).

Response Rates and Survival by Lymphocyte Percentages and IL-6 Cytokine Levels

In 61 patients (42.25%) with lymphocyte percentage >15%, the median RT response rate was 70%, (0-100%). In 81 patients (57.04%) with lymphocyte percentage ≤15%, the median RT response rate was 40%, (0-100%).

In patients with lymphocyte percentage >15%, median OS was 18 months (1-60 months). In patients with lymphocyte percentage ≤15%, median OS was 7 months (1-36 months). In patients with lymphocyte percentage >15%, median PFS was 17 months and in those with lymphocyte percentage ≤15%, median PFS was 5 months (1-31 months).

In 114 patients (80.28%) with IL-6 level >7, the median RT response rate was 40% (0-100%). In 28 patients (19.71%) with IL-6 level ≤7, the median RT response rate was 80% (0-100%).

In patients with IL-6 level ≤7, median OS was 14 months, and in 114 patients with IL-6 level >7, median OS was 7 months with a minimum of 3 and 0 and a maximum of 60 and 60 months. In patients with IL-6 level ≤7, median PFS was 9 months, and in 114 patients with IL-6 level >7, median PFS was 4 months with a minimum of 1 and 0 and a maximum of 60 and 60 months.

Survival According to RT Characteristics and Response Rates

The median daily RT fraction number and dose were 12 and 250 centigray, respectively. Stage IV disease rate was 76.05% in this study,

Table 1. Characteristics of the patients

Parameters	Number of patients	%
Age		
18-50	33	23.23
51-65	70	49.29
66-74	29	20.42
75-89	10	7.04
Stage		
1-2	8	5.63
3	27	19.01
4	108	76.05
ECOG performance status		
1	6	4.22
2	14	9.85
3	17	11.97
4	105	73.94
Comorbidity		
CAD	15	10.56
CAD+COPD	6	4.22
None	121	85.21
Patoloji		
NSCLC	115	80.98
SCLC	27	19.02
Metastasis area		
Bone	64	45.07
Brain	32	22.53
Liver	9	6.33

ECOG: Eastern Cooperative Oncology Group, CAD: Coronary artery disease, COPD: Chronic obstructive pulmonary disease, NSCLC: Non-small cell lung cancer, SCLC: Small cell lung cancer

The median RT response was 50%. Complete response was achieved in 22 (15.49%) patients.

Median OS in complete responders was 34 months, with no deaths during the study and an upper limit of 60 months [not available (NA), 95% confidence interval (CI): 34-NA]. OS was significantly longer in complete responders (p<0.001). It was 12 (95% CI: 6-14) and 5 months (95% CI: 1-3) in partial and stationary responders, respectively. Survival rate was 15% at the time of analysis (n=22) (Table 3).

Median PFS was 28 months (NA, 95% CI: 28 months-NA) in patients with complete response, 24 months (95% CI: 5-NA) in good responders, 4 months in partial responders (95% CI: 3-10), and 0 months in patients with stationary or progressive disease (95% CI: 0-3).

Statistical Analysis

Significant relationships were found between pre-RT lymphocyte percentage, OS and PFS (p=0.007 and p=0.006, respectively). Median OS was 18 months (95% CI: 9-36) in patients with lymphocyte percentage >15% and 7 months (95% CI: 6-14) in those with lymphocyte percentage ≤15%. Similarly, PFS was found to be longer in patients with lymphocyte percentage >15% with a median of 17 months (95% CI: 8-36) compared to those with lymphocyte percentage ≤ 15% (5 months, 95% CI: 3-10) (Figure 1).

Pre-RT IL-6 levels were also found to be an important prognostic indicator. Median OS was 14 (95% CI: 8-NA) in patients with IL-6 levels ≤7 pg/mL while it was 7 months (95% CI: 6-NA) in patients with IL-6 levels >7 pg/mL. Median PFS was 9 months in patients with IL-6 levels ≤7 pg/mL while it was 4 months (95% CI: 3-10) in patients with IL-6 levels >7 pg/mL (p=0.009) (Figure 2).

Table 2. Laboratory test parameters

Parameters	n=142
Hematocrit, %	
Median (min-max)	36.0 (12.2-49.3)
Lymphocyte, %	
Median (min-max)	12 (5-36)
Platelet, 10^3/µL	
Median (min-max)	274 (80-461)
CRP, mg/dL	
Medyan (min-max)	30 (1-214)
Ferritin, ng/mL	
Median (min-max)	392 (14-2,674)
IL-6, pg/mL	
Median (min-max)	12 (2-68)
D-dimer µg/mL	
Median (min-max)	1.1 (0.1-20)

IL-6: Interleukin-6, CRP: C-reactive protein

Univariate and Multivariate Survival Analyses

Univariate analyses were determined to be significant for OS and PFS including stage IV disease (p=0.005 and p=0.005, respectively), ECOG performance status (p<0.001 and p<0.001, respectively), lymphocyte percentage (p=0.007 and p=0.007, respectively), IL-6 (hazard ratio=2.15, 95% CI: 1.19-3.87, p=0.011), total RT dose (p<0.001 and p<0.001, respectively), and D-dimer levels (p<0.001 and p<0.001, respectively) (Table 4 and Table 5). Although D-dimer levels were found to be prognostically significant, they were not included in this study because the subject is very long.

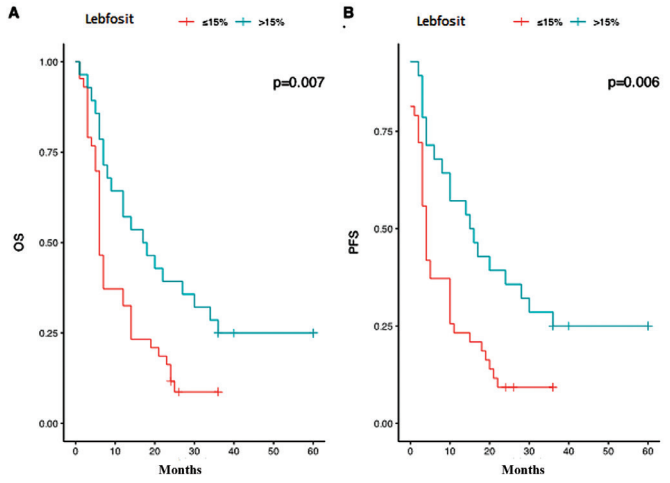

Figure 1. Kaplan-Meier curves for overall survival (OS) and progression-free survival (PFS)

A) Comparison of OS for different pre-radiotherapy (pre-RT) lymphocyte percentages, B) Comparison of PFS for different pre-RT lymphocyte percentages

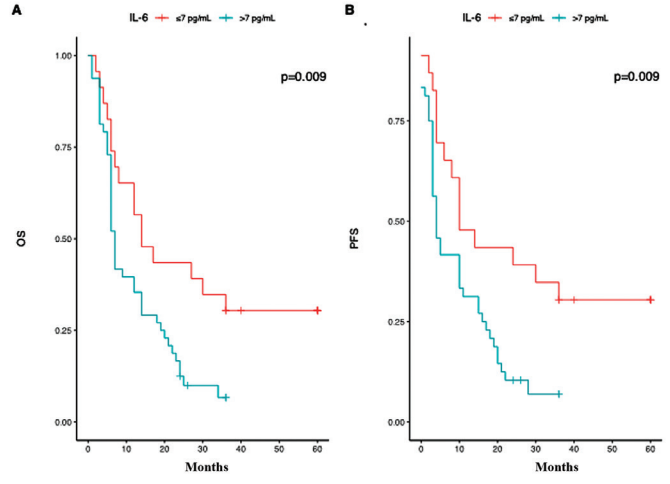

Figure 2. Kaplan-Meier curves for overall survival (OS) and progression-free survival (PFS)

A) Comparison of OS for different pre-radiotherapy (pre-RT) interleukin-6 (IL-6) levels, B) Comparison of PFS for different pre-RT IL-6 levels

In the analyses for survival, median OS and PFS were 7 and 5 months, respectively in patients with lymphocyte percentage ≤15%. In patients with lymphocyte percentage >15%, median OS and PFS were 18 and 14 months (p=0.007 and p=0.005, respectively).

OS and PFS in patients with lymphocyte percentage ≤6% were median 2 and 0 months, respectively, and were significantly lower than in patients with lymphocyte percentage >15% (p=0.001).

In patients with IL-6 level >7 pg/mL, median OS and PFS were 7 months and 4 months, respectively, and were significantly lower than in patients with IL-6 level ≤ 7pg/mL (median OS and PFS were 18 and 17 months, respectively) (p=0.011 and p=0.01, respectively).

Patient Follow-up and Response Assessment

Patients were followed up at 1-2 month intervals in the first year and at 3-5 month intervals in the second year. During follow-up, computed tomography (CT) or magnetic resonance imaging (MRI) was performed every 3 months and positron emission tomography (PET)/CT every 6 months.

