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REVIEW

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Clinical Diagnosis and Dermatological Clues in Scabies

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Abstract

Scabies, a globally prevalent parasitic infestation caused by *Sarcoptes scabiei hominis*, presents significant public health challenges, particularly in underdeveloped regions. Characterized by intense itching and distinctive rash patterns, scabies infestation requires prompt and accurate diagnosis to prevent outbreaks and additional health and economic burdens. The epidemiology of scabies underscores its high prevalence, particularly in conditions of overcrowding and poor hygiene, with an estimated 300 million cases annually worldwide. Transmission primarily occurs through prolonged skin-to-skin contact, and the risk is exacerbated in crowded living conditions and institutional settings. Clinical manifestations vary, with classic signs including burrows and intense nocturnal itching, and complications such as bacterial infections frequently arising. Diagnostic approaches range from microscopic examination of skin scrapings to non-invasive techniques like dermatoscopy and ultraviolet fluorescence. Effective management necessitates comprehensive treatment strategies, including the use of topical permethrin and oral ivermectin, emphasizing the need to treat all close contacts to curb reinfestation. Awareness and adherence to treatment protocols, alongside preventive measures, are crucial for controlling scabies outbreaks, reducing its public health impact, and improving the quality of life of affected individuals. This review highlights the importance of early detection, effective treatment, and public health strategies in managing scabies infestations, underscoring the need for increased awareness and action to address this neglected disease.

Keywords: Scabies, outbreak, diagnostic

INTRODUCTION

Scabies, also known as *Sarcoptes scabiei* infestation, is a disease caused by an infestation of the *Sarcoptes scabiei* mite, which can only live within human skin, and its main symptom is itching. Particularly in underdeveloped countries, scabies is a significant public health issue and has been declared a neglected skin disease by the World Health Organization. A classic presentation of scabies typically manifests as a characteristic distribution over the body and an intense itching rash. The diagnosis is confirmed by microscopic examination of scabies mites, eggs, or feces. Prompt diagnosis and the initiation of treatment in infected individuals are crucial. Incorrect or delayed diagnosis can lead to outbreaks, additional morbidity, and increased economic burden (1).

Etiology

S. scabiei hominis is an arthropod with eight legs, whitish in color, oval-shaped, and with a flat surface. Female mites have an average size of 0.4x0.3 mm, whereas male mites are half the size of females. After mating on the skin surface, male *sarcoptes* die. Female *sarcoptes* burrow into the stratum corneum and secrete proteolytic enzymes to create tunnels. A pregnant female continues to progress within the stratum corneum, laying 2-3 eggs per day and depositing their feces, known as *scybala*, between four to six weeks, until all eggs are laid, and then dies (2). Larvae hatch from eggs within 3-4 days and mature into adult mites within an average of 10-14 days. Scabies mites are highly sensitive to environmental temperature, losing their ability to move and penetrate the skin below 20 °C and dying in 10 minutes at temperatures above 50 °C. Mites can survive outside the host in ambient temperatures and humid environments for an average of 2-5 days.

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Epidemiology

Scabies is considered a significant public health issue with an estimated annual global prevalence of 300 million (3). Scabies infestation is particularly prevalent in regions with poor hygiene conditions and resource constraints. During wars, disasters, famines, overcrowding, poor nutrition, migration, homelessness, and similar circumstances, the parasite rapidly spreads, leading to scabies outbreaks. Transmission risk increases in crowded living conditions, resource-limited areas, childcare facilities, nursing homes, and other institutional settings (such as prisons and military barracks) (2). The incidence is higher during the fall and winter.

Transmission

Transmission of the parasite typically occurs through direct and prolonged skin contact, which can involve family members or sexual partners. The most significant transmission factor is close physical contact lasting 15-20 minutes (4). Although transmission through brief contacts is less likely in classic scabies infestations, it is possible even with short-term contacts of 1-2 minutes in crusted scabies cases. Because *sarcoptes* mites can survive for 2-5 days at room temperature after leaving the host, transmission through inanimate objects is also possible. The parasite that causes scabies in animals generally cannot survive in humans and does not cause scabies infestation (2,5).

Clinical Findings

Scabies is often seen in its classic form clinically, but it can present with different clinical findings and symptoms depending on the age of the host, current immunological status, or the presence of additional morbidities. Delayed type (type 4) hypersensitivity develops against the *sarcoptes* mite itself, its feces (*scybala*), and secretions in someone encountering *sarcoptes* for the first time. Healthy individuals who have experienced scabies infestation typically have 6-15 mites on their bodies. The main clinical feature of scabies is itching. Symptoms may appear in someone encountering the parasite for the first time within 3 to 6 weeks, but in cases of reinfestation, this period can be reduced to 1-3 days (6,7). Itching can worsen at night and be severe enough to wake the patient from sleep. Sweating and contact with hot water can intensify itching in patients with scabies.

Scabies' typical (specific) lesion, known as a burrow, appears as a serpiginous thread-like tunnel ranging from 2-15 mm in length, with a slightly raised, whitish, grayish, or brownish appearance on the skin (Figure 1). "Pearl vesicles", resembling grains of pearl, may be observed at the end or near the entrance of the tunnel. Although burrows can be visible to the naked eye, they may not be noticed because of secondary excoriation or infection (8). Lesions are typically distributed in the interdigital spaces, wrists, antecubital area, axillary region, penis, scrotum, buttocks, sacral area, periumbilical region, and areola areas in women. The imaginary area encompassing these regions is called the "Circle of Hebra". In healthy adults, the midline of the back, face, and hairy skin are spared, whereas in infants, the elderly, and immunosuppressed individuals, all skin surfaces are susceptible. Non-specific scabies lesions are polymorphic lesions characterized by symmetrical distribution and include papules, vesicles, bullae, pustules, nodules, and excoriations developed due to hypersensitivity (Figure 1).

In adults, areas typically unaffected, such as the head, neck, and palmoplantar region, are commonly affected in infants and children (9). In this age group, in addition to papules, vesicles and pustules are also more commonly observed; however, as scratching movements are limited, particularly in newborns and infants, excoriations are less frequent.

Nodular scabies is particularly observed in small children and the elderly and is characterized by round nodules ranging from 5-20 mm in size, which can be red, reddish-brown, or purple. Nodules are commonly found on the penis and scrotum, but they can also appear in the groin, perianal, and axillary regions (10). They are more prevalent in human immunodeficiency virus-positive patients. Nodules result from a deeper penetration of the scabies mite, leading to a stronger and longer-lasting local-allergic hypersensitivity reaction. Sometimes, ulcerations known as "scabetic chancre" can be observed in the genital area. Scabies nodules can persist for months even after successful treatment (post-scabetic papules) (11). Scabies mites are typically not observed in these lesions.

The bullous form of scabies, an atypical presentation, is also observed in children and the elderly. In the elderly population, this clinical picture can be confused with bullous pemphigoid. It should be considered if there is no response to topical corticosteroid treatment.

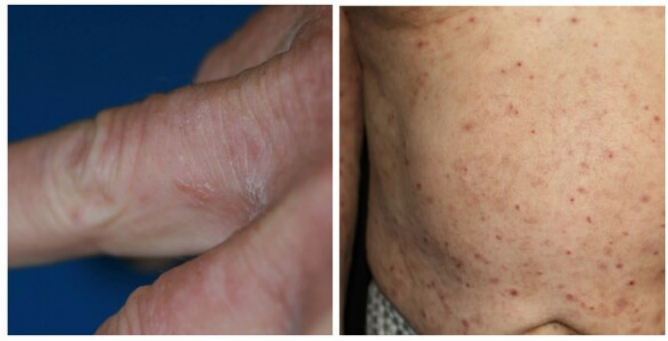

Figure 1. Specific lesion (left): burrow, non-specific lesions (right): pruritic papules

In individuals who are excessively meticulous about cleanliness and hygiene, scabies lesions may be indistinct. In addition, the anti-inflammatory effect of topical or systemic steroid use can suppress the formation of scabies lesions, leading to atypical presentations. This atypical clinical presentation is termed "scabies incognito". In this clinical scenario, although the lesions may be indistinct, there is usually no significant reduction in the severity of itching (12).

Crusted scabies (keratotic scabies/Norwegian scabies) is a severe form of scabies primarily observed in elderly, immobilized, mentally retarded, immunosuppressed, and Down syndrome patients, initially described in a patient with leprosy in Norway. While the typical scabies presentation involves an average of 12 *sarcoptes* mites, in this condition, there can be thousands or even millions of mites. Crusted scabies is one of the causes of erythroderma (13). In this clinical picture, widespread hyperkeratosis, fissures on the palms and soles, and irregularly thickened crusts are observed on the body (Figure 2). Thickening of the nails, subungual hyperkeratosis, discoloration, and dystrophy are present because of *sarcoptes* under the nails. Nail lesions can be mistaken for onychomycosis. Itchiness may be less prominent compared with classic scabies infestation because of a deficient immune response. Lymph node enlargement, peripheral blood eosinophilia, and elevated immunoglobulin E levels can be detected (14). This highly contagious condition can lead to major hospital outbreaks.

Secondary bacterial infections, such as impetigo, ecthyma, paronychia, and furunculosis, caused by *staphylococcal* or *streptococcal* bacteria are the most common complications of classic scabies clinical presentation. Impetigo due to *S. pyogenes*, scarlet fever, *streptococcal* toxic shock syndrome, rheumatic fever, and post-streptococcal glomerulonephritis are toxin-mediated diseases that can result from *streptococcal* infections. Fissures associated with crusted scabies provide an entry point for bacteria, which can lead to sepsis, particularly in elderly and immunocompromised patients. Generalized urticaria may rarely develop in patients with scabies.

Figure 2. Crusted scabies: hyperkeratotic thickened crusts and fissures

Diagnostic Methods

Various diagnostic methods are used to support the diagnosis of scabies. The sole definitive evidence for diagnosing scabies is the presence of mites, eggs, or feces (*scybala*). Skin scraping samples taken from lesions, particularly tunnels and burrows, rather than papules or nodules, can be examined under a microscope at 10x or 40x magnification to visualize adult female mites, eggs, or feces (Figure 3). Taking samples specifically from the tortuous termination part of the tunnel, where there are V-shaped scales, can increase the detection of mites and their products. For accurate and effective examination, it is recommended to puncture the burrow and tunnel with a needle, and after applying the contents to a slide, it should be examined under a microscope. The application of potassium hydroxide (KOH) can decrease the detection rate of parasites and compounds because of the rapid dissolution of mites and secretions in classic scabies. Therefore, except for crusted scabies, using saline or mineral oil instead of KOH application will increase diagnostic success (15). To increase the detection rate of mites, it is recommended not to take samples from a single lesion but to take multiple samples from different lesions. If mites are not detected, repeated samples should be taken if necessary. The absence of mites or compounds does not rule out the diagnosis. This sampling method, especially in children, may cause discomfort and decrease the success rate.

Skin samples can also be obtained using adhesive tape. This method relies on repeatedly applying and removing transparent, strong adhesive tape over the burrow and then transferring the collected sample to a slide for examination under a microscope. In microscopy, female *sarcoptes* mites are typically observed with dimensions of 0.4x0.3 mm, whereas male mites are less commonly encountered. The eggs are transparent, oval, uniform, and approximately 0.1 mm in size. Feces are brown and irregularly shaped, smaller in size than eggs, and are observed in clusters (3).

Figure 3. Microscopic image: adult mite at 40x magnification

A method similar to the tape method is described as superficial cyanoacrylate biopsy (SCAB), where cyanoacrylate is dripped onto the lesion and rapidly pulled off, and then the sample is examined under a microscope. SCAB also has the advantage of increasing the likelihood of distinguishing between live and dead mites, thus contributing to the evaluation of treatment success (16).

To better detect the burrow, the burrow ink test is applied. In this method, the suspicious papule and its surroundings are stained with ink, and the ink is then wiped off the lesion surface with an alcohol-soaked cloth to remove the ink from the lesion surface. In the case of a positive test, after wiping with alcohol, a dark, zigzag line is visible to the naked eye (17).

Dermatoscopy is an alternative, non-invasive, rapid, and sensitive assessment method. The sensitivity and specificity of dermatoscopy in diagnosing scabies are 98.3% and 88.5%, respectively (18). The triangle corresponding to the head, thorax, and front leg pairs of the *sarcoptes* mite is called the "delta sign". A linear or wavy line adjacent to it corresponds to the mite burrow. These two images together are referred to as the "jet and cloud" or "kite sign" (19) (Figure 4). The body of the mite is rarely visible because of its transparency. With this method, eggs and feces cannot be distinguished. However, after dropping blue ink into the burrows, polarized dermoscopy can be used to visualize the mite body and eggs (20).

Sarcoptes scabiei mite emits a bright reflection under ultraviolet (UV) light (21). A newly described dermatoscopy finding in recent years, called the "ball sign", refers to the portion seen as the delta sign in polarized dermoscopy appearing as a top shape due to the reflection it gives under UV-dermoscopy (22).

Wood's lamp is a practical and readily accessible diagnostic method that can be used to detect tunnels. When examined with a Wood's lamp in a dark room, tunnels emit bright yellow fluorescence. This allows for the easy detection of tunnels during both diagnosis and treatment follow-up processes (23).

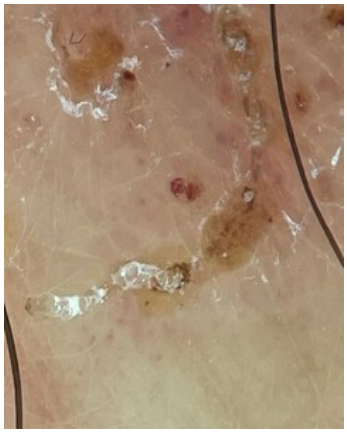

Figure 4. Dermoscopic image: spesific sign "jet and cloud"

Video dermatoscopy (VD) allows for the visualization of tunnels and mites using magnifications ranging from 40 to 100 times. It provides higher sensitivity and specificity for diagnosis than skin scraping tests. Because it does not cause any discomfort to the patient, it can be easily used in non-cooperative patients as well. VD can also be used for the post-treatment follow-up of patients. In such cases, the presence of live mites indicates ongoing infection. In addition, it can be used as a screening tool for asymptomatic family members (24).

Optical coherence tomography is similar to ultrasonography but offers higher resolution. Tunnels, mites, and eggs can be visualized and examined in the patient's skin. It is primarily used as a research tool to study mite biology and monitor treatment (25,26).