Response rates of RT were determined by thoracic CT taken in the first 2 months after treatment, brain or liver MRI in patients with brain and liver metastases, and PET/CT taken 3-5 months later. Response rates of RT assessed using Response Evaluation Criteria in Solid Tumors (version 1.1) (IV, A) (24).

Table 3. RT characteristics, OS and PFS according to lymphocyte and IL-6 ratios

RT	Patient number (n) (%)	Median lenfosit (%)	Median IL-6 pg/mL	Median RT response (%)	Median OS (months)	Median PFS (months)
RT dose/day						
150-200	51 (35.91)	21	12	70	20	14
250 cGy	34 (23.94)	12	12	50	6	3
300 cGy	32 (22.53)	9	13	60	11	9
>400 cGy	25 (17.6)	7	16	50	5	2
RT site						
Lung	49 (34.5)	21	12	70	20	14
Bone	56 (39.43)	11	13	50	7	5
Brain	30 (21.12)	10	15	70	10	8
Bone and Brain	9 (6.33)	9	21	50	2	0
Liver	1 (0.7)	6	45	70	3	1
RT response (%)						
CR	22 (15.49)	26	3	100	60	28
PR						
70--90	14 (9.85)	21	7	70-90	17	14
25-60	79 (59.63)	12	12	25-60	7	5
S/P <25	27 (19.01)	7	45	10	3	0

OS: Overall survival, PFS: Progression-free survival, IL-6: Interleukin-6, RT: Radiotherapy, CR: Complete response, PR: Partial response, S/P <25: Stationary or progression, cGy: Centigray

Table 4. Univariate and multivariate analyses for OS

	Univariate		Multivariate	
Parameters	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Stage I-II-III-IV	2.67 (1.35-5.29)	**0.005**	0.50 (0.16-1.59)	0.242
ECOG ≤2/>2	3.06 (1.58-5.91)	**<0.001**	2.71 (0.95-7.72)	0.062
Lymphocyte >15%/≤15%	0.47 (0.27-0.81)	**0.007**	0.84 (0.37-1.87)	0.667
Lymphocyte >15%/≤6%	0.52 (0.21-0.73)	**0.001**	0.48 (0.13-0.97)	**0.01**
IL-6 ≤7 pg/mL/>7 pg/mL	2.15 (1.19-3.87)	**0.011**	1.07 (0.45-2.56)	0.884
Total RT dose, ≥40-60/<40 Gy	0.96 (0.95-0.98)	**<0.001**	0.97 (0.95-1.00)	**0.026**
CT usedNo used	0.50 (0.29-0.86)	**0.013**	0.55 (0.30-1.01)	**0.055**
Pre-RT D-dimer <0.5/≥0.5 µg/mL	3.62 (1.88-7.00)	**<0.001**	3.42 (1.44-8.14)	**0.005**

OS: Overall survival, HR: Hazard ratio, CI: Confidence interval, ECOG: Eastern Cooperative Oncology Group, IL-6: Interleukin-6, RT: Radiotherapy, CT: Chemotherapy, Gy: Gray

Table 5. Univariate and multivariate analyses for PFS

	Univariate		Multivariate	
Parameters	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Stage I-II-III-IV	2.67 (1.35-5.29)	**0.005**	0.50 (0.16-1.59)	0.242
ECOG ≤2/>2	3.06 (1.58-5.91)	**<0.001**	2.71 (0.95-7.72)	0.062
Lymphocyte >15%/≤15%	0.47 (0.27-0.81)	**0.007**	0.84 (0.37-1.87)	0.824
Lymphocyte >15%/≤6%	0.54 (0.20-0.75)	**0.001**	0.45 (0.12-0.99)	**0.01**
IL-6 ≤7 pg/mL/>7 pg/mL	2.15 (1.19-3.87)	**0.011**	1.07 (0.45-2.56)	0.974
Total RT dose ≥40-60/<40 Gy	0.96 (0.95-0.98)	**<0.001**	0.97 (0.95-1.00)	**0.026**
CT used/No used	0.50 (0.29-0.86)	**0.013**	0.55 (0.30-1.01)	0.055
Pre-RT D-dimer <0.5/≥0.5 µg/mL	3.62 (1.88-7.00)	**<0.001**	3.42 (1.44-8.14)	**0.005**

PFS: Progression-free survival, HR: Hazard ratio, CI: Confidence interval, ECOG: Eastern Cooperative Oncology Group, IL-6: Interleukin-6, RT: Radiotherapy, CT: Chemotherapy, Gy: Gray

Survival Rates

Five-year OS was 25% in patients with lymphocyte percentage >15% and 12.5% in patients with ≤15%.

Five-year OS was 30% in patients with IL-6 levels ≤7 pg/mL and 8% in patients with >7 pg/mL. Median PFS was significantly longer in patients with complete response (p<0.001) (Figure 1).

RT-related Toxicity

RT-related toxicity was determined using the Common Terminology Criteria for Adverse Events, (version 6.0) (25). Grade 2 hematological and other toxicities were seen in 84 (59.15%) patients. Worse hematologic toxicity (grade 3) was seen in 14 (9.85%) patients.

Discussion

LC remains an important cause of cancer-related death worldwide, despite advances in diagnostic and therapeutic methods (26).

Systemic inflammation plays a major role in the rapid progression of many cancers by increasing tumor angiogenesis, cancer cell proliferation, tumor metastasis, and also by affecting tumor response to systemic therapy (27).

Lymphocytes are essential components of the immune response, and low ALC is associated with poor prognosis and an immunosuppressive state in patients of cancer (28). The prognostic significance of lymphocyte percentages and levels of cytokines such as IL-6 in patients undergoing RT for advanced LC has become an area of increasing interest (1).

This study is consistent with previous studies suggesting that lymphocytes play an important role in antitumor immunity, contributing to improved treatment responses and prolonged survival. Lymphopenia, which usually occurs as a result of radiation-induced cytotoxic effects, has been reported to negatively affect survival outcomes by impairing immune surveillance against tumor cells (29,30). These findings suggest that assessing pretreatment lymphocyte percentages may be a valuable tool for clinicians in determining personalized treatment strategies and improving patient outcomes.

Our findings showed that patients with higher pre-RT lymphocyte percentages (>15%) exhibited significantly longer OS and PFS compared to those with lower percentages (≤15% and ≤6%). Notably, patients with lymphocyte percentages above this threshold had a median OS of 18 months and survived significantly longer than patients with lymphocyte percentages ≤15% and ≤6% (7 and 2 months). This correlation is consistent with previous studies that identified lymphocyte counts as prognostic biomarkers in various malignancies and emphasized their role in immune response and tumor microenvironment dynamics (29).

ILs are not only important inflammatory cytokines that play a role in tumor formation, but are also being evaluated as a potential target for tumor treatment. Studies on this subject have shown that IL-6 is increased in various types of cancer, including breast (31), colorectal (32), and LC (33). It has also been determined that it has proliferation and metastasis-promoting effects on cancer cells.

IL-6 is a well-known proinflammatory cytokine that plays a role in tumor progression, immune suppression, and treatment resistance. Elevated IL-6 levels have been associated with increased tumor burden, systemic inflammation, and poor prognosis in various malignancies, including LC (34). In our study, IL-6 level was also identified as an important prognostic factor. Patients with pre-RT IL-6 levels ≤7 pg/mL survived significantly longer than those with higher IL-6 levels (>7 pg/mL), with a median OS of 14 months.

Correlation analyses between patient characteristics and D-dimer levels before and after RT provided important information regarding the inflammatory and coagulatory pathways involved in disease progression in advanced LC. Significant correlations were observed between D-dimer levels and inflammatory markers such as IL-6 highlighting the negative role of systemic inflammation in cancer prognosis (35). High CRP level has also been associated with systemic inflammation and may serve as a prognostic indicator for poorer survival rates in various cancers, including LC (36).

Our univariate and multivariate analyses confirmed that low IL-6 levels, advanced disease stage (IV), poor ECOG

performance status (>2), and high D-dimer levels in LC were also significant negative prognostic factors, while higher lymphocyte percentages, RT dose and patient CT were associated with improved survival outcomes. These results highlight the complex interaction between systemic inflammation, immune response, and therapeutic efficacy in LC. Our study was carrıed out on the analysis of lymphocyte percentage and immune-inflammatory markers in advanced LC patients receiving RT.

Study limitations

This study's limitations are its retrospective nature and its relatively small sample size. Future prospective studies with randomised larger cohorts and molecular characterization of tumors may provide more detailed information about the immunological mechanisms underlying the observed associations.

Conclusion

This study suggests that pre-RT lymphocyte percentage and IL-6 level are important prognostic biomarkers in advanced LC patients undergoing RT. Monitoring these parameters may aid in risk stratification and treatment optimization. Furthermore, strategies aimed at regulating systemic inflammation and preserving lymphocyte counts may offer potential therapeutic benefits in improving survival outcomes in LC patients.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital Ethics Committee (decision no: 149, date: 07.05.2025).

Informed Consent: Informed consents were obtained from patients.