Reflectance confocal microscopy (RCM) enables *in vivo* visualization of the skin horizontally from the epidermis to the dermis and can visualize the *sarcoptes* mite itself, its eggs, and fecal material. It is a non-invasive technique that scans different layers of the skin using the reflection of laser light. RCM allows visualization of the tunnel, which is seen as a linear segment in the epidermis, forming a "honeycomb" pattern. The biological behavior, peristalsis, and movements of the mite can be examined using RCM (27).

On histopathological examination, a mixed-type inflammatory infiltrate with widespread eosinophilia is often observed in the dermis, accompanied by edema and epidermal spongiosis depending on the type of elementary lesion from which the biopsy material is obtained. In addition, in nodular lesions, pseudolymphomatous changes may be observed. The mite itself, its eggs, and fecal remnants can be observed within the stratum corneum. In particular, when pink, pigtail-like structures representing egg fragments are observed, scabies is considered (28).

In the literature, ELISA, polymerase chain reaction, matrix-assisted laser desorption ionization time-of-flight mass spectrometry, and antigen detection systems are used in diagnosis; however, in practice, these tests are not commonly performed and some of them are quite costly (26).

A typical history, severe itching, and specific clinical findings form the basis of scabies diagnosis. However, in cases with particularly atypical clinical features, the above-mentioned ancillary diagnostic methods can be used. Recently, the International Alliance for the Control of Scabies used the Delphi method to classify scabies diagnosis into three levels based on

physical examination, history, and laboratory features: definitive diagnosis level A, clinical diagnosis level B, and suspected diagnosis level C (29) (Table 1) (29).

Informed consent was obtained from the patients in the clinical pictures.

Characteristics and General Recommendations of Scabies Treatment

When left untreated, itching can persist for weeks or even months, and the contagiousness continues. The most crucial step in effectively treating scabies is patient compliance. When developing a treatment plan for a patient diagnosed with scabies, it is mandatory for the family members and other individuals sharing the patient's living space to undergo treatment, even if they do not have symptoms, to prevent reinfestation (30,31). The absence of itching in other family members does not indicate the absence of contagion. All family members should be treated simultaneously. To control the disease, all sexual partners up to 6 weeks before the onset of the patient's symptoms should be treated and followed up, even in the absence of clinical symptoms. U.S. Food and Drug Administration approved topical permethrin and oral ivermectin as first-line treatments (32). In addition, alternative treatments include topical ivermectin, benzyl benzoate, sulfur, ivermectin, spinosad, crotamiton, malathion, and lindane.

Patients should be informed about the medication to be applied, the amount to be applied, the method of application, and the intervals of application in scabies treatment, and these instructions should be provided to the patient in written form. In fact, in recent meetings, the necessity of providing these applications to patients with short videos and digital programs has been emphasized.

If scabies treatment is provided topically, patients should take a shower before application. After showering, the body should be thoroughly dried and allowed to return to normal body temperature. The medication should then be applied to the entire body from the neck down, including the neck and behind the ears. In particular, in babies, crusted scabies, adults with immunodeficiency, or lesions on the scalp, the periorbital and perioral areas should be protected while the head area is included in the treatment area. During the treatment period, if the hands are washed, the medication should be reapplied to the hands.

Table 1. Summary of the 2018 International Alliance for the Control of Scabies criteria for the diagnosis of scabies

A: Confirmed scabies (if at least one of them is present): A1: Mites, eggs, or feces on light microscopy of skin samples A2: Mites, eggs, or feces visualized on an individual using a high-powered imaging device A3: Mite visualized on an individual using dermoscopy
B: Clinical scabies (if at least one of them is present): B1: Scabies burrows B2: Typical lesions affecting the male genitalia B3: Typical lesions in a typical distribution and two history features
C: Suspected scabies (if at least one of them is present): C1: Typical lesions in a typical distribution and one history feature C2: Atypical lesions or atypical distribution and two history features
History features H1: Itch H2: Close contact with an individual who has an itch or typical lesions in a typical distribution

Close contacts, family members sharing the same household, and sexual partners within the last 6 weeks, even if asymptomatic, must be treated, and all individuals should start treatment simultaneously. For those not exposed to the medication during the initial treatment or for the treatment of newly hatched mites from eggs, a second application is necessary 1-2 weeks later.

Especially within the last 3 days, clothing and items used should be considered contaminated and washed at a high temperature (>50 °C) for at least 10 minutes and then ironed with a hot iron. Items that cannot be washed should be kept in a sealed plastic bag for at least 72 h.

Patients should be called for follow-up appointments every 2 weeks and examined for the emergence of new lesions. In cases where new lesion development is observed despite repeated treatment, the adequacy of the aforementioned treatment practices and whether there has been contact with new infected individuals should be questioned.

In cases of recurrent infections despite all applications being performed correctly, drug resistance may be considered. Classic scabies patients can return to work or school with contact isolation 24 h after the initial treatment. However, patients with crusted scabies should be isolated until a cure is achieved.

In the first few days after treatment, temporary exacerbation of itching may occur because of immunological reactions and irritation from topical treatments. This should be explained patients and should not be considered as treatment failure. Because allergic sensitization to scabies mites and eggs developed up to 6 weeks after treatment (post-scabetic pruritus), symptomatic treatment with emollients, topical and systemic corticosteroids, and antihistamines may be required during this period. It is expected that itching will decrease and disappear over time.

Patients should be called for follow-up appointments 2 weeks and 1 month after the end of treatment to evaluate itching complaints and active lesions through physical examination. Furthermore, at the end of this period, patients who continue

to complain of itching, show no specific findings on physical examination, and do not respond to symptomatic treatments should be evaluated for parasite delusion.

CONCLUSION

As a result, it is important for the clinical features and diagnostic methods of scabies, which can cause epidemics, to be known not only by dermatologists but also by all healthcare professionals for public health. Recognizing and planning the treatment of the disease at the primary care level and taking preventive measures will not only prevent its spread and improve the patient's quality of life but also reduce workforce loss and provide economic benefits.

Ethics

Informed Consent: Informed consent was obtained from the patients in the clinical pictures.

Authorship Contributions

Surgical and Medical Practices: Y.Ö., N.Ö., İ.O.T., Concept: Y.Ö., N.Ö., İ.O.T., Design: Y.Ö., N.Ö., İ.O.T., Data Collection or Processing: Y.Ö., N.Ö., İ.O.T., Analysis or Interpretation: Y.Ö., N.Ö., İ.O.T., Literature Search: Y.Ö., N.Ö., İ.O.T., Writing: Y.Ö., N.Ö., İ.O.T.

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Frequency of Phlebitis Development and Associated Factors in Hospitalised Adult Patients: A Descriptive and Correlational Study

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Abstract

Objective: The aim of this study was to determine the incidence and associated factors of peripheral venous catheter-related (PVC-related) phlebitis in hospitalised patients.

Methods: In this study, 315 catheters inserted in 247 patients hospitalised in the clinic were examined. Data were collected using the "patient identification form", the "peripheral catheter characteristics table", the "visual infusion phlebitis diagnosis scale" recommended by the Infusion Nurses Society (INS), and "intravenous drugs administered to the patient form". Data analysis performed using Statistical Package for Social Sciences 25.

Results: The frequency of PVC-related phlebitis was 15.6%. When phlebitis development at the peripheral venous catheter site was compared according to the individual and medical characteristics of the patients, no statistically significant difference was observed between phlebitis development and age, gender, body mass index, smoking status, chronic disease, anatomical location, catheter placement, and catheter size ($p>0.05$). However, there was a significant difference between the development of phlebitis and repeated catheter use, duration of catheter stay, type of medication used, and type and frequency of medication administration ($p<0.05$).

Conclusion: The frequency of PVC-related phlebitis is higher than the acceptable rate defined by the INS. It is essential for nurses to be aware of phlebitis risk factors, and it is recommended that they monitor the catheterised site at an appropriate frequency.

Keywords: Phlebitis, peripheral venous catheterization, incidence, complication

INTRODUCTION

Peripheral venous catheter (PVC) insertion is an intervention used in most hospitalised patients (1). PVC insertion is used to administer intermittent or continuous medication to the patient, to provide fluid support, to administer blood and blood products, to provide total parenteral nutrition of the patient, or to take blood samples (2). Although PVCs are a vital tool when administered correctly and effectively, they can cause many complications because of patient-related factors and incorrect practice. These complications include ecchymosis, hematoma, extravasation, occlusion, phlebitis, and catheter-related infections (3-5). Phlebitis is one of the common complications associated with PVC (6).

Phlebitis is defined as inflammation of the tunica intima layer of the vein using PVC (7). Phlebitis is a complication of bacterial phlebitis with symptoms of redness, pain, edema, a red line along the vein, palpation as a straight tube, and purulent discharge (8). Phlebitis causes significant pain and disruption of the peripheral vascular line. It may also require the placement of a new PVC. In addition, making a new diagnosis and requiring new treatments related to this new diagnosis prolongs the hospital stay of the patients and causes adverse effects such as

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increased workload for the nursing staff, stress for the patient/relatives, and additional costs (9-12). The Infusion Nurses Society (INS) states that the acceptable incidence of phlebitis should not exceed 5% in any population (13). However, when the literature is examined, it is seen that the incidence of phlebitis varies between 6.1% and 44% in studies on the development of phlebitis related to PVC conducted between 2010 and 2020 in the world and our country (13-18). In a study conducted in Serbia in 2018 to determine the incidence, severity, and risk factors of complications caused by PVCs, 1428 PVCs applied to 368 adult patients were analysed, and it was reported that phlebitis development with 44% ranked first among the complications that developed after PVC insertions (16).

When the risk factors affecting the frequency of phlebitis development are evaluated, the material from which the catheter is made (19,20), the length and diameter of the catheter (19), the duration of catheter stay in the vein (15,21,22), the anatomical region used (14,17,21), aseptic technique (8,17), immobility (17), and the properties of the drugs and fluids used (17,22) are considered. Individual characteristics such as age, gender (23), chronic diseases (17) and decreased mobility, family history of deep vein thrombosis, catheterisation of veins above the hand, pain, and use of certain drugs are also effective factors in phlebitis formation (17).

Along with the wide range of reported incidences of phlebitis and various risk factors, a detailed and recent analysis is missing. Therefore, the purpose of this study was to investigate the frequency of peripheral venous catheter-related (PVC-related) phlebitis and related factors in hospitalised adult patients. This study will reveal the development of phlebitis and the factors affecting the development of phlebitis in patients undergoing PVC and thus will guide nursing practice. Our aims were twofold. First, we attempted to determine the frequency of PVC-related phlebitis. Second, we tried to identify the risk factors for developing PVC-related phlebitis.

METHODS

This descriptive and correlational study was conducted in the adult inpatient clinic of a training and research hospital in İstanbul province between October 2020 and March 2021. The sample size of the study was calculated as 270 catheters because of G*Power (3.1.9.4) analysis (power: 0.8, β:0.20, α:0.05) based on the data of a previous similar study (24). Considering the possibility of patients dropping out, 315 catheters applied to 247 patients who met the sampling criteria and were accepted to participate were included in this study, which was slightly above 10% of the calculated sample size. Inclusion criteria: catheters inserted for the first time during hospitalisation and patients aged 18 and over. Exclusion criteria: receiving any immunosuppressive treatment, undergoing chemotherapy treatment, and existing phlebitis in the same extremity. The primary outcome of this study was the development of phlebitis. The variables analysed in the study were the patient's age, gender, body mass index, presence of chronic disease, smoking, PVC size, duration of catheter stay in the vein, extremity and anatomical region where the catheter was inserted, repeated use of the catheter site, intravenous (IV) treatment, frequency and method of treatment. The data of the study were collected from the "patient identification form", "visual infusion phlebitis diagnosis scale (VIPDS)", "peripheral catheter characteristics table," and "IV drugs administered to the patient form" which were created by the researcher as a result of the literature review. The patient identification form was created by the investigator because of a literature review (8,14-17). The patient identification form included characteristics such as age, gender, height, weight, history of chronic disease, smoking, number of IV catheters used, extremity used, and anatomical region used. The VIPDS was developed by Alyce Schultze and Paulette Gallant and published by the INS. The VIPDS comprises five stages. The VIPDS includes the steps of observing the catheter in terms of possible risks and/or grading phlebitis with the symptoms of phlebitis seen at each stage in case of phlebitis development while treatment is administered through a PVC (18,24). IV drugs administered to the patient form was created by the investigator to check whether the drugs administered to the patient through the IV catheter had a direct relationship with phlebitis. In this form, the names of the drugs initiated by the physician, starting times, doses, method of administration, frequency of administration, and the development of phlebitis during or after treatment were included.

In this study, data were collected using data collection forms in collaboration with the researcher and the primary nurses. Service nurses were previously trained on the documents for data collection. The process started with catheter insertion and subsequent catheter monitoring by the patient's primary nurse using the VIPDS. It continued until the patient was discharged or referred. As per the hospital policy, catheter site asepsis was provided in the wards using 2% chlorhexidine solutions. Semipermeable dressings/plasters supplied by the institution were used for fixation. In the case of phlebitis findings, the patient's PVC was removed. Catheters inserted in the ward were routinely changed every 72 h, except for complications. Because the patient was followed up only until discharge, phlebitis findings that may develop after discharge could not be reached.

Statistical Analysis

Data analysis was performed using Statistical Package for Social Sciences 25 (IBM SPSS Statistics Version 25, USA). Descriptive statistical methods (number, percentage, mean, standard deviation) were used to evaluate the demographic and disease-related characteristics of the patients, PVCs, phlebitis development, and medications. The chi-square test was used to compare the development of phlebitis in PVCs with demographic and disease-related, PVC-related, and drug-related characteristics. Post-hoc chi-square analyses were performed to determine the group causing significance in more than two groups. Because of chi-square analyses, a significant difference was observed between the groups according to five variables (repeated use of the catheter insertion site, duration of catheter stay in the vein, antiarrhythmic treatment, method of drug administration, and frequency of drug administration). In the evaluation of the data, p-values below 0.05 were considered statistically significant in all comparisons.

The study's ethics approval was obtained from the Üsküdar University Non-Interventional Clinical Ethics Committee (approval number: 61351342/2020-31, date: 29.01.2020). Written permission were obtained from the institution where the research was conducted. The purpose of the study was explained to the patients and their relatives, and written consent was obtained.