Footnotes

Authorship Contributions

Surgical and Medical Practices: K.Ç., H.S.K., Concept: K.Ç., H.S.K., Design: K.Ç., H.S.K., Data Collection or Processing: T.D.U., T.H.U., Analysis or Interpretation: K.Ç., H.S.K., Literature Search: K.Ç., T.D.U., T.H.U., H.S.K., Writing: K.Ç., H.S.K.

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Case Report

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Hydatid Cyst Recurrence 24 Years After Thoracotomy: Multiple Daughter Vesicles Removed by VATS

Torakotomiden 24 Yıl Sonra Kist Hidatik Nüksü: VATS ile Çıkarılan Çok Sayıda Kız Vezikül

Caner İŞEVİ, Gökhan PİRZİRENLİ, Feyza Bahar DOĞAN, Yasemin BİLGİN BÜYÜKKARABACAK

Ondokuz Mayıs University Faculty of Medicine, Department of Thoracic Surgery, Samsun, Türkiye

ABSTRACT

Hydatid disease usually affects the liver and lungs, while thoracic wall involvement is extremely rare. We present a case of a 27-year-old woman with a history of right thoracotomy for hydatid cyst excision at age 3, now presenting with right upper back pain. Computed tomography revealed a cystic lesion in the right apical thoracic wall. Video-assisted thoracoscopic surgery was performed; daughter cysts were aspirated, and the cyst wall was excised completely. Histopathology confirmed recurrent hydatid cyst. The patient recovered uneventfully and received postoperative albendazole. This case highlights the potential for very late recurrence and the value of minimally invasive treatment.

Keywords: Hydatid cyst, thoracic wall, recurrence, VATS, echinococcosis

ÖZ

Kist hidatik hastalığı genellikle karaciğer ve akciğerleri etkilerken, toraks duvarı yerleşimi son derece nadirdir. Üç yaşında sağ torakotomi ile kist hidatik eksizyonu yapılan 27 yaşındaki kadın hasta, sağ üst sırt ağrısı ile başvurdu. Bilgisayarlı tomografi, sağ apikal toraks duvarında kistik bir lezyon gösterdi. Video destekli torakoskopik cerrahi ile cerrahi yapıldı; kız veziküller aspire edildi ve kist duvarı tamamen çıkarıldı. Histopatolojik inceleme nüks kist hidatik tanısını doğruladı. Hasta sorunsuz iyileşti ve postoperatif albendazol tedavisi aldı. Bu olgu, çok geç dönemde nüks olasılığına ve minimal invaziv cerrahinin önemine dikkat çekmektedir.

Anahtar Kelimeler: Kist hidatik, toraks duvarı, nüks, VATS, ekinokokkoz

Introduction

Hydatid disease, resulting from infection with the larval form of *Echinococcus granulosus*, most commonly involves the liver and lungs. Although thoracic hydatidosis typically affects pulmonary or mediastinal structures, primary involvement of the chest wall is rare. Moreover, recurrence after several decades is an exceptional phenomenon. While recurrence rates remain low when complete surgical excision and adequate follow-up are ensured (1), delayed reappearance may still occur, particularly in cases where cyst content is spilled intraoperatively, or resection is incomplete (2,3).

We present a rare case of recurrent thoracic wall hydatid cyst diagnosed 24 years after the initial surgery in childhood. This highlights the need for long-term vigilance in patients from endemic regions with a known history of echinococcosis.

Address for Correspondence: Caner İşevi MD, Ondokuz Mayıs University Faculty of Medicine, Department of Thoracic Surgery, Samsun, Türkiye
E-mail: drcanerisevi@gmail.com
ORCID IDs of the authors: C.İ.: 0000-0002-7496-8220, G.P.: 0000-0002-1831-2710, F.B.D.: 0009-0000-3566-9781, Y.B.B.: 0000-0001-9676-9313

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Case Report

A 27-year-old woman presented with a 3-month history of right upper back pain radiating to the shoulder. She did not report any systemic symptoms. Physical exam was notable only for a healed thoracotomy scar. Laboratory tests, including complete blood count, liver function, and inflammatory markers, were normal. Abdominal ultrasonography was performed to evaluate possible hepatic involvement, and no hepatic hydatid cyst was detected. She had undergone a right posterolateral thoracotomy with excision of a thoracic wall hydatid cyst at the age of 3. Medical history included smoking (5 pack-years), migraine, and gastritis. Thoracic computed tomography showed a 24×16 mm cystic lesion abutting the right upper thoracic wall, with an adjacent 12×9 mm solid component, raising suspicion for a nerve sheath tumor (Figure 1). Given the history, recurrent hydatid cyst was suspected. Video-assisted thoracoscopic surgery (VATS) was performed in left lateral decubitus position. A single 3-cm incision (uniportal approach) was made in the 4th intercostal space at the anterior axillary line. Through this incision, a 30° thoracoscope and standard thoracoscopic instruments were introduced and manipulated simultaneously. No carbon dioxide insufflation was used. A cystic lesion with fibrotic adhesions to the apical parietal pleura and 3rd-4th ribs, in close proximity to the thoracic sympathetic chain, was observed. The sympathetic chain was carefully preserved, and no intraoperative injury was detected. The postoperative course was uneventful, with no evidence of Horner's syndrome or sweating abnormalities. To prevent contamination and secondary dissemination, the operative field around the lesion was protected with gauze pads soaked in povidone-iodine. Cystotomy revealed multiple daughter vesicles, which were aspirated (Figure 2). The entire cyst wall was excised. The cavity was irrigated with hypertonic saline, followed by povidone-iodine and isotonic saline. A 32 Fr chest tube was placed. Histopathology confirmed hydatid disease. Hematoxylin and eosin staining revealed an acellular laminated cyst wall with surrounding chronic inflammatory infiltrates and foreign body-type giant cell granulomas. The cyst wall displayed hypocellular laminated structures consistent with echinococcal membranes. Postoperative recovery was uneventful. The patient was discharged with albendazole (2×300 mg/day) for six weeks. At 4-month follow-up, she was asymptomatic and imaging showed complete resolution. Written informed consent was obtained from the patient for the publication of this case report and accompanying images.

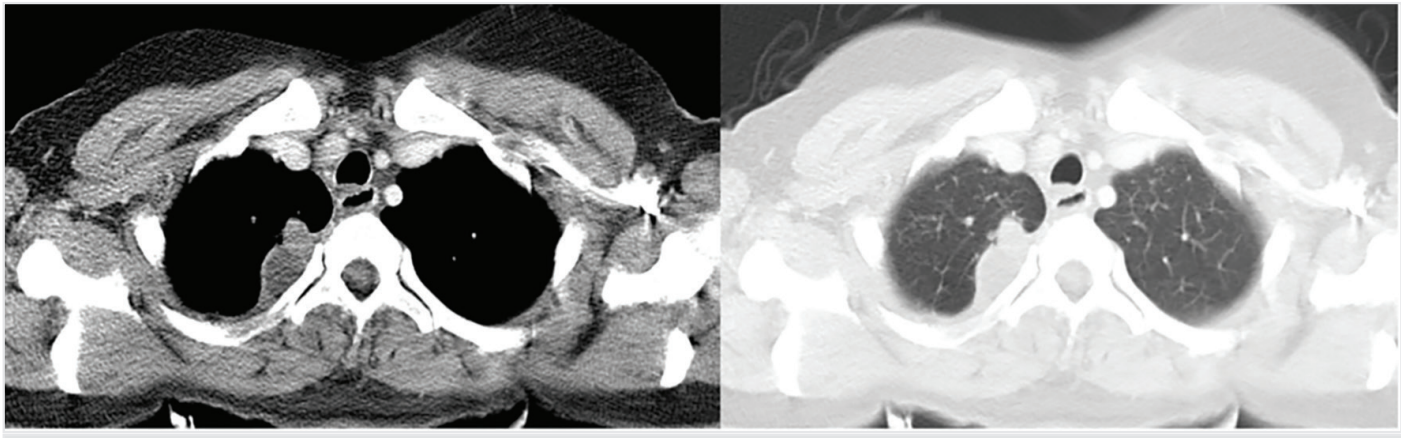

Figure 1. Axial thoracic CT showing a cystic lesion in the right apical thoracic wall, abutting ribs
CT: Computed tomography

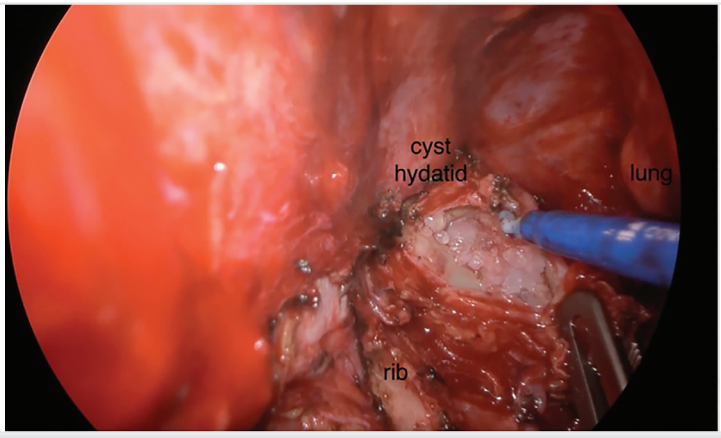

Figure 2. Intraoperative VATS view showing multiple daughter cysts within the opened hydatid cyst cavity
VATS: Video-assisted thoracoscopic surgery

Discussion

Hydatid cyst recurrence is uncommon in pulmonary or thoracic wall disease when complete excision is achieved (1). However, in rare instances, viable protoscolices or daughter cysts may persist for years before becoming symptomatic. This case demonstrates an extremely late recurrence 24 years after the initial hydatid cyst surgery. Such latency highlights the parasite's capacity for dormancy and slow progression.