RESULTS

When the demographic characteristics of the patients who participated in the study were analysed, it was found that the mean age was 60.00±16.81 years, 59.9% were male, 42.9% were overweight, 83.8% had never smoked or quit smoking, 66% had chronic diseases, and 50.2% had a diagnosis of hypertension (Table 1). It was found that 60% of the PVCs were applied to the left arm of the patients, 35.2% of all catheters were applied to the antecubital fossa, and 71.4% of the catheters were not 20 G catheters. It was determined that 92.7% of the patients used the catheter for the first time, 75.2% of the catheters stayed in the vein for 49-72 h, and 90.8% were inserted in the ward. The frequency of PVC-related phlebitis was 15.6%. According to the VIPDS, 84.4%, 7.3%, 4.8%, 4.8%, 3.5%, and 3.5% of the sites where PVC was performed were found to be at level 1, level 2, level 3, and level 4, respectively. IV treatment was administered in 124 of 315 PVCs administered to the patients included in the study, and 21.3% of the IV treatments were in the antibiotic group. It was determined that 54.0% of the drugs administered to the patients were administered as bolus and 52.4% were administered twice or more daily (Table 2).

When phlebitis development at the site of PVC was compared according to the individual and medical characteristics of the patients, no statistically significant difference was observed between phlebitis development and age, gender, body mass index, smoking status, chronic disease, anatomical site of catheter insertion, and catheter size ($p>0.05$). When phlebitis development was compared according to the frequency of intervention at the site of PVC insertion, it was determined that the frequency of phlebitis development was significantly higher at the catheter sites repeated after intervention than at the catheter sites used for the first time ($p=0.041$). When phlebitis development was compared according to the duration of stay in the vein after PVC insertion, it was determined that phlebitis development was higher at the site of catheter insertion between 0-24 h and 25-48 h ($p<0.001$). In the post-hoc chi-square advanced statistical analyses performed to determine the group causing the significance, it was determined that there was no significant difference between the rate of phlebitis development in catheters left in the vein between 0-24 hours and 25-48 hours ($\chi^2=0.053$, $p=0.819$), 0-24 and 49-72 hours ($\chi^2=71.995$, $p<0.000$) and 25-48 and 49-72 hours ($\chi^2=75.014$, $p<0.001$).

Table 1. Demographic and disease-related characteristics of patients (n=247)

Variables	Mean	SD
Age (years)	60	16.81
BMI	27.86	5.35
	n	**%**
Age (years)		
18-40	53	19.92
41-64	116	43.60
65+	146	54.88
Gender		
Female	99	40.1
Male	148	59.9
BMI		
18.5-24.9	74	30.0
25-29.9	106	42.9
30=>	67	27.1
Smoking		
Yes	40	16.2
No	207	83.8
Chronic disease		
Yes	163	66.0
No	84	34.0
Chronic diseases		
Diabetes mellitus	64	25.9
Hypertension	124	50.2
Heart failure	86	34.8
Chronic renal failure	9	3.6
Chronic obstructive pulmonary disease	13	5.3

SD: Standard deviation, BMI: Body mass index

Tablo 2. Characteristics related to peripheral venous catheters and drugs administered through peripheral venous catheters (n=315)		
Variables	**n**	**%**
Extremity where the PVC is inserted		
Left arm	126	40
Right arm	189	60
PVC insertion site		
Dorsum of the hand	51	16.2
Forearm	89	28.3
Antecubital fossa	111	35.2
Upper arm	64	20.3
PVC size		
20 Fr	225	71.4
22 Fr	90	28.6
Frequency of use of the PVC site		
First time	292	92.7
Repeated use	23	7.3
Time of PVC		
0-24 hours	33	10.5
25-48 hours	45	14.3
49-72 hours	237	75.2
Phlebitis development		
Yes	49	15.6
No	286	84.4
Level of phlebitis		
Level 1	266	84.4
Level 2	23	7.3
Level 3	15	4.8
Level 4	11	3.5
IV drug use		
Yes	124	39.3
No	191	60.6
Antibiotic drug use		
Yes	67	21.3
No	248	78.7
Antiarrhythmic drug use		
Yes	22	6.9
No	293	93.1
Other drug use		
Yes	35	11.5
No	280	88.6
Development of phlebitis during the drug administration period		
Yes	38	30.6
No	86	69.3
Method of administration of the drug		
Bolus	67	54.0
Infusion	57	46.0
Frequency of drug administration		
One time	59	47.5
Two and more	65	52.4
PVC: Peripheral venous catheter, IV: Intravenous		

A statistically significant difference was found between the groups when phlebitis developed at the catheter site where antibiotics, antiarrhythmics, and other drugs were administered ($p<0.001$). Among these groups, the highest rate of phlebitis development was observed in patients receiving antiarrhythmic treatment, with 54.5% (n=12). Post-hoc chi-square advanced statistical analyses performed to determine the group causing the significance showed a highly significant difference between the development of phlebitis in catheters receiving antibiotics and those receiving antiarrhythmic therapy ($\chi^2=13.904$, $p<0.001$). There was a highly significant difference between the rates of phlebitis development at the catheter site in the antiarrhythmic and other drug groups ($\chi^2=10.697$, $p=0.001$). A statistically significant difference was observed between the groups when phlebitis development at the PVC site was compared according to the way the drugs were administered ($p=0.001$). Phlebitis developed in 38.6% of the infused catheter sites. According to the frequency of administration of the drugs, 46.7% of the drugs caused phlebitis at the catheter site in the first administration, and there was a highly significant difference between the groups ($p=0.014$) (Table 3).

DISCUSSION

The most important finding of this study was that the incidence of phlebitis in peripheral IV catheter use was 15.6%. This descriptive study determined the incidence of phlebitis and related factors in hospitalised patients by analysing 315 catheters used in 247 patients. The limitations of this study include the fact that the study was conducted in a single clinic, catheters were inserted by different nurses, and phlebitis development was evaluated by different nurses. In recent years, studies on this subject in Turkey have been limited. This study contributes to the national literature in terms of giving an incidence.

The INS recommends an acceptable phlebitis incidence of 5% or less (13). When the literature is analysed, it is seen that the phlebitis rates reported in other studies vary between 6.1% and 44% (13-18). The wide range of results in the literature may be due to the difference in phlebitis assessment tools and the different experiences of nurses evaluating phlebitis. The results of this study are compatible with the literature, but both the results and other results are above the acceptable values recommended by the INS. In this study, according to the findings determined by VIPDS, 84.4% of the catheters had phlebitis symptoms at level 1 and 7.3% had phlebitis symptoms at level 2. Unlike other phlebitis scales, level 1 phlebitis was defined as the stage in which phlebitis symptoms were not observed. In the study, 4.8% had level 3 phlebitis, 3.5% had level 4 phlebitis, and level 5 phlebitis was not detected. In this direction, in the study of Paşalıoğlu (24), similar to this study, it was reported that

Table 3. Comparisons of phlebitis development at PVC sites, drugs, and individual characteristics of patients (n=315)

Variables	Phlebitis development				χ^2	p-value
	Yes		No			
	n	%	n	%		
Age						
18-40	12	22.6	41	77.4	3.104	0.212
41-64	14	12.1	102	87.9		
>65	23	15.8	123	84.2		
Gender						
Female	18	14.8	104	85.2	0.097	0.755
Male	31	16.1	162	83.9		
BMI						
18.5-24.9	9	10.3	78	89.7	3.022	0.221
25-29.9	26	19.0	111	81.0		
30=>	14	15.4	77	84.6		
Smoking						
Yes	9	18.8	39	81.3	0.440	0.507
No	40	15.0	227	85.0		
Extremity where the PVC is inserted						
Left arm	18	14.3	108	85.7	0.258	0.612
Right arm	31	16.4	158	83.6		
PVC insertion site						
Overhand	9	17.6	42	82.4	1.401	0.705
Forearm	14	15.7	75	84.3		
Antecubital fossa	14	12.6	97	87.4		
Upper arm	12	18.8	52	81.3		
PVC size						
20 G	34	15.1	191	84.9	0.118	0.731
22 G	15	16.7	75	83.3		
Time of PVC						
0-24 hours	17	51.5	16	48.5	93.735	<0.001
25-48 hours	22	48.9	23	51.1		
49-72 hours	10	4.2	227	95.8		
Drugs						
Antibiotics	10	14.9	57	85.1	15.834	<0.001
Antiarrhythmics	12	54.5	10	45.5		
Other	4	11.4	31	88.6		
Method of administration of drugs						
Bolus	9	13.4	58	86.6	10.401	0.001
Infusion	22	38.6	35	61.4		
Frequency of drug administration						
One time	28	46.7	32	53.3	5.985	0.014
Two and more	17	25.8	49	74.2		
Chronic disease						
Yes	29	13.5	186	86.5	2.203	0.138
No	20	20.0	80	80.0		
Diabetes mellitus						
Yes	9	10.8	74	89.2	1.905	0.168
No	40	17.2	192	82.8		
Hypertension						
Yes	21	12.7	145	87.3	1.285	0.526
No	28	18.8	121	81.2		
Heart failure						
Yes	22	18.2	99	81.8	1.285	0.526
No	27	13.9	167	86.0		
Chronic renal failure						
Yes	0	0.00	12	100.0	1.232	0.267
No	49	16.2	254	83.8		
Chronic obsrtuctive pulmonary disease						
Yes	2	13.3	13	86.7	0.026	0.873
No	47	15.7	253	84.3		

χ^2: Chi-square, PVC: Peripheral venous catheter

90.1% of patients developed level 2 phlebitis. However, Berşe et al. (15), Braga et al. (25), and Atay et al. (14) reported that the most common level 1 phlebitis (the stage in which the first stages of phlebitis are seen) was observed in their studies using the phlebitis scale recommended by the INS. This was thought to be due to the withdrawal of catheters in patients with early signs of phlebitis at level 2.

When the development of phlebitis was compared according to the duration of stay in the vein after PVC application, it was observed that phlebitis was higher in catheters that stayed in the vein between 0-24 h and 25-48 h. The results of this study are similar to those of Paşalıoğlu (24) and Saini et al. (26). However, Berşe et al. (15) found that the incidence of phlebitis was higher in patients whose catheters remained for 72-96 h, and Lulie et al. (27) found that the incidence of phlebitis was higher in catheters that remained for more than 96 h. PVCs removed due to complications remain in the vein for a shorter time than those removed due to completion of treatment. Therefore, it is thought that the phlebitis rates were higher in catheters that remained in the vein for a shorter time in this study. The fact that phlebitis was observed with a rate of 51.5% in the first 24 h in this study is thought to be because antiarrhythmic and antibiotic group drugs administered in the clinic were started in the first hospitalisation of the patient and these drugs caused phlebitis in the first 24 h (20,28).

When the development of phlebitis was analysed according to the drugs administered through the catheter, a statistically significant difference was found between the districts and the development of phlebitis ($p<0.001$). The highest rate of

phlebitis development among these groups was found in patients receiving antiarrhythmic treatment (54.5%). In this study, the increased risk of phlebitis with antiarrhythmic treatment was interpreted as a result of using antiarrhythmic drugs with the active ingredient amiodarone, which has been reported to cause phlebitis in different studies. In a study performed to determine the incidence of IV amiodarone-induced phlebitis, the incidence of amiodarone-related phlebitis was found to be 44% (28). In a systematic review in which 20 studies were analysed to determine the incidence of amiodarone-related phlebitis, phlebitis was found to be between 0% and 85% (29). It is thought that the effect of pH and osmolarity of antiarrhythmic therapies on the vessel wall and the fact that they are continued in long-term infusions from the same PVC due to treatment procedures increase the incidence of phlebitis (8).

When the results of the study were analysed, it was observed that there was a statistically significant difference between the two groups according to the way the drugs were administered ($p=0.001$). The rate of phlebitis at the PVC sites of drugs administered by infusion was 38.6%. When the frequency of drug administration through the catheter was compared with the development of phlebitis, it was observed that phlebitis developed more frequently in catheters where the drug was applied twice or more times ($p<0.05$). It is thought that this result occurs because of repeated administration and primarily by infusion of drug groups such as antibiotics and antiarrhythmics with high phlebitis rates (20,29).

Study Limitations

The limitations of this study include the fact that the study was conducted in a single clinic, catheters were inserted by different nurses, and phlebitis development was evaluated by different nurses. In recent years, studies on this subject in Turkey have been limited. This study contributes to the national literature in terms of giving an incidence.

CONCLUSION

In conclusion, the rate of phlebitis due to PVCs in hospitalised adult patients was 15.6%. This study found a statistically significant difference between the duration of catheter stay in the vein, antiarrhythmic drugs, type and frequency of drug administration through the PVC, and the development of drug phlebitis. The results of this study expand our knowledge about the risk factors and frequency of phlebitis in adult patients using PVCs. In addition, feedback on the results to the healthcare team provides awareness of phlebitis and risk factors. In the future, multicenter, large-sample, prospective studies are recommended to clarify phlebitis development risks and develop strategies to reduce them.

Ethics

Ethics Committee Approval: The study's ethics approval was obtained from the Üsküdar University Non-Interventional Clinical Ethics Committee (approval number: 61351342/2020-31, date: 29.01.2020).

Informed Consent: Informed written consent was obtained from all participants.

Authorship Contributions

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

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ORIGINAL ARTICLE

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Exploring Childhood Trauma's Influence on Obesity: A Comprehensive Investigation

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Abstract

Objective: The study investigated the association between childhood trauma (CT), which is an environmental factor, and obesity.

Methods: The study was planned as a cross-sectional descriptive survey. Our study was conducted between 01.07.2022 and 01.08.2022. After obtaining informed consent from all participants over 18 years of age who presented to our outpatient clinic, they were examined using a face-to-face questionnaire. All subjects were interviewed using a 28-item CT scale form and a researcher-prepared questionnaire with 25 questions. The data obtained from the study were analyzed using the SPSS statistics 21 program and $p<0.05$ was considered significant.

Results: In our study, 63.67% of the 256 participants were female and 36.33% were male. The mean age of the participants was 38.53±14.61 years, and the mean body mass index was 30.01±7.14 kg/m^2. No statistically significant association was found between the variables of current and childhood obesity status of the study participants and their CT questionnaire (CTQ) score ($p>0.05$). In the study, the mean CTQ total score was 36.92±11.88. There was no statistically significant association between children's overweight/obesity problem and their childhood CTQ subgroup scores compared with their childhood peers ($p<0.05$).

Conclusion: In our study, no association was found between adult obesity and CTQ score. However, a significant association was found between emotional abuse, physical abuse, physical neglect, and obesity in adults, which are CTQ subsets.