Risk factors for recurrence include intraoperative rupture, incomplete resection, and complex anatomical involvement (2,4). In this case, although surgical details from childhood were unavailable, a likely scenario involves incomplete excision or microscopic residual disease that remained dormant until adulthood.

VATS provides a minimally invasive yet effective approach to thoracic hydatidosis. The use of scolicidal agents such as hypertonic saline and adjunctive antiparasitic therapy (e.g., albendazole) is essential in reducing the risk of secondary dissemination (5). In addition, several intraoperative measures are recommended to minimize recurrence risk. These include isolating the operative field with gauze pads soaked in scolicidal agents (e.g., povidone-iodine or hypertonic saline), controlled aspiration of cyst contents before opening, and meticulous removal of the cyst wall without rupture. The combination of these techniques reduces the likelihood of contamination and secondary implantation. In our case, the lesion was surrounded with povidone-iodine-soaked gauze, the cavity was irrigated with hypertonic saline followed by povidone-iodine and isotonic saline, and the patient was discharged on postoperative albendazole therapy. These steps collectively represent the standard multimodal strategy to minimize recurrence after surgery for hydatid disease.

Several reports comparing VATS with open thoracotomy have shown that both approaches achieve similarly low recurrence rates when complete excision and adjunctive albendazole therapy are applied. However, VATS offers additional advantages such as reduced postoperative pain, shorter chest tube duration, and faster recovery, contributing to improved patient satisfaction (6-8). Thoracotomy, on the other hand, remains preferable in cases with giant, complicated, or multiple cysts where extensive adhesions or uncontrolled spillage risk are anticipated. In our case, the uniportal VATS technique was sufficient for safe excision, highlighting its feasibility in selected thoracic wall recurrences.

Thoracic wall hydatid disease is especially rare and often misdiagnosed as soft tissue tumors, hematoma, or abscess (3). In lesions adjacent to the sympathetic chain, dissection can be technically demanding. Careful preservation is critical to avoid complications such as Horner's syndrome or altered sweating patterns. In our patient, the sympathetic chain was preserved, and no postoperative neurological or autonomic complications were observed, underscoring the safety of the uniportal VATS approach when meticulous dissection was performed.

Reported recurrence rates for hydatid disease vary widely, ranging from 4.6% to 22%, with most series citing values around 8-16% depending on the organ and follow-up duration (9,10). Recurrences usually appear within months to a few years after the initial operation, with the majority detected in the first decade (9,11). However, late recurrences beyond 10 years, though rare, have been documented in the literature, including pulmonary, spinal, and even cardiac locations (12,13). Our case is remarkable in demonstrating a recurrence 24 years after the first thoracotomy, which to our knowledge represents one of the longest latency periods reported. This exceptional delay underscores the parasite's ability to remain dormant and emphasizes the importance of long-term, possibly lifelong, surveillance in patients treated for hydatid disease in endemic areas. Long-term follow-up is essential, as recurrence may remain asymptomatic for years. Most authors recommend regular annual imaging, at least during the first decade, with continued surveillance in endemic regions given the possibility of extremely late recurrences (9-13).

Conclusion

This case demonstrates that recurrence of thoracic hydatid disease may occur even decades following initial surgical intervention. In individuals with a history of echinococcosis living in endemic areas, newly emerging thoracic wall lesions should be evaluated thoroughly for possible recurrence. An additional diagnostic challenge is differentiating between a true recurrence and a new lesion acquired through reinfection. While genetic or molecular analyses could theoretically distinguish these scenarios, such methods are rarely feasible in routine clinical practice. Therefore, clinical judgment relies on factors such as the lesion's anatomical location, continuity with prior operative fields, absence of hepatic or pulmonary involvement, and long latency. In our case, given the lesion's proximity to the prior surgical site and the absence of other organ involvement, recurrence was considered the most plausible explanation.

Ethics

Informed Consent: Written informed consent was obtained from the patient for the publication of this case report and accompanying images.

Footnotes

Authorship Contributions

Surgical and Medical Practices: C.İ., G.P., Y.B.B., Concept: F.B.D., Design: F.B.D., Data Collection or Processing: F.B.D., Analysis or Interpretation: G.P., Y.B.B., Literature Search: C.İ., Writing: C.İ., Y.B.B.

Conflict of Interest: No conflict of interest was declared by the authors.

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Review

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Mpox and Public Health in Türkiye: Epidemiology, Diagnostics, Vaccination and Prevention

Mpox ve Türkiye'de Halk Sağlığı: Epidemiyoloji, Tanısal Yaklaşım, Aşılama ve Korunma

Simge PEŞDERE, Süleyman Utku UZUN

Pamukkale University Faculty of Medicine, Department of Public Health, Denizli, Türkiye

ABSTRACT

Mpox, formerly known as monkeypox, has transformed from a localized African threat into a global public health concern, notably with the 2022 multi-country outbreak and the 2024 resurgence of clade I in Central Africa, both leading to public health emergency of international concern declarations. This review synthesizes the current understanding of mpox, covering its microbiology, global and regional epidemiology (with a specific focus on Türkiye), transmission dynamics, clinical manifestations, diagnostic criteria, specific case definitions as outlined by the Türkiye General Directorate of Public Health, therapeutic options, and vaccination strategies for public health professionals. The review also addresses the complexities of mpox in Türkiye, marked by inconsistent official reporting, underscoring the need for transparent surveillance. Besides, this review underscores the necessity of adaptive public health responses, ongoing genomic monitoring, and coordinated global efforts to mitigate mpox's evolving threat.

Keywords: Mpox, monkeypox, epidemiology, Türkiye, public health

ÖZ

Maymun çiçeği olarak bilinen mpox, Afrika ile sınırlı bölgesel bir tehdit olmaktan çıkarak küresel bir halk sağlığı sorunu haline gelmiştir. Özellikle 2022'deki çok ülkeli salgın ve 2024'te Orta Afrika'da clade I'in yeniden ortaya çıkışı, her iki durumda da uluslararası önemi haiz halk sağlığı acil durumu ilanına yol açmıştır. Bu derleme, mpox'a ilişkin güncel bilgileri özetlemekte; mikrobiyolojisi, küresel ve bölgesel epidemiyolojisi (özellikle Türkiye bağlamında), bulaşma dinamikleri, klinik belirtileri, tanısal ölçütleri, Türkiye Halk Sağlığı Genel Müdürlüğü tarafından tanımlanan olgu tanımları, tedavi seçenekleri ve halk sağlığı profesyonellerine yönelik aşılama stratejilerini kapsamaktadır. Ayrıca, resmi bildirimlerdeki tutarsızlıklarla karakterize edilen Türkiye'deki mpox durumuna dikkat çekilerek şeffaf sürveyans ihtiyacı vurgulanmaktadır. Bunun yanında, mpox'un giderek evrilen tehdidini azaltmak için uyarlanabilir halk sağlığı yaklaşımları, sürekli genomik izlem ve uluslararası koordineli çabaların gerekliliği üzerinde durulmaktadır.

Anahtar Kelimeler: Mpox, maymun çiçeği, epidemiyoloji, Türkiye, halk sağlığı

Introduction

Mpox, formerly known as monkeypox, is a zoonotic viral disease caused by the mpox virus (MPOXV), a member of the *Orthopoxvirus* genus. This virus is known to cause a smallpox-like illness in both humans and animals (1). While historically confined to Central and West Africa, mpox garnered significant global attention with an unprecedented multi-country outbreak that began in 2022. This rapid international dissemination, extending beyond traditional endemic regions, led the World

Address for Correspondence: Res. Assist. Simge Peşdere, Pamukkale University Faculty of Medicine, Department of Public Health, Denizli, Türkiye
E-mail: spesdere@pau.edu.tr
ORCID IDs of the authors: S.P.: 0009-0005-0267-0950, S.U.U.: 0000-0002-8876-2848

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Health Organization (WHO) to declare the outbreak a public health emergency of international concern (PHEIC) on July 23, 2022 (1). This declaration fundamentally altered the perception of mpox, transforming it from a localized threat into a pressing global health challenge. The previous understanding of mpox as an "exclusively African disease with sporadic cases" has been superseded by evidence of sustained human-to-human transmission in non-endemic areas, necessitating a re-evaluation of global public health surveillance, preparedness, and response strategies (1). In August 2024, rising clade I transmission in Central Africa led WHO to declare mpox a PHEIC (2).