Keywords: Obesity, psychological trauma, childhood

INTRODUCTION

It is widely recognized that obesity is a significant global public health issue that is steadily increasing in both developed and developing countries. According to the Turkish Epidemiology Survey of Diabetes, Hypertension, Obesity and Endocrine Disease study, 34.6% of individuals aged 19 years and above in Turkey are overweight, with 30.3% classified as obese. Health-related expenses associated with obesity, a worldwide chronic disease, account for 2-7% of the average healthcare spending (1). Previous research has established a link between adult obesity and traumatic childhood experiences. The World Health Organization defines obesity as "excessive fat accumulation that may harm health". Recent statistics reveal that the global prevalence of obesity has reached 47.1% in children and 27.5% in adults (2). The development of adult obesity is influenced not only by diet, genetic factors, and lifestyle but also by the social and environmental characteristics of communities and families. Key factors associated with the development of adult obesity related to family dynamics include anxiety, depression, anger, sexual abuse (SA), and childhood traumas (CTs) (2). When discussing the psychological factors contributing to the development of obesity, it is essential to highlight CTs. CTs encompass experiences such as sexual, physical, and emotional abuse (EA) and neglect endured by individuals before the age of 18 years. These traumas also

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include parental loss, divorce, migration, accidents, separation from parents, witnessing violence, and natural disasters (3). Numerous studies have consistently shown a significant relationship between adult obesity and exposure to CT (4,5). Despite this body of research, the precise mechanisms underlying the increased risk of obesity following CT remain incompletely understood (6). It has been demonstrated that disrupted eating behavior, often accompanied by psychological dysfunction, may explain the heightened risk of adult obesity (7). In line with findings that emphasize nutritional conditions and physiological factors during childhood, numerous studies indicate that emotionally distressing experiences during childhood may contribute significantly to the development of adult obesity (2,8). The primary objective of this study was to evaluate the prevalence of traumatic experiences during childhood among both obese and non-obese individuals and to determine the relationship between childhood traumatic experiences and adult obesity.

METHODS

Our study is a descriptive cross-sectional research carried out during the period from July 1, 2022, to August 1, 2022. We determined the sample size for our study by considering group means and standard deviations to estimate the effect size using G*Power 3.1.9.7 software. The α error probability was set at 0.05, and the study power (1-α error probability) was set at 0.95. With these parameters, we calculated the study's actual power to be 96%, thereby necessitating a total sample size of 246. Using a simplified sampling method, between the specified dates, we conducted face-to-face interviews with individuals aged 18 years and above, both obese and non-obese, who visited the Family Medicine Clinic at Prof. Dr. Cemil Taşcıoğlu City Hospital and willingly consented to participate in the study. In our research, all participants received a 28-item CT questionnaire (CTQ) developed by Bernstein et al. (9) and adapted and validated in Turkish (10).

The primary purpose of the CTQ is to retrospectively evaluate CTs. The CTQ consists of 28 items, 25 of which measure childhood maltreatment (total) and includes five subscales of five items each: EA, physical abuse (PA), SA, emotional neglect (EN), and physical neglect (PN). Three items were designed to measure minimization/denial. All five abuse and neglect subscales are the sum of ratings from "never true" (score 1) to "very often true" (score 5), and all subscales can therefore range from 5 to 25 after reversing seven items. When determining the minimization score, only the highest 5 (maximum) scores for each of these items are considered, each contributing 1 point. Separate calculation of scores for the traumatic experience subscales and the total score is possible. Each subscale ranges from 5 to 25 points. The total score from the scale ranges from 25 to 125. In addition, participants completed a 25-question survey created by our research team to gather information on their height, weight, sociodemographic details, chronic ailments, and distinctive attributes.

This study was approved by İstanbul Prof. Dr. Cemil Taşcıoğlu City Hospital Clinical Research Ethics Committee (approval number: E-48670771-514.99, date: 25.05.2022).

Statistical Analysis

To analyze our research outcomes, we used SPSS 21 (Statistical Package for the Social Sciences, version 21) statistical software. Normal distribution was assessed using the Kolmogorov-Smirnov test. Descriptive statistics were provided for numerical variables, including minimum, maximum, median, mean, and standard deviation, whereas categorical variables were presented in terms of frequency and percentage. For comparing means, the Mann-Whitney U test and Kruskal-Wallis test were utilized, and for comparing qualitative data, Pearson's chi-square test and Fischer exact test were applied. The impact of certain variables on CTQ scores was examined using multivariate linear regression analysis (method: enter). We considered a p-value less than 0.05 to be statistically significant when interpreting our results.

RESULTS

Among the 256 participants, 63.67% were female and 60.94% were married. Over half of the participants were university graduates. Of the participants, 52.34% were employed, and 71.48% had three or more siblings. 93.36% had lived with their biological parents during childhood (Table 1). The prevalence of obesity was found to be statistically significantly higher among those who experienced other traumas (like divorce traumas, natural disaster traumas etc.) during childhood ($p<0.01$) (Table 2).

In the study, the total score average CTQ was determined as 36.92±11.88. Among the subgroups, EA was found to be 7.05±3.07, PA 6.21±2.95, PN 7.45±3.10, EN 10.58±5.14, SA 5.64±1.98, and minimization 0.91±1.07. Table 3 presents the average scores of CTQ scale subgroups according to gender.

The results of the linear regression analysis predicting the CTQ scores for various variables are presented in Table 4. When examining the model outcomes, it was observed that the variable of living with a stepmother/stepfather during childhood ($p=0.044$), the variable of obesity within relatives (present) ($p=0.033$), and the variable of diagnosed psychiatric illness

(present) (p<0.001) significantly predicted CTQ scores. Living with a stepmother/stepfather during childhood increases CTQ scores by 11.137 points, the presence of obesity in relatives increases scores by 3.060 points, and having a diagnosed psychiatric illness increases scores by 7.806 points. These variables collectively account for 18.3% of the total variance in CTQ scores.

DISCUSSION

In our study, no relationship was found between adult obesity and CTQ scores. However, significant associations were observed between adult obesity and specific CTQ subscales, namely PA, EA, and PN. Observational studies on CT conducted in the literature show a positive relationship with adult obesity, with a positive association of 1.46 between CT and adult obesity in a meta-analysis of multiple studies, indicating a 46% likelihood of adult obesity after exposure to multiple CTs during childhood (11). Similarly, Bentley and Widom (12) found a significant relationship between PA and obesity. Another study confirmed the link between all forms of abuse and adult obesity, highlighting the significant role of EA during childhood in the development of obesity (13). The significant increase in PN scores found in our study among obese individuals has been associated in previous research with dietary restriction in women. This study observed that women who experienced PN during childhood were more likely to engage in dietary restrictions in adulthood. The same study found that EA was significantly associated with higher levels of body dissatisfaction, increased depression, and lower

Table 1. Comparison of sociodemographic characteristics and CTQ scores

		Total CTQ score					
		Min	Max	Median	Mean	SD	p-value
Age group	<33	25	73	33	35.20	9.62	0.127
	≥33	25	83	34	38.63	13.59	
Gender	Female	25	83	33	37.30	12.88	0.797
	Male	25	73	34	36.25	9.91	
Relationship status	Married	25	83	34	37.95	12.99	0.533
	Single	25	71	33	34.96	8.93	
	Divorced/widow	25	70	33	36.70	12.62	
Education level	Primary school	25	83	36	40.39	14.83	0.144
	High school	25	53	33	34.91	7.81	
	University	25	73	34	35.52	9.48	
	Master/doctorate	25	61	32	33.19	8.46	
Employment status	Not working	25	83	35	38.78	14.17	0.296
	Working	25	73	33	35.22	9.04	
Income level	Low	25	83	34	38.34	10.27	0.013
	Medium	27	65	39	39.82	8.81	
	High	25	73	32	34.02	11.04	
Who did you live with during childhood?	Mother/father	25	83	33	36.08	11.04	0.001
	Stepmother/stepfather	32	79	48	53.36	15.47	
	Non-family members	25	70	36	40.00	16.64	
Number of siblings	<3	25	73	32	34.44	9.55	0.052
	≥3	25	83	34	37.91	12.57	

CTQ: Childhood trauma questionnaire, SD: Standard deviation, Min: Minimum, Max: Maximum

Table 2. Comparison of the obesity status of individuals with childhood traumas

		Obese		Non-obese		
		n	%	n	%	p-value
Experiencing other traumas during childhood	Yes	61	60.40	40	39.60	0.006*
	No	62	42.76	83	57.24	

Pearson chi square test *p<0.01

self-esteem in both men and women (14). In Bennet et al. (15), no relationship was found between PN and body mass index (BMI). High BMIs were only associated with lower obesity risk in neglected children aged 8 years. It is likely that children subjected to PN may experience nutritional deficiencies, resulting in lower BMIs. However, studies suggest that children tend to gain weight as they age. Considering that other types of trauma (EA, etc.) often coexist with cases of PN, it could indirectly influence obesity.

Wiederman et al. (16) investigated the connection between SA and obesity among women and found a statistically significant association. Furthermore, obese women with a history of SA displayed notably lower levels of body dissatisfaction than their non-abused obese counterparts. Obese women who have experienced SA display less weight fluctuation compared with their non-abused obese counterparts. Among participants enrolled in a hospital-based weight management program, individuals with a history of SA had a lower rate of success in weight loss compared with a control group matched with non-abused peers (17). In the Felitti (18) study, some women with a history of SA were found to be less willing to lose weight. A significant number of adult women with obesity reported that they became obese shortly after experiencing childhood SA. An alternative hypothesis suggests that some sexually abused obese women may exhibit a reduced willingness to shift from an obese to a non-obese state as a coping mechanism to avoid close physical relationships with men. As a result, these women might have felt greater psychological comfort at a higher weight but may not have fully understood the psychodynamic implications of their usual "barrier weight". In contrast to our study, a significant negative correlation was found between obesity and the CTQ subcategory of SA in obese individuals. Given this context, it is important to recognize that societal factors such as reticence, shyness, stigma, and traditional lifestyles may contribute to inaccurate responses to inquiries about SA.

No significant relationship was found between obesity and EN in our study ($p>0.05$). Pederson and Wilson (19), in a study of 207

Table 3. CTQ subgroup average scores according to gender

		n	Minimum	Maximum	Mean	SD
Physical abuse	Female	163	5	23	6.52	3.450
	Male	93	5	13	5.66	1.632
Emotional abuse	Female	163	5	21	7.34	3.350
	Male	93	5	16	6.54	2.434
Physical neglect	Female	163	5	21	7.39	3.343
	Male	93	5	16	7.56	2.639
Emotional neglect	Female	163	5	25	10.29	5.099
	Male	93	5	24	11.08	5.213
Sexual abuse	Female	163	5	19	5.76	2.211
	Male	93	5	15	5.42	1.477
Minimization	Female	163	0	3	0.91	1.070
	Male	93	0	3	0.91	1.080

CTQ: Childhood trauma questionnaire, SD: Standard deviation

Table 4. Linear regression analysis for the prediction of some variables on the CTQ score

	B	Std. Error	Beta	t	p-value	Lower	Upper
Income level (high)	-2.586	1.757	-0.105	-1.472	0.142	-6.047	0.874
Income level (medium)	1.124	2.273	0.030	0.495	0.621	-3.352	5.601
Who did you live with in childhood (mother/father)	-1.536	4.497	-0.032	-0.342	0.733	-10.393	7.320
Who do you live with during childhood (stepmother/ stepfather)	11.137	5.491	0.191	2.028	0.044	0.322	21.951
Obese	-1.893	1.717	-0.080	-1.103	0.271	-5.275	1.488
Diagnosed obesity in a first-degree relative	3.060	1.425	0.129	2.147	0.033	0.253	5.868
Diagnosed psychiatric illness	7.806	1.695	0.284	4.604	0.000	4.467	11.145
Diagnosed psychiatric illness in a first-degree relative	1.910	1.824	0.061	1.407	0.296	-1.682	5.502

CTQ: Childhood trauma questionnaire, Std.: Standard, B: Regression coefficient, t: t-statistic

women, found a relationship between obesity and EN but did not find a relationship between other subcategories of CTs and obesity.

Among those who lived with a stepmother/stepfather during childhood, a higher prevalence of adult obesity and a higher likelihood of experiencing CTs were found compared with those who lived with their biological parents. Our findings suggest that any trauma experienced during childhood may contribute to obesity in adults. Further comprehensive studies are required to illuminate the mechanisms of this relationship.

CONCLUSION

In our study, we did not discover a link between adult obesity and CTQ scores. Nevertheless, notable connections were identified between adult obesity and distinct CTQ subcategories, including PA, EA, and PN. Conversely, no correlation was established between EN, SA during childhood, and obesity in adults. Notably, a higher incidence of obesity was observed among individuals who experienced different CTs, such as family members departing, parental divorce, family member loss, significant illnesses, surgeries, or exposure to natural disasters.

Considering that family medicine practitioners have the opportunity to get to know both children and their families in the patient population they serve, it is crucial for them to always be vigilant regarding any suspicious situations that may suggest child abuse and neglect. By taking appropriate measures, the negative effects of CT and the impact on the development of obesity, a chronic disease, can be mitigated.

Ethics

Ethics Committee Approval: This study was approved by İstanbul Prof. Dr. Cemil Taşcıoğlu City Hospital Clinical Research Ethics Committee (approval number: E-48670771-514.99, date: 25.05.2022).

Informed Consent: Informed written consent was obtained from all participants.

Authorship Contributions

Surgical and Medical Practices: H.B., Concept: H.B., F.E., S.A., E.K., Design: H.B., E.K., Data Collection or Processing: H.B., F.E., H.H.M., E.K., Analysis or Interpretation: H.B., F.E., H.H.M., S.A., Literature Search: H.B., F.E., S.A., Writing: H.B., F.E., H.H.M.

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Exploring the Relationship Between Obesity and Social Anxiety Disorder: A Cross-sectional Study on Quality of Life Impacts in Adults Aged 18-45

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Abstract

Objective: Obesity and social anxiety disorders (SADs) are prevalent conditions that significantly impact individuals' quality of life. Understanding the relationship between these conditions is crucial for effective healthcare interventions. This study aimed to investigate the presence of SADs among obese and non-obese individuals aged 18-45 years and assess their impact on quality of life.

Methods: Participants were evaluated using a sociodemographic information form and the Liebowitz social anxiety scale (LSAS). Measurements of height, body mass, hip circumference (HC), and waist circumference (WC) were also performed to assess obesity status.

Results: Analysis revealed that as body mass index increased, LSAS scores significantly increased (p=0.008, r=0.223), indicating a strong correlation between obesity and social anxiety levels. Among the obese and non-obese groups, obese participants showed a significantly higher likelihood of having SAD [Liebowitz social anxiety disorder (LSAD)] (p=0.026). This trend was particularly pronounced among women; obese females had significantly higher LSAD scores than non-obese females (p=0.023). Furthermore, LSAD scores significantly increased with waist and HCs (p=0.018, p=0.031, respectively), with a notable gender difference where increased WC was associated with higher LSAD scores in women (p=0.035).

Conclusion: The findings underscore the importance of psychological support in obesity treatment and advocate for comprehensive psychiatric evaluations for all patients. Addressing gender-specific challenges through targeted interventions could improve overall mental and physical health outcomes. Incorporating psychological support is vital for achieving sustained weight loss and enhancing quality of life.

This study highlights the integral role of mental health support in treating obesity, emphasizing the need for gender-specific approaches to address the intertwined issues of obesity and social anxiety. A multidisciplinary strategy that includes psychological care is essential for effective treatment and long-term success.

Keywords: Obesity, social anxiety disorder, waist-to-hip ratio, waist circumference, hip circumference

INTRODUCTION

Obesity is defined as excessive or abnormal fat accumulation that jeopardizes health, embodying a complex condition with multifactorial origins. The World Health Organization (WHO) classifies an adult with a body mass index (BMI) of 25 or higher as overweight and 30 or above as obese. Globally, 39% of adults were overweight or obese in 2016, a figure that rose to 66.8% within our nation (1,2). Data from the Turkish Statistical Institute in 2022 highlighted a higher prevalence of obesity among women (23.6%) than among men (16.8%) in Turkey (3).

The epidemic of overweight and obesity is acknowledged as a chronic disease, significantly contributing to the global surge in

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chronic, non-communicable diseases (4). Obesity is implicated in at least 13 types of cancer and is associated with numerous conditions affecting various body systems. Its adverse health consequences stem from mechanical, metabolic, and mental health issues, including musculoskeletal disorders, increased cardiovascular risk, type 2 diabetes, and psychological effects such as depression and low self-esteem due to societal stigma (2,4,5).

Social anxiety disorder (SAD), or social phobia, is characterized by intense, persistent fear or anxiety in social settings (6). Those afflicted experience severe discomfort and avoidance of situations where they might be judged or scrutinized, which impacts personal, academic, and professional life, leading to isolation and diminished quality of life (7).

The confluence of obesity and social phobia markedly diminishes individuals' well-being and quality of life. The bidirectional influence where SAD potentially alters eating behaviors, and conversely, where eating habits may signal the presence of SAD, underscores the complexity of these conditions (8).

This study was designed to explore the intricate relationship between obesity and social phobia, specifically investigating the presence and impact of social phobias on the quality of life among obese and non-obese individuals aged 18-45 years. Our aim is to shed light on these interactions to enhance healthcare delivery, raise awareness, and alleviate the stigma associated with these prevalent conditions.

METHODS

Research Setting and Participants

This descriptive study was conducted at University of Health Sciences Turkey, Şişli Hamidiye Etfal Training and Research Hospital, focusing on a single-center approach. We included 140 individuals aged 18-45 years who sought care at family medicine outpatient clinics for various reasons from November 15, 2022, to January 16, 2023. The participant count was determined on the basis of a 95% confidence level from 443 visits by this age demographic in the preceding three months to our clinic. The exclusion criteria were any psychiatric diagnoses, communication impediments, or refusal to participate in the research.

Data Collection Instruments

Data were gathered using a sociodemographic questionnaire developed by the researchers alongside the Liebowitz social anxiety scale (LSAS) through direct interviews after obtaining the consent of the participants. Measurements of height, body weight, hip circumference (HC), and waist circumference (WC) were conducted with precision up to 0.1 kg for weight and 0.1 cm for height and circumference, using standardized methods and equipment (9). Obesity was classified according to BMI based on WHO standards (1). WC and HC measurements were taken with a flexible, non-stretch tape measure to the nearest 0.1 cm, under minimal clothing conditions, with the WC measured midway between the lower rib and the iliac crest, and HC at the buttocks' widest point. Waist-hip ratios (WHR) calculations followed WHO guidelines, categorizing ≥0.90 cm in men and ≥0.85 cm in women as elevated (10).

Liebowitz Social Anxiety Scale

The LSAS, introduced by Michael Liebowitz in 1987, is an extensively validated instrument for quantifying the severity of SAD symptoms (11). This 24-item questionnaire evaluates fear and avoidance of social situations over the previous week, including 13 items on public performance and 11 on social interaction. Each item is rated on a 4-point Likert scale for fear (0-3) and avoidance (0-3), with subscale scores derived from the sum of these ratings. The Turkish adaptation of LSAS by Dilbaz (12) has confirmed its reliability. A threshold score of 30 was identified to optimally discriminate between individuals with and without SAD, offering high sensitivity and specificity (13). Consequently, our analysis considered scores of 30 or higher on the LSAS as indicative of potential SAD.

Statistical Analysis

IBM SPSS version 25.0 (SPSS Inc., Chicago, Illinois, USA) was used for all statistical analyses. Continuous data are presented as mean ± standard deviation, whereas categorical data are displayed as frequency (N) and percentage (%). The independent samples t-test and one-way ANOVA were used to assess differences across two or more groups regarding scale scores and other participant data. Student's t-test and Mann-Whitney U test were applied based on the normality of data distribution. Chi-squared tests examined the variation in categorical data across groups, with the Sidak test pinpointing significant differences when they arose. A p-value of ≤0.05 was considered statistically significant.

The study received approval from the Clinical Research Ethics Committee of University of Health Sciences Turkey, Şişli Hamidiye Etfal Training and Research Hospital (approval number: 3724, date: 15.11.2022).

RESULTS

The analysis encompassed 140 participants aged between 18 and 45 years, with a mean age of 32.27±7.90 years. Of these, 94 (67.1%) were female. Detailed sociodemographic characteristics and family obesity history are presented in Table 1.

Of the participants, 69 (49.3%) were classified as obese. Heights averaged 167.77±8.45 cm (range: 150-190 cm), while weights were on average 79.82±18.55 kg (range: 46-130 kg). The mean waist and HCs measured were 91.82±14.27 cm (range: 62-132 cm) and 110.27±11.87 cm (range: 90-143 cm), respectively.

A comparative analysis of sociodemographic data against obesity status revealed significant findings, as detailed in Table 2. Notably, individuals without a family history of obesity showed a higher tendency to be non-obese (p=0.000).

Within the cohort, 104 participants (74.3%) were identified with Liebowitz social anxiety disorder (LSAD), comprising 71 females (75.5%) and 33 males (71.7%). The distribution of LSAD across various BMI categories is depicted in Graphic 1.

Table 1. Sociodemographic data and family history of obesity of the participants

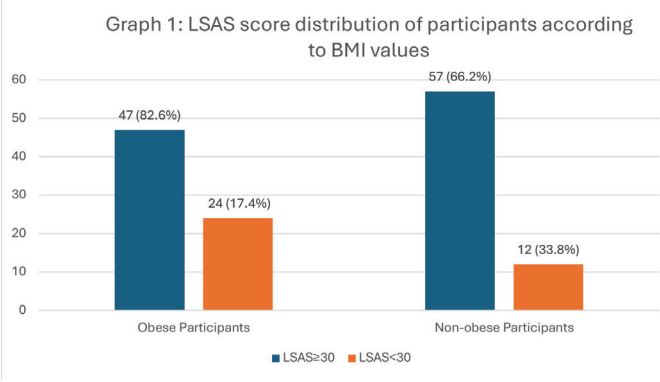
Variables		n	%
Gender	Female	94	67.1
	Male	46	32.9
Marital status	Married	80	57.1
	Not married	60	42.9
Educational status	Below high school	40	28.6
	High school and above	100	71.4
Employment status	Employed	84	60.0
	Unemployed	56	40.0
Income status	Low	71	50.7
	Medium	36	25.7
	High	33	23.6
Is there anyone in your family diagnosed with obesity?	Yes	30	21.4
	No	110	78.6

Table 2. Comparison of sociodemographic data and obesity status of participants

Demographic variables	Non-obese n (%)	Obese n (%)	p-value
Gender			
Female	46 (48.9%)	48 (51.1%)	0.547
Male	25 (54.3%)	21 (45.7%)	
Marital status			
Married	37 (46.3%)	43 (53.8%)	0.222
Not married	34 (56.7%)	26 (43.3%)	
Educational status			
Below high school	18 (45.0%)	22 (55.0%)	0.392
High school and above	53 (53.0%)	47 (47.0%)	
Employment status			
Employed	43 (51.2%)	41 (48.8%)	0.890
Unemployed	28 (50.0%)	28 (50.0%)	
Income status			
Low	36 (50.7%)	35 (49.3%)	0.992
Medium	18 (50.0%)	18 (50.0%)	
High	17 (50.7%)	16 (49.3%)	
Is there anyone in your family diagnosed with obesity?			
Yes	5 (16.7%)	25 (83.3%)	0.000
No	66 (60.0%)	44 (40.0%)	

An investigation into the correlation between BMI values and LSAS scores indicated a significant increase in LSAS scores parallel to an increase in BMI (p=0.008, r=0.223). Furthermore, when subjects were categorized into obese and non-obese groups, LSAS scores were significantly higher in obese individuals (p=0.026). A gender-specific analysis revealed this difference to be significant only among females, with obese women exhibiting higher LSAS scores than their non-obese counterparts (p=0.023). When regression analysis was performed according to whether the subjects were obese or not, no significant results were found with gender, SAD, and WHR (R^2=0.068).

Examining the relationship between waist and HCs and LSAS scores (Table 3) revealed a significant correlation; higher waist and HCs were associated with increased LSAS scores (p=0.018 and p=0.031, respectively). Focusing on gender disparities, an increase in WC significantly affected LSAS scores among women (p=0.035).



Graphic 1. LSAS score distribution of participants according to BMI values
LSAS: Liebowitz social anxiety scale, BMI: Body mass index

Additionally, participants with elevated WHR demonstrated higher LSAS scores (p=0.007), a trend particularly pronounced in women, where those with increased WHR showed significantly higher LSAS scores (p=0.031).

DISCUSSION

Our research aimed to illuminate the complex interplay between obesity and social anxiety by assessing participants using the LSAS and examining the correlation between obesity and SAD. Apart from the family history of obesity, sociodemographic comparisons between the obese and non-obese groups revealed no significant differences (2,4). Obesity emerges as a multifactorial condition, shaped by a blend of genetic, environmental, and lifestyle factors, with adult obesity often tracing back to familial and childhood instances, underscoring the role of inherited and environmental influences (14,15).

Moreover, obesity's ramifications extend beyond metabolic disorders such as diabetes and cardiovascular diseases to encompass mental health issues, including various anxiety disorders and depressive states (16,17). The link between obesity and anxiety disorders, particularly SAD, might stem from obesity-induced body image dissatisfaction, societal stigma, and lowered self-esteem, making obese individuals more susceptible to anxiety disorders than their non-obese counterparts (18,19). Discrimination and reduced social support further intensify the psychological distress of obese individuals, limiting their social and psychological resources (20-22).

Remarkably, our study found a 74.3% prevalence of SAD, which is significantly higher than the general population's estimated lifetime prevalence of 13% (23) and previous findings in obese

Table 3. Relationship between waist circumference and hip circumference and LSAS scores of participants

			LSAS score <30	LSAS score ≥30	p-value
			Mean ± SD	Mean ± SD	
Waist circumference			87.69±13.89	107.11±11.56	0.018
Hip circumference			93.25±14.18	111.36±11.84	0.031
Waist circumference	Female		84.47±14.54	90.47±13.46	0.035
	Male		93.38±10.98	99.24±14.03	0.187
Hip circumference	Female		107.30±12.57	111.49±11.45	0.080
	Male		106.76±10.00	111.09±12.81	0.322
			n (%)	n (%)	
Waist circumference / hip circumference	Female	Normal	28 (65.1%)	15 (34.9%)	0.031
		Increased	43 (84.3%)	8 (15.7%)	
	Male	Normal	20 (64.5%)	11 (35.5%)	0.118
		Increased	13 (86.7%)	2 (13.3%)	

LSAS: Liebowitz social anxiety scale, SD: Standard deviation

populations (24,25). This heightened prevalence could be attributed to the post-pandemic context, aligning with studies indicating an increase in social anxiety incidences during and after the pandemic (26,27).

A pivotal discovery was the disproportionate impact of obesity on social anxiety based on gender, with women bearing a greater burden. This disparity likely arises from societal and cultural norms that impose stricter body image standards on women than on men, contributing to increased anxiety and body dissatisfaction among women (28). Studies corroborate this finding, showing a higher prevalence of severe anxiety among obese women compared with their non-obese counterparts (29), and a significant relationship between increased WHRs and social anxiety in women, a pattern not observed in men, indicating that females are more frequently exposed to idealized body images in daily life (30,31).

Pathophysiological explanations for these findings may include hormonal imbalances in obese women that affect mood-regulating neurotransmitters, thereby influencing anxiety levels (32). The societal preference for certain body shapes intensifies body image concerns, potentially leading to behaviors that further entrench obesity (33,34). While societal pressures are undeniable, not everyone is equally affected.

Research on gender differences in body appreciation shows that women are more likely to engage in harmful social comparisons, worsening body dissatisfaction and its psychological effects (35-37). Addressing obesity thus necessitates a holistic approach that includes psychiatric evaluation, acknowledging the interconnection between obesity and mental health (16,17). Although it is important to note that not everyone with social anxiety will be obese, and vise versa, social anxiety and obesity can influence each other through various behavioral, psychological, and social factors. Social anxiety can cause isolation, which may lead to emotional eating, lack of exercise, and low self-esteem (38). Bariatric surgery, despite its effectiveness in weight management, highlights the complex nature of obesity treatment, emphasizing the importance of considering pre-operative factors, eating behaviors, and mental health (39,40).

CONCLUSION

Integration of psychological support is crucial in obesity treatment, underscoring the need for comprehensive psychiatric evaluations before and during treatment. Addressing the psychological aspects of obesity enhances the effectiveness of medical and dietary interventions. Furthermore, recognizing gender-specific challenges can improve both mental and physical health outcomes, advocating for interventions tailored to address these unique needs. Ultimately, a multidisciplinary approach, including psychological support, is pivotal for achieving sustainable weight management.