This review aims to synthesize the current understanding of mpox disease, providing healthcare professionals with an updated, evidence-based resource. This review will cover general information, microbiology, global and regional epidemiology (with a specific focus on Türkiye), transmission dynamics, clinical manifestations, diagnostic criteria, therapeutic options, vaccination strategies, and public health prevention measures. The objective is to facilitate informed clinical practice and public health interventions in light of the evolving epidemiological landscape.

Methods

This narrative review was conducted by searching scientific literature published between 2000 and July 2025. The primary databases utilized were PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar. Key search terms included: "mpox", "monkeypox", "*Orthopoxvirus*", "epidemiology", "transmission", "diagnosis", "treatment", "vaccination", "Türkiye", and "Turkey". Additional sources were identified from the references of retrieved articles, official reports from the WHO, the European Centre for Disease Prevention and Control (ECDC), the United States (US) Centers for Disease Control and Prevention (CDC), and the Turkish Ministry of Health. The selection criteria prioritized recent systematic reviews, meta-analyses, original research articles, and authoritative guidelines relevant to the topics covered.

General Information and Historical Context

Definition, Microbiology and Classification of Mpox

Mpox is an infectious disease caused by the MPOXV, a double-stranded DNA virus. It belongs to the *Orthopoxvirus* genus, which is part of the *Poxviridae* family. Notably, MPOXV shares genetic similarities with the variola virus (~96% genome identity), the causative agent of smallpox (3). As a zoonotic disease, mpox can be transmitted between animals and humans. Rodents and primates are recognized as primary reservoirs for the virus, playing a crucial role in its natural cycle (4).

MPOXV exhibits genetic diversity, primarily categorized into two distinct clades: clade I (historically referred to as the Congo Basin clade) and clade II (historically known as the West African clade) (5). These clades differ significantly in their historical pathogenicity and current epidemiological patterns, influencing disease severity and transmission dynamics.

Clade I: This clade is currently responsible for the rise in mpox cases observed in Central and Eastern Africa (5). Clade I infections have historically been linked to more severe disease, with case fatality rates of up to 10%. However, in subsequent epidemics, fatality rates have decreased to about 1-3.3% (5). Clade I further comprises two subclades: clade Ia and clade Ib (6). Clade Ia is predominantly found in Central Africa, with transmission often linked to contact with infected animals and household spread. The majority of cases reported in this category were among children under the age of 15. Clade Ib, on the other hand, has been found to spread in eastern Democratic Congo through sexual interaction, as well as heterosexual transmission via sex trade workers. This subclade has shown a lower case-fatality rate compared to clade Ia, suggesting ongoing viral evolution that may affect virulence (6).

Clade II: Endemic to West Africa, clade II was the primary cause of the global mpox outbreak that commenced in 2022 (5). Infections resulting from clade II mpox are generally less severe, with a survival rate exceeding 99.9%. The ongoing global outbreak is specifically attributed to subclade IIb. Since 2022, clade II has predominantly circulated outside the African continent, with a notable prevalence among men who have sex with men (MSM) (7).

The distinct epidemiological patterns associated with each clade highlight a crucial aspect of MPOXV: while both are MPOXVs, their biological properties, particularly pathogenicity and transmissibility, appear to vary. This variation influences their capacity for sustained human-to-human spread and the severity of the disease. The prominence of sexual transmission for clade IIb, especially among specific demographic groups, suggests an adaptive or opportunistic shift in transmission routes for this particular clade. This divergence in transmission dynamics carries profound implications for the design and implementation of targeted public health interventions and risk communication strategies. Continuous genomic surveillance is therefore essential to monitor these evolving characteristics and adapt public health responses accordingly.

Discovery and Early Human Cases

The MPOXV was first identified in 1958 in Copenhagen, Denmark, during two distinct outbreaks of a pox-like disease observed in colonies of research monkeys. This discovery led to the disease being named "monkeypox". The first documented human case of mpox occurred in 1970, affecting a nine-month-old boy in Bokenda, Equateur Province, Democratic Republic of the Congo (DRC) (8). The child manifested symptoms that were similar to those of smallpox, including a pustular rash, malaise, and fever (9). Between September 1970 and March 1971, more cases of the disease were reported in West Africa, mostly in young children who had not been vaccinated against smallpox (10).

Evolution of Mpox as a Public Health Issue

Historically, mpox was largely confined to Central and West Africa, with cases considered sporadic (11). During the intense global efforts to eradicate smallpox, surveillance for MPOXV

was limited, and early outbreaks were often overshadowed by the prevailing focus on smallpox elimination. The success of smallpox eradication, while a monumental public health achievement, inadvertently led to a global decline in cross-protective immunity against orthopoxviruses, as routine smallpox vaccination ceased. This waning population immunity likely contributed to increased susceptibility to mpox, particularly in regions where it was not historically endemic, making subsequent outbreaks more impactful.

A pivotal shift occurred in 2003 when mpox was reported outside Africa for the first time. An outbreak in the US was traced to a shipment of animals from Ghana, which included several rodent species identified as MPOXV carriers. Fourty seven confirmed and probable cases were reported in six Midwestern states as a result of the virus being spread by these infected rodents to prairie dogs that were marketed as pets (9). This event highlighted the potential for international dissemination through animal trade. The possibility of the virus spreading from person to person is indicated by the return of over 200 cases in Nigeria in 2017 and 2018 (1). The most significant turning point was the 2021-2022 outbreak, which saw MPOXV spread extensively across multiple continents, including Europe, North America, South America, and parts of Asia. The possibility of endemic occurrence in recently impacted areas by 2022-2023 is indicated by ongoing transmission outside of Africa, underscoring the critical need for long-term surveillance and control efforts.

Worldwide Epidemiology

Historical Endemic Regions and Sporadic Outbreaks

Mpox was first recognized in humans in 1970 in the DRC (formerly Zaire) (12). Thereafter, cases occurred sporadically in Central and West African countries, often in remote forested areas, with occasional secondary cases from human-to-human spread. Endemic regions included DRC, Nigeria, Cameroon, and surrounding countries. The virus's cross-border spread gained attention in 2003 when an imported shipment of rodents from Africa caused an outbreak in the US (clade II virus) via transmission to pet prairie dogs (1,8).This incident underscored the potential for international dissemination of the virus through animal trade. Subsequent limited outbreaks occurred in United Kingdom (2018), Israel, Singapore and other non-African countries, typically linked to travelers from endemic areas (13).

The Global Outbreak: Trends, Geographical Distribution, and Demographics

The 2022-2025 Clade IIb Pandemic

The global epidemiology of mpox has changed significantly since the emergence of widespread outbreaks in 2022. Beginning in May 2022, the clade IIb strain of mpox spread rapidly beyond its traditional endemic zones, first reaching countries that had never before reported the virus. By September 2022, more than 62,000 cases had been logged across over 100 nations, and by mid-2025 this figure had exceeded 100,000 in 122 countries (6,8,14). The vast majority of these infections occurred among adult men (median age ~35), with well over 90% of transmission events linked to intimate contact within networks of MSM (7,15). In high-resource settings, the clinical course was generally mild, and mortality remained below 0.1% (16). Following relentless case rises in non-endemic regions, the WHO designated the 2022 outbreak a PHEIC in July of that year (1).

Resurgence of Clade I in Endemic Regions

In parallel, clade I mpox has continued to pose a significant public health threat in endemic regions, particularly Central Africa. Since mid-2022, countries like the DRC and neighboring nations have experienced a marked increase in clade I cases. In 2023, the WHO African region reported a dramatic surge, including cases among heterosexual individuals and children, suggesting sustained community spread beyond the MSM networks observed elsewhere (17). On August 14, 2024, the WHO declared the clade I surge, centered in the DRC, a PHEIC (1,2). As of June 2025, ongoing human-to-human transmission of clade I mpox persisted in several African countries, including the DRC, Kenya, and Uganda, with over 100 reported deaths (6). Sporadic travel-associated clade I cases have also been detected in various countries outside Africa, including the US, Europe, and Asia, in 2024-2025 (6).

Current Global Distribution and Clade-specific Patterns

According to the WHO's global mpox trends report published on July 4, 2025, from January 2022 through May 31, 2025, global surveillance documented 148,892 confirmed pox cases with 341 deaths across all WHO regions (18). The current regional distribution shows the Americas leading with 69,234 cases and 151 deaths, followed by the African region with 41,652 cases and 148 deaths, the European region with 30,189 cases and 9 deaths, the Western Pacific region with 5,869 cases and 16 deaths, the South-East Asia region with 1,038 cases and 14 deaths, and the Eastern Mediterranean region with 910 cases and 3 deaths.