Further randomized controlled trials are necessary to confirm these findings and deepen our understanding of the intricate relationship between obesity, social anxiety, and gender.

Ethics

Ethics Committee Approval: The study received approval from the Clinical Research Ethics Committee of University of Health Sciences Turkey, Şişli Hamidiye Etfal Training and Research Hospital (approval number: 3724, date: 15.11.2022).

Informed Consent: Informed written consent was obtained from all participants.

Authorship Contributions

Concept: T.Ç., G.Z.Ö., Design: T.Ç., G.Z.Ö., Data Collection or Processing: T.Ç., G.Z.Ö., Analysis or Interpretation: T.Ç., G.Z.Ö., S.B.A., Literature Search: T.Ç., G.Z.Ö., S.B.A., Writing: G.Z.Ö., S.B.A.

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ORIGINAL ARTICLE

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Evaluation of Vaccine-preventable Disease Immunity and Influencing Factors Among Healthcare Workers: A Cross-sectional Study

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Abstract

Objective: Healthcare workers are at an elevated risk of exposure to vaccine-preventable diseases because of their close contact with patients. Understanding their immunity levels against diseases such as hepatitis A and B is crucial for implementing effective vaccination strategies. This study aimed to assess the immunity status of healthcare workers against certain vaccine-preventable diseases and to identify the factors influencing this immunity.

Methods: In a retrospective, cross-sectional analysis, we evaluated 865 healthcare workers from Prof. Dr. Cemil Taşcıoğlu City Hospital Institutional outpatient clinic in 2019. We collected data on antibody levels [anti-hepatitis A virus immunoglobulin G (anti-HAV IgG), anti-hepatitis B surface (anti-HBs), anti-Rubeola IgG, anti-Rubella IgG, anti-Mumps IgG] alongside demographic and professional information. Statistical analysis was performed using SPSS 26, considering $p<0.05$ as significant.

Results: Among the participants, 64.74% (n=560) were female and 35.26% (n=305) were male. Hepatitis B surface antigen negativity was observed in 99.54% (n=861) of the cohort, with a 92.95% (n=804) positivity rate for anti-HBs. Positivity rates for anti-Rubella IgG, anti-Rubeola IgG, and anti-Mumps IgG exceeded 90%. Of the 249 vaccines administered to 192 workers, 61% were for hepatitis A. Significant differences in anti-HAV IgG levels were noted across educational levels and between genders ($p=0.011$ and $p=0.015$, respectively), with higher positivity in primary school graduates and males. Anti-HBs positivity was significantly higher in females than in males ($p=0.033$), and increased with educational attainment ($p<0.001$).

Conclusion: The study highlights a 56.76% immunity rate against hepatitis A among healthcare workers, underscoring the need for enhanced vaccination efforts, particularly for those in frequent contact with patients or patient fluids. These findings emphasize the importance of targeted vaccination programs within healthcare settings to protect workers from vaccine-preventable diseases, ultimately safeguarding both healthcare personnel and patients.

Keywords: Healthcare personnel, immunity, vaccine, antibodies

INTRODUCTION

Hepatitis A virus (HAV), an enveloped RNA virus with a diameter of 27-32 nm, is classified within the Hepatovirus genus of the *Picornaviridae* family, primarily transmitting through the fecal-oral route. This virus can cause a range of clinical presentations from asymptomatic infections to severe conditions such as fulminant hepatitis (1). Given its public health significance, vaccination against hepatitis A is advocated for individuals at increased risk, including travelers to endemic regions, military and diplomatic personnel, and those working in high-risk settings such as healthcare and food service sectors (2).

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The global burden of hepatitis B virus (HBV) infection remains a significant public health challenge, with over 257 million carriers worldwide and nearly 887,000 deaths annually from complications such as cirrhosis and hepatocellular carcinoma. HBV transmission primarily occurs through contact with infected bodily fluids, highlighting the increased risk faced by healthcare workers. The introduction of vaccination and prophylactic measures post-exposure has substantially reduced HBV infection rates among healthcare professionals (3). In response, Turkey launched a national hepatitis B vaccination program in 1998 targeting newborns and individuals at high risk, with the objective of curtailing the spread of HBV (4).

In addition, the Turkish Ministry of Health incorporated the measles, mumps, and rubella vaccine into the national vaccination schedule in 2006, further underscoring the commitment to controlling vaccine-preventable diseases. The advisory board's recommendation for an additional measles-containing vaccine dose for children in regions prone to outbreaks reflects ongoing efforts to enhance immunization coverage and public health outcomes (5).

This study aimed to assess the immunity status of healthcare workers against certain vaccine-preventable diseases and to explore factors influencing vaccine efficacy. The importance of this research lies in its potential to inform strategies for improving vaccination coverage among healthcare workers, thereby enhancing their protection against infectious diseases and contributing to broader public health goals.

METHODS

Design and Participant Selection

Employing a retrospective and cross-sectional approach, our analysis encompasses data from 865 healthcare workers who underwent periodic examinations at the institutional outpatient clinic of Prof. Dr. Cemil Taşcıoğlu City Hospital from January 1, 2019, to December 31, 2019. Following the acquisition of ethical approval, informed consent was obtained from all participants. The study measured the levels of anti-hepatitis A virus immunoglobulin G (anti-HAV IgG), hepatitis B surface antibody (anti-HBs), anti-Rubeola IgG, anti-Rubella IgG, and anti-Mumps IgG among consenting healthcare workers during their routine periodic health assessments. Ethical approval was obtained from the İstanbul Prof. Dr. Cemil Taşcıoğlu City Hospital Clinical Research Ethics Committee (approval number: E-48670771-514.10, date: 09.04.2021). The study was conducted in line with the principles of the "Helsinki Declaration".

Methodology

The evaluation of antibody levels involved comparison with predefined reference values to determine the immune status of the participants. Healthcare workers with antibody levels below these reference benchmarks underwent subsequent re-evaluation of their vaccination status and control antibody levels during their subsequent periodic examination. Additionally, the study incorporated demographic information of the participants, including gender, age, education level, blood group, known diseases, occupation, and lifestyle factors such as smoking and alcohol consumption. Demographic data were retrieved from archived recruitment and periodic examination forms.

Statistical Analysis

The SPSS 26 software (Statistical Package for the Social Sciences, version 26) facilitated our statistical analysis. Descriptive statistics calculated for numerical data included mean, minimum, maximum, and standard deviation values, whereas categorical data were summarized using frequencies and percentages. Comparative analyses of qualitative data were conducted using the chi-square and Fisher's exact tests, with a significance threshold set at $p<0.05$.

RESULTS

Participant demographics revealed an average age of 29.72±8.29 years, with 64.74% (n=560) identifying as female, 35.26% (n=305) as male, and a majority, 74.57% (n=645), holding university degrees. Among these, 35.84% (n=310) were physicians, predominantly working in internal medicine, accounting for 58.5% (n=506) of the cohort (Table 1).

Table 1. Sociodemographic and occupational characteristics of the participants

		n	%
Gender	Female	560	64.74%
	Male	305	35.26%
Education level	Primary care	22	2.54%
	High school	198	22.89%
	University	645	74.57%
Occupation	Doctor	310	35.84%
	Nurse	251	29.02%
	Other	304	35.14%
Branch of employment	Internal	506	58.50%
	Surgical	293	33.87%
	Other	66	7.63%
Smoking status	Smoker	186	21.53%
	Non-smoker	678	78.47%

Investigation into hepatitis markers showed that 99.54% (n=861) of participants were negative for hepatitis B surface antigen (HBsAg), whereas 92.95% (n=804) exhibited positivity for anti-HBs antibodies. Additionally, the presence of antibodies against Rubella, Rubeola, and Mumps was notably high, exceeding 90% for each (n=835, n=804, and n=808, respectively), contrasting with a 56.76% (n=491) positivity rate for anti-HAV IgG (Table 2).

Of the 865 healthcare workers studied, 413 (47.74%) had positive antibody tests. Institutional vaccination was provided to 22.89% (n=198) of the participants, culminating in the administration of 249 vaccines, with hepatitis A vaccines constituting 61% (n=152) of these immunization (Table 3).

A detailed analysis of the distribution of anti-HBs antibodies indicated a significantly higher positivity among female healthcare workers than among their male counterparts. The rate of anti-HBs positivity also escalated with higher educational attainment and was particularly elevated among doctors and nurses compared with other professional groups. Employees in internal and surgical departments similarly showcased greater antibody positivity rates than those in other areas ($p<0.05$) (Table 4).

Conversely, anti-HAV IgG positivity was statistically lower in females than in males, with those having primary education showing higher positivity rates than individuals with secondary or higher education levels. Workers in surgical departments exhibited lower anti-HAV IgG positivity than colleagues in other specialties ($p<0.05$) (Table 5).

Table 2. Antigen-antibody status of the participants

		n	%
HbsAg	Positive	4	0.46%
	Negative	861	99.54%
Anti-HBs	Positive	804	92.95%
	Negative	61	7.05%
Anti-HAV IgG	Positive	491	56.76%
	Negative	374	43.24%
Anti-Rubella IgG	Positive	835	96.53%
	Negative	30	3.47%
Anti-Rubeola IgG	Positive	804	92.95%
	Negative	61	7.05%
Anti-Mumps IgG	Positive	808	93.41%
	Negative	57	6.59%

HBsAg: Hepatitis B surface antigen, Anti-HBs: Hepatitis B surface antibody, Anti-HAV IgG: Anti-hepatitis A virus immunoglobulin G

Table 3. Examination of vaccines administered to participants

		Administered		Total %
		n	%	
Vaccine name	**Hepatitis A**	152	61.0%	76.8%
	Hepatitis B	39	15.7%	19.7%
	Measles, mumps, and rubella	58	23.3%	29.3%
Total		249	100.0%	125.8%

Table 4. Comparison of anti-HBs results with sociodemographic and occupational characteristics of participants

		Anti-HBs				p-value
		Positive		Negative		
		n	%	n	%	
Gender	Female	528	94.29%	32	5.71%	0.037
	Male	276	90.49%	29	9.51%	
Education level	Primary care	13	59.09%	9	40.91%	0.000
	High school	169	85.35%	29	14.65%	
	University	622	96.43%	23	3.57%	
Occupation	Doctor	297	95.81%	13	4.19%	0.000
	Nurse	246	98.01%	5	1.99%	
	Other	261	85.86%	43	14.14%	
Branch of employment	Internal	486	96.05%	20	3.95%	0.000
	Surgical	276	94.20%	17	5.80%	
	Other	42	63.64%	24	36.36%	
Smoking status	Smoker	167	89.78%	19	10.22%	0.058
	Nonsmoker	636	93.81%	42	6.19%	

Anti-HBs: Hepatitis B surface antibody

Table 5. Comparison of anti-HAV IgG results with the sociodemographic and occupational characteristics of the participants						
		Anti-HAV IgG				p-value
		Positive		Negative		
		n	%	n	%	
Gender	Female	301	53.75%	259	46.25%	0.015
	Male	190	62.30%	115	37.70%	
Education level	Primary care	19	86.36%	3	13.64%	0.011
	High school	117	59.09%	81	40.91%	
	University	355	55.04%	290	44.96%	
Occupation	Doctor	183	59.03%	127	40.97%	0.091
	Nurse	128	51.00%	123	49.00%	
	Other	180	59.21%	124	40.79%	
Branch of employment	Internal	304	60.08%	202	39.92%	0.000
	Surgical	138	47.10%	155	52.90%	
	Other	49	74.24%	17	25.76%	
Smoking status	Smoker	106	56.99%	80	43.01%	0.960
	Nonsmoker	385	56.78%	293	43.22%	
Anti-HAV IgG: Anti-hepatitis A virus immunoglobulin G						

No significant differences were observed in the sociodemographic and occupational profiles of participants when correlated with anti-Rubella and anti-rubeola IgG outcomes ($p>0.05$). However, the anti-mumps IgG positivity rate was significantly lower among nurses than in other professional groups ($p<0.05$). Additionally, no discernible relationship was established between the Rh blood groups of the healthcare workers and their antigen-antibody statuses ($p>0.05$).

DISCUSSION

The transmission risk of HBV, a critical blood-borne pathogen in healthcare settings, to healthcare workers post-exposure to fluids from HBsAg-positive patients is estimated to be between 5% and 30% (6). The primary revelation of this study was the high anti-HBs positivity rate of 92.95% among participants, with only 0.46% testing positive for HBsAg. Our institution vaccinated 39 individuals against hepatitis B, achieving adequate antibody formation in all cases.

Comparatively, anti-HBs positivity rates in prior Turkish studies were lower: 63.8% as reported by Tekin and Deveci (7), 68.4% by Uzun et al. (8), and 75.7% by Öksüz et al. (9). The elevated rates observed in our study may be attributed to the predominance of doctors in our sample and the increasing awareness and accessibility to hepatitis B vaccination over the years. Notably, anti-HBs positivity correlated with educational attainment, being highest among physicians and nurses, indicating an educational influence on vaccine uptake, consistent with findings by Ciliz et al. (10) and Apaydın et al. (11).

Regarding HAV, known as the leading agent of acute viral hepatitis globally, transmitted through contact with infected individuals or contaminated resources (12), our findings showed a 56.76% seropositivity for anti-HAV IgG. This was lower than the seropositivity rates found in other Turkish studies, potentially due to reduced exposure risks in İstanbul's urban setting. Köse and Temoçin (13) and Apaydın et al. (11) reported varying seropositivity rates, reflecting the impact of socioeconomic status, hygiene practices, and demographic factors on HAV exposure.

Healthcare workers' risk of droplet-transmitted infections, in addition to fluid-borne diseases, underscores the importance of vaccinations for this group. Our study found a 92.95% anti-Rubeola IgG positivity rate among healthcare workers, with no significant differences across sociodemographic or occupational characteristics ($p>0.05$). The history of measles vaccination in Turkey and the recent surge in cases highlight the critical need for ongoing vaccination efforts among healthcare professionals to prevent potential nosocomial outbreaks (14,15).

The retrospective and cross-sectional design of this study introduces potential biases, including recall bias, and may limit the ability to establish causality. The specific focus on healthcare workers and the high prevalence of vaccinated physicians may also affect the generalizability of our findings.

The results emphasize the importance of educational level and professional status in influencing vaccination rates and immunity levels among healthcare workers. Our findings align with previous research, suggesting that targeted vaccination strategies are essential for protecting healthcare workers and their patients from vaccine-preventable diseases.