Clade I mpox remains predominantly endemic in Central and Eastern Africa, with outbreaks primarily affecting children through household or zoonotic transmission. Countries most affected include the DRC, Uganda, and neighboring states (6). Sporadic travel-associated clade I cases have also been reported outside the region, including in Australia, Europe, and North America. In contrast, clade IIb, responsible for the 2022 global outbreak, continues to circulate at low levels across multiple non-endemic regions, particularly within networks of MSM (6,7). Its demographic profile remains mostly male, with intimate contact being the primary mode of transmission (7).

The simultaneous circulation of clade I and clade II underscores the complexity of mpox epidemiology. In summary, mpox now circulates on multiple continents. The coexistence of these two distinct epidemiological patterns underscores the need for tailored public health responses. For clade I outbreaks in Central and Eastern Africa, strategies should focus on zoonotic spillover prevention and addressing household transmission (1). In contrast, for the global clade IIb outbreak, interventions should emphasize targeted measures like vaccination and promoting

safe sexual practices within specific risk groups in non-endemic regions. As highlighted in Table 1, the two clades differ significantly in terms of transmission dynamics, fatality rates, and affected populations, requiring context-specific strategies. The challenges in data interpretation, particularly in areas with limited testing capacity, can obscure the true burden of the disease, especially among vulnerable populations. The emergence of sexually transmitted clade Ib within Africa further highlights the dynamic nature of mpox epidemiology, necessitating enhanced diagnostic capabilities and nuanced demographic surveillance to accurately assess disease burden and refine intervention strategies. Continued global monitoring and adaptive disease management are crucial to effectively control the spread of mpox.

Epidemiology in Türkiye

The epidemiological situation of mpox in Türkiye presents a complex picture, marked by varying reports from different official sources. The first human case in Türkiye was confirmed on 30 June 2022. In a press briefing on 2 August 2022, the former Turkish Health Minister Fahrettin Koca stated that five cases had been identified by early August (four recovered, one isolated) (19). Early cases in Türkiye, particularly those reported in 2022, primarily involved men who had sexual contact with other men, with several cases highlighting underlying conditions such as human immunodeficiency virus (HIV) positivity and other immunocompromised states (20). However, subsequent official statements regarding the number of infected individuals have been inconsistent.

As of August 15, 2024, the Turkish Health Ministry publicly stated that no mpox cases had been detected in Türkiye in 2024 (21,22). This statement was made in the context of the WHO declaring a mpox outbreak in Africa a public health emergency. The ministry further indicated that there was no need for any restrictions or additional measures against the spread of the virus at that time (21). Health Minister Kemal Memişoğlu reiterated this stance, emphasizing that the ministry was closely monitoring developments related to mpox and coronavirus disease 2019, but saw no immediate cause for alarm (22).

In contrast, data from the US CDC provides a different perspective. As of January 1, 2024, and updated through June 3, 2025, the CDC's global mpox case dashboard lists Türkiye within the category of countries reporting 26 to 100 confirmed mpox cases (6). Also, according to the joint ECDC-WHO Regional Office for Europe mpox Surveillance Bulletin produced on 24 April 2025, a total of 34 cumulative mpox cases in Türkiye were identified through data submitted to The European Surveillance System, or identified via International Health Regulations mechanisms or official public sources between 2022 and 2025 (23). Furthermore, the Turkish Medical Association, a prominent doctors' union in Türkiye, released a statement citing CDC data from September 2023, which indicated that 12 mpox cases had been detected in Türkiye by that time (24).

This discrepancy in reporting between national health authorities and international bodies, as well as between different national sources, highlights a significant challenge in accurately assessing the epidemiological landscape of mpox within Türkiye. The absence of a centralized, publicly accessible, real-time national surveillance dashboard for mpox, coupled with potential under-testing and under-reporting due to stigma associated with the primary transmission routes (e.g., among MSM), likely contributes to this data gap (25). Such inconsistencies can undermine public trust and hinder effective public health communication and response. Opposition parties in Türkiye have voiced concerns regarding the potential spread of mpox, particularly with the return of African students to Turkish universities at the end of summer, and have called for greater transparency and clearer measures from the government (24). The situation underscores the critical need for robust, transparent, and real-time epidemiological surveillance systems and consistent data reporting to ensure that healthcare professionals and the public receive accurate and timely information, enabling appropriate preventive and control measures in Türkiye.

Modes of Transmission

Mpox is a zoonotic disease caused by the MPOXV, with transmission occurring both from animals to humans and between individuals. Historically endemic in West and Central

Table 1. Key epidemiological trends of mpox clades (worldwide)

Feature	Clade I (Congo Basin)	Clade II (West African)
Historical endemicity	Central and Eastern Africa (5)	West Africa (5)
Current geographical focus	Central and Eastern Africa (ongoing outbreaks) (5)	Global (low-level spread in many countries) (6)
Historical case fatality rate	Up to 10% (5)	Less severe, >99.9% survival (5)
Recent case fatality rate	1-3.3% (5)	Very low fatality rate (5)
Subclades	Clade Ia, clade Ib (6)	Subclade IIb (6)
Primary transmission patterns	Contact with infected animals, household transmission (clade Ia); intimate/sexual contact (clade Ib) (6)	Close contact, intimate/sexual contact, contaminated materials (7)
Key demographics	High proportion in children <15 years (clade Ia); adults, including sex trade workers (clade Ib) (6)	Predominantly men who have sex with men (7)
Global outbreak role	Sporadic travel-associated cases outside Africa (6)	Caused the 2022 global outbreak (5)

Mpox: Monkeypox

Africa, the virus is believed to be maintained in nature by small mammals, such as rodents and monkeys, although the exact animal reservoir has not yet been conclusively identified (4). Human infections may result from direct exposure to infected animals through activities like hunting, handling, processing, or consuming bushmeat. Contact with animal fluids, bites, scratches, or contaminated materials (e.g., bedding or cages) can also facilitate transmission (4). Consequently, individuals in or traveling to endemic regions are advised to avoid contact with wild or sick animals and to take precautions during activities that may increase exposure risk.

While zoonotic transmission remains a primary concern in endemic areas, recent outbreaks—particularly the 2022-2023 global surge—have underscored the virus's capability for sustained human-to-human spread (1). Transmission between people typically requires close, prolonged contact, with the virus entering the body through broken skin, mucous membranes, or the respiratory tract (4).

Direct contact with infectious lesions or body fluids remains the most frequent route of transmission. Skin-to-skin contact, including during sexual activity, has been a major driver in recent outbreaks, especially within sexual networks involving MSM (1,3,4). Although MPOXV has been detected in semen and genital secretions, it is unclear whether the virus is a conventional sexually transmitted infection (STI) or primarily spreads through intimate physical contact.

Fomite transmission via contaminated objects such as clothing, bedding, towels, or utensils has also been documented. Sharing personal items or surfaces used by an infected individual can contribute to indirect spread, particularly if these items are not properly disinfected (4,5).

Respiratory transmission, though theoretically possible through droplets during prolonged face-to-face contact, appears to play a less prominent role in real-world scenarios (5). Unlike airborne diseases, mpox does not seem to spread easily across large distances or in casual public settings (5). Nonetheless, healthcare authorities recommend wearing masks during close interactions, especially in caregiving situations, as a precautionary measure.

Vertical transmission from a pregnant person to the fetus has been observed, either transplacentally during pregnancy or perinatally at the time of delivery, posing risks of congenital infection and adverse neonatal outcomes (4,5). Additionally, while rare, there have been concerns about reverse zoonosis, with infected humans potentially transmitting the virus to pets through close physical contact.

The evolving understanding of mpox transmission, particularly the prominence of intimate contact in the 2022 global outbreak, has significant implications for prevention strategies. Initially, the focus was heavily on zoonotic spillover, but the sustained human-to-human spread, especially via sexual networks, has necessitated a shift in public health messaging and interventions. This highlights the virus's adaptability in finding new transmission routes, emphasizing that public health responses must be dynamic and responsive to observed epidemiological shifts.

Incubation Period, Clinical Signs and Symptoms

The incubation period for mpox generally ranges from 5 to 21 days, with most cases developing symptoms within 7 to 14 days. The disease commonly begins with a prodromal phase characterized by non-specific systemic symptoms (3). During this time, individuals are usually not contagious and may remain asymptomatic.

The prodromal symptoms often include fever, fatigue, headache, muscle aches, and back pain (3,5,26). A notable clinical hallmark that distinguishes mpox from other poxvirus infections, such as smallpox and chickenpox, is lymphadenopathy, typically affecting the cervical, axillary, or inguinal lymph nodes (3). This phase generally lasts between 1 and 5 days before the appearance of skin lesions. Following the prodrome, most patients develop a characteristic rash, which generally appears 1 to 4 days after fever onset. The lesions are usually well-demarcated, deep-seated, and may have a central depression (umbilication). While the classical rash distribution is centrifugal, beginning on the face and spreading to the trunk and extremities (including palms and soles), mucosal surfaces such as the mouth, genitals, and anus may also be affected, presenting as painful ulcers or vesicles (3,26). The rash phase generally lasts two to four weeks, after which lesions crust over and fall off, leaving healed skin that may result in permanent scarring. Lesions are often painful during early stages and become itchy during healing. The number of lesions can vary widely, from a few localized spots to thousands across the body.