CONCLUSION

The study indicates that while immunity against HBV is high among healthcare workers, hepatitis A immunity levels are concerningly low, highlighting the need for increased vaccination efforts. The hepatitis B vaccine was the most frequently administered vaccine among the healthcare workers surveyed. These findings underscore the necessity of enhanced vaccination strategies to bolster healthcare workers' immunity and curb disease transmission. Further randomized controlled trials are required to confirm these results and address the identified gaps in vaccination coverage and immunity.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the İstanbul Prof. Dr. Cemil Taşcıoğlu City Hospital Clinical Research Ethics Committee (approval number: E-48670771-514.10, date: 09.04.2021).

Informed Consent: Informed consent was obtained from all participants.

Authorship Contributions

Surgical and Medical Practices: S.A., Concept: B.E., S.A., Design: B.E., S.A., Data Collection or Processing: S.A., Analysis or Interpretation: F.E., N.Ç.A., Literature Search: B.E., F.E., N.Ç.A., Writing: F.E., N.Ç.A.

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ORIGINAL ARTICLE

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Comparing the Effectiveness of Adductor Canal and Popliteal Artery Capsule Block Combination Versus Epidural Analgesia for Postoperative Pain Management in Arthroscopic Knee Surgery: A Prospective Observational Study

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Abstract

Objective: Peripheral nerve blocks have gained popularity in recent years because of advancements in ultrasound-guided techniques and their proven effectiveness in providing targeted analgesia. In knee surgeries, combining a femoral nerve block or adductor canal block (ACB) with a subgluteal sciatic block, popliteal sciatic block, or the infiltration between the popliteal artery and the capsule of the posterior knee (IPACK) block has been shown to offer superior analgesia due to the comprehensive sensory innervation of the knee region.

Methods: This study was designed to compare the analgesic efficacy of ACB + IPACK block combination with single-dose epidural analgesia in arthroscopic knee surgery. The primary outcome was to assess analgesic efficacy at different time points (1st, 8th, and 24th hours post-block administration) between the ACB + IPACK block combination and epidural analgesia. Secondary outcomes included chronic pain outcomes at the 3-month post-surgery mark, discharge times, patient mobilization times, and postoperative analgesic requirements. This prospective observational study was conducted between August 15, 2022, and February 15, 2023. The study included patients over the age of 18 years who were scheduled to undergo arthroscopic knee surgery under spinal anesthesia and who had no limitations in cooperation or orientation.

Results: Both IPACK, ACB, and epidural analgesia demonstrated comparable efficacy in providing pain relief in arthroscopic knee surgery patients. The block group showed comparable postoperative analgesia to the epidural group at the 8th and 24th h, whereas the combined spinal epidural group provided more effective analgesia at the 1st h. Additionally, the block group was associated with shorter mobilization times than the epidural group. No significant differences were found in discharge times or chronic pain at 3 months between the two groups ($p>0.05$).

Conclusion: Both IPACK, ACB, and epidural analgesia can be effective options for managing postoperative pain in patients undergoing arthroscopic knee surgery. The findings of this study suggest that IPACK, ACB, and epidural analgesia can be effective options for managing postoperative pain in patients undergoing arthroscopic knee surgery. However, further randomized controlled trials are needed to confirm these findings.

Keywords: Knee arthroplasty, IPACK block, adductor canal block, pain management, mobilization, quadriceps strength

INTRODUCTION

Knee surgeries often involve a variety of postoperative pain management strategies, including peripheral nerve blocks, central neuraxial blocks, local anesthetic infiltration, and systemic analgesics. Among these, peripheral nerve blocks targeting the knee region have become increasingly popular because of their effectiveness in providing analgesia (1). Recently, the combination of adductor canal block (ACB) and infiltration

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between the popliteal artery and capsule of the knee (IPACK) block has emerged as a promising strategy (2,3).

The rationale for this study stems from the unique advantages of ACB and IPACK block. ACB selectively blocks the anterior sensation of the knee while minimizing motor loss compared with traditional femoral nerve blocks. IPACK block is a newer technique that targets sensory branches of the sciatic nerve supplying the posterior knee joint. When combined, these blocks have shown enhanced analgesia and reduced opioid consumption in knee surgeries (4). However, despite the advantages of these blocks, epidural analgesia remains the gold standard method in knee surgeries because of its effectiveness, reproducibility, and ability to reduce opioid consumption. However, its side effects, such as urinary retention, delay in mobilization, nausea, and hypotension, have led to a preference for peripheral nerve blocks.

Therefore, this study was designed to compare the analgesic efficacy of ACB + IPACK block combination with single-dose epidural analgesia in arthroscopic knee surgery. Our aim was to assess the primary outcome of analgesic efficacy at different time points (1st, 8th, and 24th hours post-block administration) between the ACB + IPACK block combination and epidural analgesia. Secondary outcomes include chronic pain outcomes at the 3-month post-surgery mark, discharge times, patient mobilization times, and postoperative analgesic requirements. The hypothesis of this study was that the ACB + IPACK block combination would provide comparable or superior analgesia to epidural analgesia, with potential benefits in terms of side effects and recovery times.

METHODS

Study Design

This study was conducted as a prospective observational study.

Setting

The study was conducted between August 15, 2022, and February 15, 2023, following the approval of the University of Health Sciences Hamidiye Faculty of Medicine Ethics Committee (approval number: E-48865165-302.14.06-139413, date: 08.07.2022). This study was conducted in accordance with the Declaration of Helsinki. Informed consent forms were obtained from all patients.

Participants

The study included patients over the age of 18 years who were scheduled to undergo arthroscopic knee surgery under spinal anesthesia and who had no limitations in cooperation or orientation. Patients who did not consent to participate, were under 18 years old, were scheduled for general anesthesia, had diseases limiting cooperation, and were using more than 3 months of gabapentin, pregabalin, or opioid were excluded. In addition, patients with one or more of the following conditions were excluded from the study: previous coagulation or bleeding disorder, receiving anticoagulant therapy, allergy/sensitivity to local anesthetics and/or opioids, and infection in the procedure area.

Variables

The primary outcome compares analgesic efficacy at different time points (1st, 8th, and 24th hours post-block administration) between the ACB + IPACK block combination and epidural analgesia. Secondary outcomes include chronic pain outcomes at the 3-month post-surgery mark, discharge times, patient mobilization times, and postoperative analgesic requirements.

Data Sources/Measurement

Patient data, including age, gender, American Society of Anesthesiologists physical status classification system (ASA) scores, comorbidities, postoperative visual analog scale (VAS) scores, mobilization and discharge times, VAS score at 3 months, and postoperative analgesic requirements, were recorded. The severity of pain was assessed using the VAS at the 1st, 8th, and 24th h after block administration. Mobilization and discharge times were also documented. Follow-up was conducted by contacting the patients again on the 90th day.

Bias

The study was designed to minimize potential bias by excluding patients with certain conditions and using a standardized protocol for the administration of ACB + IPACK block and epidural analgesia.

Study Size

Statistical power analysis was performed, determining a sample size of 70 patients to achieve 95% power based on similar studies. A total of 80 patients were included in the study, with 40 receiving IPACK and ACBs and 40 undergoing combine spinal epidural, after excluding case losses.

Quantitative Variables

Quantitative variables such as age, ASA scores, postoperative VAS scores, mobilization and discharge times, and VAS score at 3 months were recorded and analyzed.

Statistical Analysis

Data analysis was performed using Python version 3.9.12 and the SciPy package. The Shapiro-Wilk test was used to assess data distribution. Chi-square and Fisher's exact tests were employed for categorical data, independent t-tests for parametric data, and Mann-Whitney U tests for non-parametric data. Statistical significance was set at $p<0.05$.

RESULTS

Participants

A total of 90 patients who underwent arthroscopic knee surgery under regional anesthesia between August 15, 2022, and February 15, 2023 were initially included in this study. However, ten patients were excluded at different stages because of incomplete data and the procedure being changed to general anesthesia. Therefore, the final analysis was conducted on 80 patients who were divided into two groups based on the chosen method for postoperative analgesia: IPACK and ACB (group 1) and epidural analgesia (group 2) (Figure 1).

Descriptive Data

Demographic characteristics, including age, gender, and ASA scores, were comparable between the two groups, with no significant differences observed. In group 1 (IPACK and ACB), the mean age was 50.1 years, whereas in group 2 (epidural analgesia), it was 49.4 years. The gender distribution in group 1 comprised 18 males and 22 females, whereas in group 2, there were 21 males and 19 females. Regarding the ASA scores, group 1 included 11 ASA I, 24 ASA II, and 5 ASA III patients, whereas group 2 comprised 14 ASA I, 23 ASA II, and 3 ASA III patients. In terms of comorbidities, group 1 had 32 patients with additional diseases and 12 patients without any additional disease, whereas group 2 had 29 patients with additional diseases and 11 patients without any additional disease. All demographic data are presented in Table 1.

Outcome Data

Comparison of postoperative pain scores between the two groups revealed that the block group (group 1) provided equally effective postoperative analgesia as the epidural group (group 2) at the 8th and 24th hours ($p>0.05$). However, at the 1st hour, the combined spinal epidural group (group 2) provided more effective analgesia than the block group ($p=0.021$). The mean 1st hour VAS score in group 1 was 2.12±0.76, significantly higher than the score of 1.64±0.62 in group 2 ($p=0.021$). No significant differences were found in the 8th hour (group 1: 2.17±0.88, group 2: 1.92±0.74) and 24th hour (group 1: 2.49±1.04, group 2: 2.24±0.94) VAS scores. The VAS scores of the patients at the 1st, 8th, and 24th h are presented in Table 2. Regarding mobilization time, the patients in group 1 had a significantly shorter duration of 1.16 days than the patients in group 2, whose mobilization time was 1.68 days ($p=0.037$). However, there was no significant difference in discharge times between the two groups, with

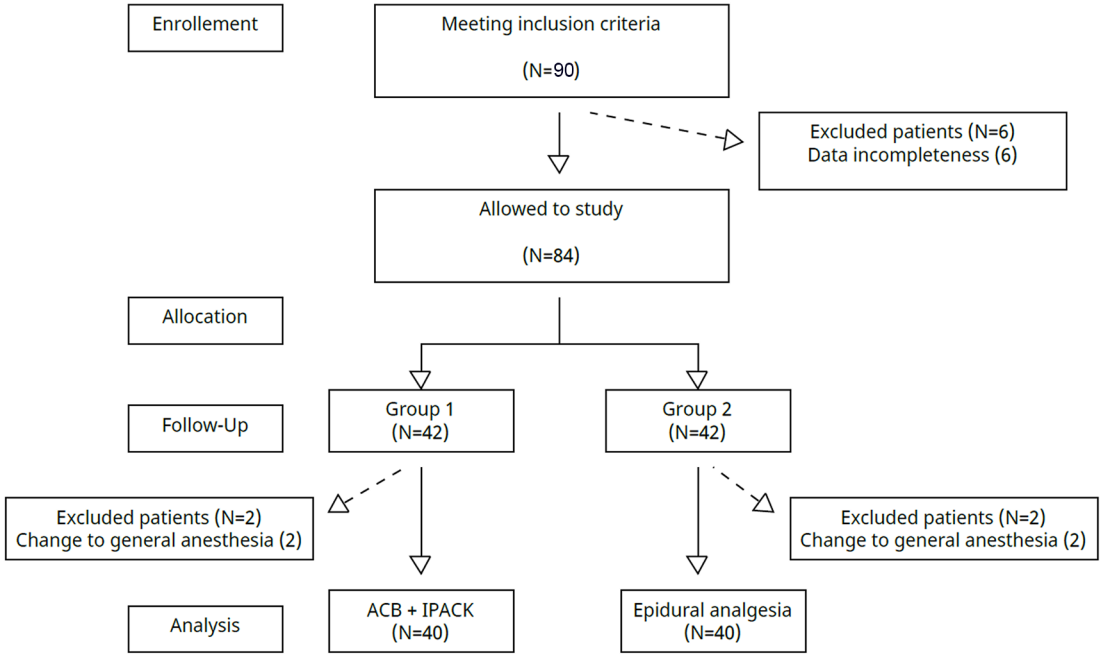

Figure 1. Consolidated standards of the reporting trials flow diagram
ACB: Adductor canal block, IPACK: Infiltration between the popliteal artery and the capsule of the posterior knee

Table 1. Demographic data of the groups			
	Group 1 (n=40)	Group 2 (n=40)	p-value
Age (years)	50.1±16.8	49.4±18.4	0.82
Gender (M/F)	18/22	21/19	0.76
ASA (I/II/III)	11/24/5	14/23/3	0.59
Additional disease yes/no	32/12	29/11	0.8
ASA: American Society of Anesthesiologists physical status classification system, M/F: Male/Female			

Table 2. VAS scores of the patients at the postoperative 1st, 8th, and 24th h			
	Group 1 (n=40)	Group 2 (n=40)	p-value
VAS (1st hour) Mean ± SD (min/med/max)	2.12±0.76 1/2/4	1.64±0.62 1/2/3	0.021
VAS (8th hour) Mean ± SD (min/med/max)	2.17±0.88 1/2/3	1.92±0.74 1/2/3	0.095
VAS (24th hour) Mean ± SD (min/med/max)	2.49±1.04 1/2/4	2.24±0.94 1/2/4	0.101
VAS: Visual analog scale, SD: Standard deviation, min: Minimum, med: Medium, max: Maximum			

group 1 having a mean discharge time of 2.24 days and group 2 having a mean discharge time of 2.4 days (p=0.33).

Main Results

If the patient failed to tolerate pain, 1000 mg paracetamol and 100 mg contramal as rescue analgesia were administered. Rescue analgesia was required in 5 patients in both groups, and no significant difference was detected (p>0.999). To evaluate chronic pain at 3 months, VAS scores were assessed for all 80 patients in the study. The mean VAS score in group 1 was 1.22, whereas it was 1.16 in group 2. No significant difference was observed between the two groups in terms of this parameter (p=0.1).

DISCUSSION

The most important finding of this study was that both IPACK, ACB, and epidural analgesia demonstrated comparable efficacy in providing pain relief in arthroscopic knee surgery patients. The block group showed comparable postoperative analgesia to the epidural group at the 8th and 24th h, whereas the combined spinal epidural group provided more effective analgesia at the 1st h. Additionally, the block group was associated with shorter mobilization times than the epidural group. No significant differences were found in discharge times or chronic pain at 3 months between the two groups.