Atypical presentations have been increasingly reported in recent outbreaks. In particular, some individuals—especially those infected through sexual contact—may present with a rash localized to the genital or perianal region, sometimes without preceding systemic symptoms such as fever (3). These atypical cases may involve a small number of lesions, which may be mistaken for other STIs such as herpes simplex virus (HSV), syphilis, or varicella-zoster virus (VZV) (27). Furthermore, in some instances, lesions may develop asynchronously, with different types of lesions appearing at the same time on different body parts, complicating diagnosis.

Additional symptoms associated with mpox can include anorectal pain, tenesmus, and rectal bleeding, particularly in patients with genital or rectal mucosal involvement. Co-infections with other STIs are not uncommon and should be considered in the differential diagnosis (3).

Although most mpox cases are mild or moderate, the disease can be severe, particularly among vulnerable populations. Complications may include secondary bacterial infections, dehydration (especially when mucosal lesions hinder eating or drinking), eye involvement (e.g., conjunctivitis, keratitis), bronchopneumonia, sepsis, and central nervous system involvement such as encephalitis (3,8). Higher risks are observed in young children, pregnant individuals, and immunocompromised

persons, especially those with advanced HIV (5). In such cases, the disease may be more extensive, painful, and prolonged.

Case Definitions (According to the Türkiye General Directorate of Public Health's Mpox Guideline)

Standardized case definitions are essential for surveillance, reporting, and public health response. According to the Türkiye General Directorate of Public Health's mpox guideline, updated in August 2024, mpox cases are categorized into "possible case" and "confirmed case" to guide clinical and epidemiological actions (28).

As also detailed in Table 2, the possible case definition includes systemic symptoms combined with contact history or characteristic rash presentations, with particular emphasis on mucosal lesions to broaden clinical suspicion. These definitions provide a structured approach for healthcare professionals in Türkiye to identify suspected cases and guide laboratory testing. The emphasis on both systemic symptoms with contact history and characteristic rash presentations, particularly including mucosal lesions, broadens the scope for initial clinical suspicion. The definitive confirmation relies on laboratory testing, specifically polymerase chain reaction, which is the most common and accurate diagnostic method (26). This standardization is critical for accurate data collection, which in turn informs public health interventions and resource allocation.

Differential Diagnosis

Mpox rash and symptoms overlap with many other infectious and non-infectious conditions. Key differentials include: VZV (chickenpox or shingles), HSV, molluscum contagiosum, hand-foot-and-mouth disease; eczema herpeticum; and other poxviruses (e.g. cowpox) (27). In travelers from endemic areas, rickettsial infections (e.g. "African tick-bite fever") might be considered, as might drug reactions or allergic eruptions. Visual comparison of the characteristic lesions can be crucial for differential diagnosis. Figure 1A-D provides a comparative illustration of mpox lesions alongside those of common differentials like varicella and HSV (29). Furthermore, a detailed comparative analysis of the morphological and clinical characteristics of select poxviruses relevant to human disease, which is essential for the differential diagnosis of mpox, is provided in Table 3.

Treatment Options

Currently, there is no single treatment specifically approved for MPOXV infections (26,30). For most patients who do not develop severe illness or have risk factors for poor outcomes, management primarily involves supportive care aimed at facilitating natural recovery. This includes pain control for lesions, ensuring adequate hydration and nutrition, and meticulous wound care to prevent secondary bacterial infections. Patients are also advised to isolate until their rash has fully healed, avoiding contact with others and pets.

For individuals with severe or life-threatening mpox manifestations, or those identified as being at high risk for severe disease (e.g., severely immunocompromised individuals, very young children, pregnant women, or those with eczema), antiviral medications may be considered. Tecovirimat is generally the first-line investigational treatment (26,30). While studies have shown it to be safe, its effectiveness in reducing lesion duration has been limited, suggesting that robust supportive care, including hospitalization and comprehensive pain management, plays a crucial role in improving outcomes. Other antiviral options, such as cidofovir and its oral prodrug brincidofovir, which inhibit viral DNA polymerase, may be considered, particularly for severely immunocompromised patients or if tecovirimat is unavailable. vaccinia immune globulin, consisting of pooled antibodies, is also available from national stockpiles for severe cases, often in combination with antivirals (30). These specialized treatments are typically accessed under specific protocols due to their stockpile status. Close clinical monitoring and comprehensive hospital support are critical for reducing mortality, especially in severe or high-risk cases.

Vaccination

Preventing mpox relies on both behavioral precautions and vaccination with orthopoxvirus vaccines. Smallpox vaccination

Table 2. Mpox case definitions (Türkiye General Directorate of Public Health)

Case category	Criteria
Possible case	A person meeting one of the following: **1a.** Acute onset of fever **AND** one or more of the following symptoms: weakness, headache, muscle pain, joint pain, lymphadenopathy **AND** **1b.** A history of contact with a confirmed mpox case within 21 days prior to the onset of symptoms **OR** **2.** Presence of skin rashes (macular, papular, or vesicular or pustular lesions of the same age/stage), ulcerative or vesicular mucosal lesions (including oral and anal mucosa). This must be supported by a clinician's medical history consistent with criteria 1a or 1b, or a history of travel to a high-risk area (Note: Mucosal lesions can be single or multiple and may be found in the mouth, conjunctiva, urethra, penis, vagina, or anorectal area)
Confirmed case	Polymerase chain reaction positivity is detected in a sample taken from a person who fits the possible case definition

Mpox: Monkeypox

Table 3. Comparative characteristics of select poxviruses relevant to human disease

Feature	Mpox virus	Variola virus (smallpox)	Vaccinia virus	Cowpox virus
Primary host(s)	Rodents, primates (zoonotic) (4)	Humans (eradicated) (3)	Unknown (laboratory strain)	Rodents, cats, cows (zoonotic)
Human-to-human transmission	Moderate (requires close contact) (1,4)	High (airborne/droplet)	Very low (accidental inoculation)	Low (direct contact with lesions)
Case fatality rate (historical)	Clade I: up to 10%; clade II: <1% (5)	~30% (ordinary type) (3)	Negligible (in immunocompetent)	Very low (<1%)
Rash distribution	Centrifugal (face -> extremities), often palms/soles (3)	Centrifugal (face -> extremities) (3)	Localized (inoculation site)	Localized (often hands/face)
Lymphadenopathy	Prominent (3)	Not typical	Not typical	Common
Vaccine cross-protection	Yes (smallpox vaccine ~85% effective) (31,32)	N/A (target of vaccine)	N/A (used as vaccine)	Yes (smallpox vaccine protective)
Antiviral treatment	Tecovirimat, brincidofovir, cidofovir (30)	Tecovirimat (not used clinically)	Supportive	Supportive, tecovirimat if severe

Mpox: Monkeypox, N/A: Not applicable

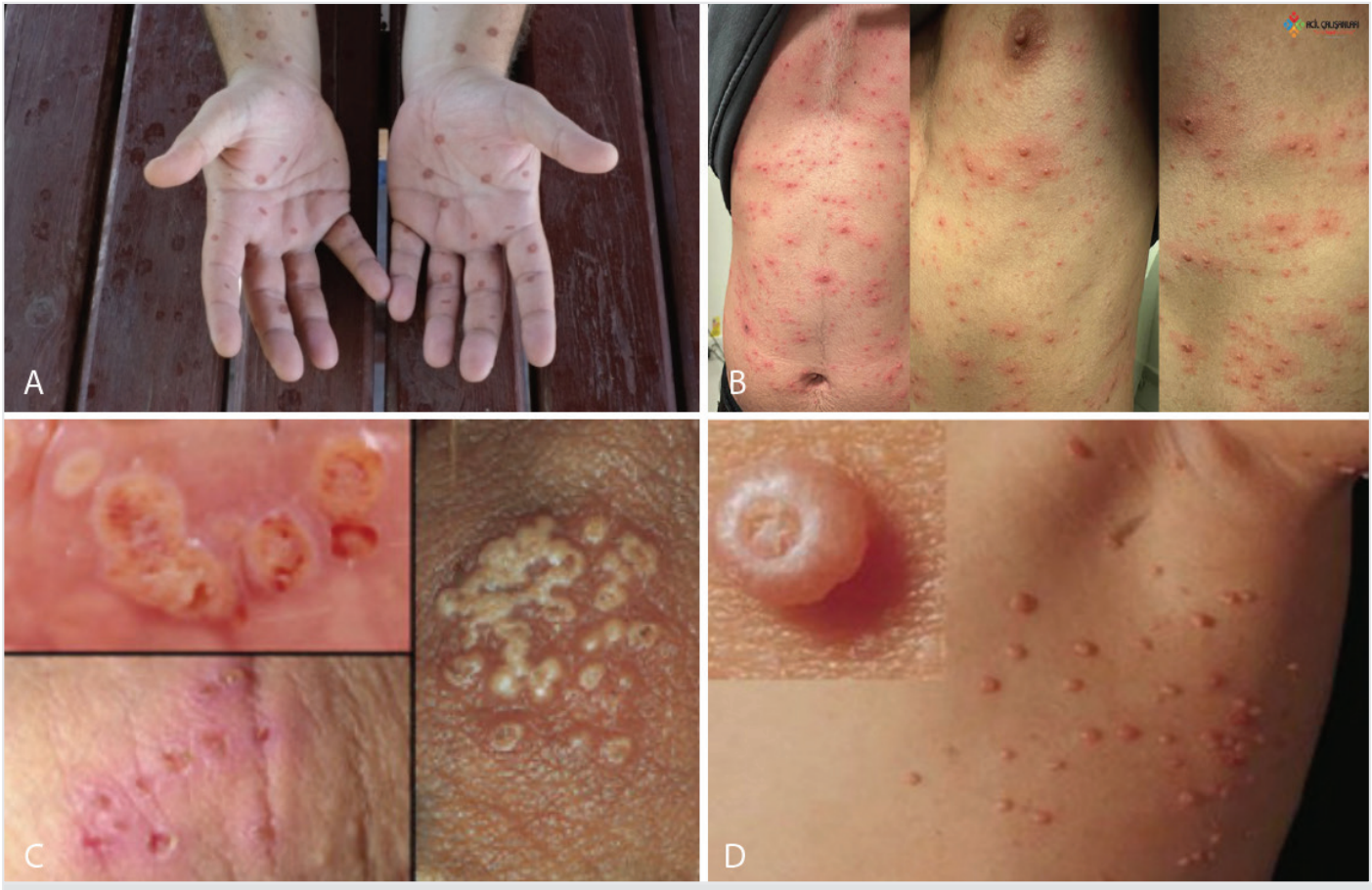

Figure 1. Comparative dermatological presentation of monkeypox (mpox) and common differential diagnoses

A) Typical mpox lesions (deep-seated, umbilicated, at similar stages) on arm/face. B) Varicella (chickenpox) lesions (superficial, in different stages) on trunk. C) Herpes simplex virus (HSV) lesions (grouped vesicles) on genital area. D) Molluscum contagiosum lesions (pearly, umbilicated papules)

Mpox lesions are often deeper, more uniform in stage, and frequently involve the palms/soles compared to varicella. Unlike the grouped vesicles of HSV, mpox lesions are more disseminated. Molluscum lesions are typically smaller and lack a prodromal illness

historically provided cross-protection against mpox due to the antigenic similarity between the viruses. Estimates suggest that smallpox vaccination is about 85% effective in preventing mpox (31). This cross-protective immunity is the basis for using existing orthopoxvirus vaccines against mpox. The primary vaccine used is JYNNEOS (also known as Imvamune/Imvanex), a live, non-replicating modified vaccinia Ankara vaccine, favored for its superior safety profile (32,33). It is administered as a two-dose series, typically 28 days apart, and has demonstrated substantial effectiveness (approximately 75-86% after two doses) in preventing mpox (33). JYNNEOS is recommended by organizations like the WHO and CDC and is generally available in limited supply for high-risk individuals in many countries. An older alternative, ACAM2000, is a live, replicating vaccinia vaccine that offers cross-protection but carries a higher risk of adverse effects, such as myocarditis, making it less preferred, especially for immunocompromised individuals (33). In Türkiye, JYNNEOS (Imvanex) is the primary vaccine used for pre- and post-exposure prophylaxis (PEP) in high-risk groups, as per the Ministry of Health guidelines. ACAM2000 is not typically used in the national program due to its safety profile. Another smallpox vaccine, LC16, has shown strong protective efficacy in animal models and excellent safety outcomes in human trials (32).

Vaccination strategies prioritize individuals with known exposure or those at high risk. This includes healthcare workers who care for mpox patients, laboratory personnel handling orthopoxviruses, and individuals within communities experiencing high transmission rates, such as MSM with multiple sexual partners, sex workers, or attendees of large events where mpox could spread (32). However routine vaccination against mpox is not recommended for the general public or healthcare personnel (32). PEP with JYNNEOS is recommended as soon as possible after potential exposure, ideally within four days to prevent illness, though it may still reduce severity if given up to 14 days post-exposure (32).

Preventive Measures

Preventive efforts against mpox hinge on interrupting transmission through a combination of personal behaviors and organized public health actions. At the individual level, minimizing direct contact with infected persons or potentially contaminated materials is paramount; this entails avoiding skin-to-skin interactions (including intimate or sexual contact) with anyone exhibiting rash or lesions, refraining from sharing personal items (such as clothing, bedding, utensils, or sexual devices) without thorough disinfection, and practicing rigorous hand hygiene using soap and water or alcohol-based sanitizers (5,34). In regions where mpox is endemic, additional caution around wild animals—particularly rodents and primates—is advised, as zoonotic spillover remains a recognized risk (5). When infection occurs, patients should isolate until all lesions have healed and scabs have detached, covering any remaining lesions and wearing a mask when around others; they must also abstain from close contact with pets to prevent reverse zoonosis. Within healthcare and other institutional settings, strict infection control protocols are essential. Personnel examining suspected or confirmed mpox cases should adhere to airborne and contact precautions, including the use of N95 respirators, eye protection, gloves, and gowns (5,34). Environmental decontamination of surfaces, textiles, and instruments must employ agents proven effective against enveloped viruses. PEP via vaccination can be considered for high-risk contacts within four days of exposure to avert illness or, if administered up to 14 days post-exposure, to lessen disease severity (5,32,34).

The multi-faceted nature of mpox prevention, encompassing both vaccination and behavioral changes, is crucial for effective disease control. The emphasis on avoiding direct skin-to-skin contact and contaminated materials, particularly in the context of intimate activities, reflects the primary transmission routes identified in recent outbreaks. The limitations of certain measures, such as condoms not providing complete protection, highlight the need for comprehensive risk reduction strategies rather than relying on single interventions. Public health efforts must continuously adapt their messaging and interventions based on the evolving epidemiological understanding of the virus, ensuring that preventive measures are both relevant and effectively communicated to at-risk populations.

At the population level, surveillance systems and prompt case reporting enable timely identification of clusters, while comprehensive contact tracing helps break chains of transmission. Clear risk communication—tailored to affected communities and disseminated through diverse channels—promotes early symptom recognition, reduces stigma, and encourages rapid healthcare seeking. Although routine travel restrictions are generally unnecessary, advisories for travelers to endemic areas stress avoidance of wildlife contact and compliance with local health guidance (34). Collectively, these layered interventions—spanning personal precautions, clinical infection control, and public health strategies—form the cornerstone of effective mpox prevention.

Conclusion

Mpox has rapidly evolved from a regional zoonosis into a global public health concern, underscored by the unprecedented 2022-2025 multi-country outbreak and the ongoing surge of clade I cases in Africa. This transformation highlights a fundamental shift in the virus's behavior, moving beyond isolated animal-to-human spillover to sustained human-to-human transmission. This necessitates a critical re-evaluation of global public health surveillance, preparedness, and response strategies, acknowledging the distinct epidemiological and pathological characteristics of the two main clades. Despite typical clinical presentations involving rash and lymphadenopathy, atypical cases complicate diagnosis, emphasizing the need for high clinical suspicion and accurate laboratory confirmation. Challenges in consistent data reporting, as seen in Türkiye, further highlight the need for robust and transparent surveillance systems.

From a public health standpoint, key takeaways include the paramount importance of surveillance and rapid response, even in areas with no current reported cases. Prevention relies on isolating infected individuals and strategically vaccinating exposed or at-risk populations with safer orthopoxvirus vaccines like JYNNEOS. Treatment primarily remains supportive, with antivirals reserved for severe cases and vulnerable groups, as their impact on milder illness is limited.

For Türkiye, specific public health recommendations include:

1) Strengthening the national surveillance system for mpox to ensure real-time, transparent, and accurate data reporting, potentially through a dedicated dashboard.

2) Ensuring adequate and accessible stockpiles of JYNNEOS vaccine and tecovirimat for high-risk groups and severe cases, respectively.

3) Implementing targeted vaccination campaigns for high-risk populations, such as MSM with multiple partners, based on ethical and non-stigmatizing approaches.

4) Enhancing genomic surveillance capacity to track circulating clades and variants.

5) Conducting continuous training for healthcare professionals on case identification and management, focusing on the evolving atypical presentations.

The global mpox experience underscores that eradicating one poxvirus does not guarantee immunity to related viruses, making continued research into viral ecology, vaccines, and therapeutics essential. Coordinated global efforts, guided by international recommendations and supported by national authorities, are crucial to control mpox and protect populations in an interconnected world where the emergence of unexpected outbreaks remains a constant threat.

Footnotes

Authorship Contributions

Concept: S.U.U., Design: S.P., S.U.U., Data Collection or Processing: S.P., Analysis or Interpretation: S.P., S.U.U., Literature Search: S.P., S.U.U., Writing: S.P.

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