Peripheral nerve blocks have become increasingly favored in recent years because of the advancements in ultrasound-guided techniques and their proven effectiveness in providing targeted pain relief. In knee surgeries, the combination of femoral nerve block or ACB with subgluteal sciatic block, popliteal sciatic block, or IPACK block has been identified to provide superior pain relief because of the comprehensive sensory innervation of the knee region (5).

IPACK block, which targets the sensory articular branches of the sciatic nerve that innervate the posterior knee joint, has emerged as an effective technique for alleviating posterior knee joint pain. When combined with the ACB, it enhances postoperative pain relief and reduces opioid consumption compared with the ACB alone (6,7). Studies have also reported comparable efficacy between the IPACK block and the genicular nerve block, another peripheral nerve block for posterior sensory block of the knee (8). Moreover, surgeons have achieved similar results to the combination of IPACK and ACB through periarticular local anesthetic infiltration on the posterior part of the knee (9).

The use of peripheral nerve blocks and local anesthetic infiltration in knee surgeries achieves effective postoperative pain relief with minimal motor block. This approach is particularly advantageous considering the undesirable side effects of opioids, such as nausea, vomiting, and constipation (10-12). In addition to reducing opioid consumption, IPACK block and ACB have demonstrated effective postoperative pain relief for knee surgeries, aligning with the principles of multimodal pain control (7,10).

In terms of patient mobilization and discharge, continuous peripheral nerve blocks have been associated with longer durations than single-dose blocks (13,14). However, it has been observed that ACB catheters, which aim to minimize motor loss, facilitate earlier mobilization and discharge compared with femoral nerve catheters (15). The duration of hospitalization and mobilization times were shortened in the IPACK block group compared with that in the epidural analgesia group (16,17). Another study comparing subgluteal sciatic nerve block + femoral nerve block with ACB + IPACK block found that the IPACK group exhibited better early motor function (18).

Postoperative chronic pain is a significant concern in knee surgeries, affecting approximately 10% of patients and increasing to 20% in some cases (19,20). Epidural analgesia has been widely recognized as an effective method for preventing chronic pain by providing successful perioperative analgesia control (17).

The efficacy of IPACK block in preventing chronic pain is still limited, with few studies available (11). However, our study found that ACB + IPACK block was as effective as epidural analgesia in preventing chronic pain.

In addition to knee surgeries, the versatility of IPACK block is evident in other clinical applications such as algology and perioperative analgesia, as well as in procedures such as radiofrequency ablation (21,22). Emerging techniques such as the IPACK block and saphenous, peroneal, accessory obturator, nerve to vastus medialis, and articular branch of the obturator nerve (SPANK) block have expanded the options for sensory blockade in the lower extremities (23).

Study Limitations

This study has several limitations that should be considered. The lack of randomization and the potential for confounding factors should be considered when interpreting the results. The only criterion for mobilization time was the patient's ability to get out of bed and walk. The VAS score was used to define chronic pain. Symptoms such as paresthesia, burning, and stinging were not questioned. The volume of local anesthetic used for the block may not be standardized because of the lack of a minimum effective concentration for the IPACK block.

CONCLUSION

In conclusion, this study found that IPACK, ACB, and epidural analgesia demonstrated comparable efficacy in providing pain relief in arthroscopic knee surgery patients. The block group showed comparable postoperative analgesia to the epidural group at the 8th and 24th h, whereas the combined spinal epidural group provided more effective analgesia at the 1st h. Additionally, the block group was associated with shorter mobilization times than the epidural group. No significant differences were found in discharge times or chronic pain at 3 months between the two groups. Further randomized controlled trials are needed to confirm these findings.

Ethics

Ethics Committee Approval: The study was conducted between August 15, 2022, and February 15, 2023, following the approval of the University of Health Sciences Turkey, Hamidiye Faculty of Medicine Ethics Committee (approval number: E-48865165-302.14.06-139413, date: 08.07.2022).

Informed Consent: Obtained.

Authorship Contributions

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

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Identifying Biomarkers for Cervical Neoplasia: A Label-free Proteomic Analysis of Cervicovaginal Fluid

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Abstract

Objective: Cervicovaginal fluid (CVF) is a rich reservoir of biomolecules reflective of the health status of the female reproductive tract. The intricate proteome of CVF contains potential biomarkers for various gynecological conditions, including cervical neoplasia. This study aimed to elucidate the proteome of CVF at different stages of cervical neoplasia using a label-free proteomics approach, employing liquid chromatography and tandem mass spectrometry. The primary purpose of this study was to identify proteins that could serve as biomarkers for the early detection of cervical cancer (CxCa).

Methods: A total of 60 CVF samples were analyzed, including 40 from women diagnosed with cervical intraepithelial neoplasia (CIN) (CIN-1, CIN-2, CIN-3) and 20 from healthy controls. Label-free spectral counting was used to quantify the relative abundance of proteins in these samples.

Results: Analysis of the CVF proteome from the study participants revealed 244 proteins. Among these, calmodulin-like protein-3, profilin-1, and annexin-A3 were significantly differentiated between the neoplastic and non-neoplastic samples. Calmodulin-like protein-3 showed a significant decrease in abundance in the neoplastic samples compared with the controls, with a $p<0.001$. Profilin-1 and annexin-A3 exhibited significant variations in expression levels, with p-values of 0.024 and 0.057, respectively, thereby distinguishing between the different groups.

Conclusion: The identification of significant proteins such as calmodulin-like protein-3, profilin-1, and annexin-A3 underscores the potential of CVF proteomics for the early detection of CxCa. These findings pave the way for further research into CVF as a source of diagnostic biomarkers for cervical neoplasia. Understanding the CVF proteome alterations associated with cervical neoplastic stages offers a promising avenue for non-invasive screening strategies. This approach could significantly enhance early detection efforts, ultimately facilitating timely intervention and prevention of CxCa progression.

Keywords: Proteomics, cervical intraepithelial neoplasia, protein biomarker, cervicovaginal fluid, cancer screening

INTRODUCTION

Human papillomavirus (HPV) infection is one of the most common sexually transmitted infections worldwide and is known as the major cause of cervical cancer (CxCa), despite the improvements in vaccines against multiple variants of the virus. CxCa represents one of the global health burdens of HPV-related cancers as being the fourth most common cancer in women, especially squamous cell carcinoma, with mainly subtypes HPV-16, 18, 45, and 56 (1). CxCa follows virus-related tissue dysplasia, progresses slowly (2-10 years), and has a high incidence and prevalence largely in younger sexually active women (1). The management of CxCa screening (see Figure 1A) follows current

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guidelines and universal classification; according to the Bethesda System (2), cervical intraepithelial neoplasias (CINs) are graded on a scale of 1 to 3: CIN-1, CIN-2, and CIN-3, which are also referred to as "mild dysplasia"; "moderate dysplasia"; and "severe dysplasia", respectively (2).

Body fluids represent a vital source of biomarkers for the early detection of diseases, offering a unique insight into the pathological state of the body (3,4). Cervicovaginal fluid (CVF), in particular, has emerged as a significant biological fluid for proteomic analyses because of its rich content of proteins that may serve as indicators for various gynecological conditions, including endometrial and ovarian cancers, as well as preterm birth (5-7). The exploration of CVF through proteomics can unveil distinctive biomarkers that reflect the up- or downregulation of proteins in response to specific pathological conditions (8-10).

Despite the advancements in proteomic technologies and their application to CxCa research, the complexity and variability of the proteome in body fluids present considerable challenges (5,11-13). Previous studies have identified numerous proteins associated with CxCa from various sample types; however, the dynamic nature of the proteome, especially in CVF, complicates the identification of reliable biomarkers (5). Unlike genomics, proteomics research faces hurdles due to the intricate interactions and modifications of proteins, which are not fully understood (14,15). CVF's unique composition, isolated from other bodily systems and easily collected, presents a promising avenue for non-invasive diagnostic and prognostic biomarker discovery (16,17). The role of this fluid in vaginal health and defense against pathogens further underscores its potential for disease marker identification (18). Given the limitations of current diagnostic methods, such as the inaccuracies associated with colposcopic biopsies and the invasive nature of these procedures, there is a pressing need for alternative, non-invasive screening methods (19,20).

Therefore, this study was designed to harness the potential of CVF in the search for biomarkers indicative of cervical neoplasia (see Figure 1B), using label-free tandem mass spectrometry to identify proteins associated with the early stages of CxCa development. We established a profile of neoplasia-associated proteins within CVF and identify markers that could signal the risk of cancerous transformation in the cervix. This two-fold objective seeks not only to contribute to the early detection of CxCa but also to enhance the accuracy and reliability of the population screening methods given in Figure 1A. This study hypothesized that specific proteins within CVF could serve as early indicators of neoplastic changes, offering a novel approach to CxCa screening and diagnosis.

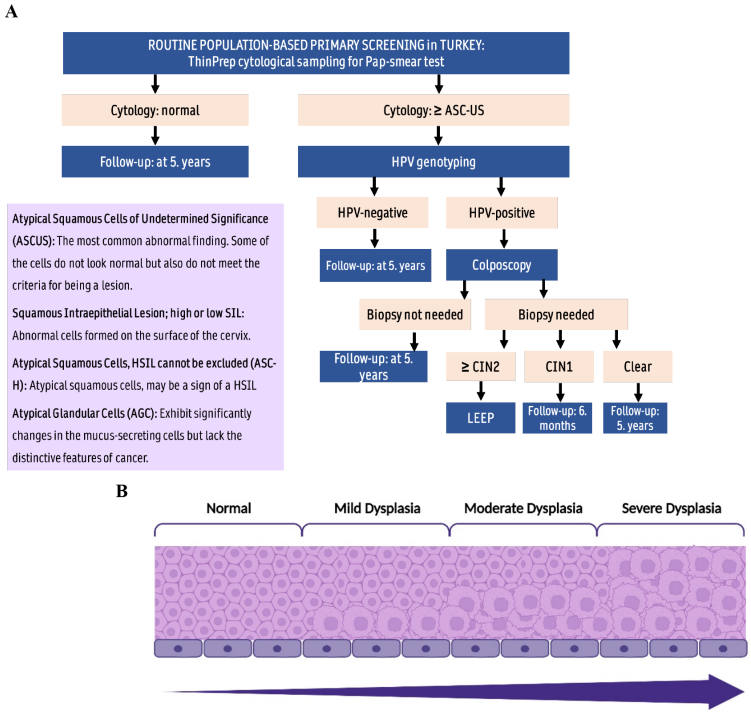

Figure 1. (A) Current cervical cancer population-based screening guideline in Turkey. (B) CIN development on the cervical layer.
ASC-US: Atypical squamous cells of undetermined significance, LSIL: Low-grade squamous intraepithelial lesions, HSIL: High-grade squamous intraepithelial lesions, AGC: Atypical glandular cells, AGUS: Atypical glandular cells of undetermined significance, CIN: Cervical intraepithelial neoplasia

METHODS

Design and Patient Selection

This study was meticulously planned to gather and analyze samples from a specific demographics group: women aged 20 to 49 years. The mean age of the participants was 34.46 years, with a standard deviation of 6.60, highlighting a median age of 34 and a mode of 32 years. Ethical considerations were paramount, and the study received approval from the Acıbadem Mehmet Ali Aydınlar University Medical Research Evaluation Board (ATADEK) (approval number: 2020-01/30, date: 09.01.2020). To ensure confidentiality and ethical compliance, each participant was assigned a unique identification code. This measure was critical in maintaining the anonymity of the participant's medical and demographic information throughout the study.

Patient Selection Criteria

The recruitment strategy targeted patients undergoing colposcopy because of either abnormal Pap smear test results or a positive test for high-risk HPV. This case-control cohort was divided into three groups based on their HPV status, presence or absence of intraepithelial lesions or malignancy, and histopathological examination results. The groups included individuals without HPV and lesions, patients with mild dysplasia (CIN-1), and those with moderate to severe dysplasia (CIN-2&3). The study's exclusion criteria were aligned with those typically applied to Pap smear sampling, excluding individuals experiencing menstruation, engaging in unprotected sexual intercourse, or using vaginal douches within 48 h before sampling. Notably, symptoms of gynecological infections did not disqualify participants from the study, ensuring a wide and inclusive participant base.

Sample Collection and Preliminary Processing

As seen in Figure 2A, the current study started with sample collection, followed by a series of experiments and ended with statistical analysis. All participants provided written informed consent before sampling, and the experiments were performed following the approved institutional guidelines. Enrollment and sampling were performed at Acıbadem Altunizade Hospital and Acıbadem Maslak Hospital in İstanbul, Turkey. The criteria of eligibility were women with (patient group) and without (control group) cervical neoplasia development. Exclusion criteria were unprotected sexual intercourse within 72 h of sampling, vaginal bleeding within the current or previous week before sampling, or any vaginal pomade or wick use within 72 h.

The procedure for sample collection was rigorously designed to prevent contamination. Each sample was collected at the beginning of the colposcopic examination, immediately labeled with the patient's identification number, and refrigerated at +4 °C. Upon arrival at the laboratory, the samples underwent

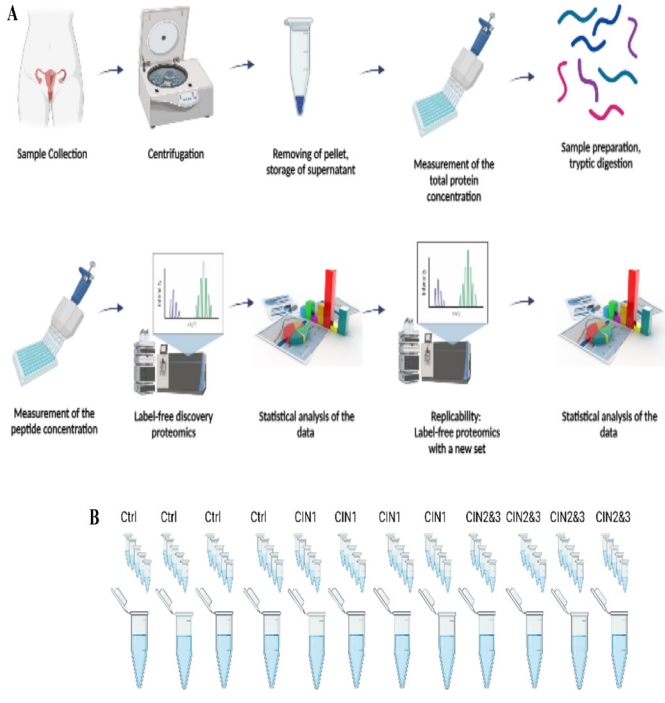

Figure 2. (A) Schematic representation of the study workflow (Created with BioRender.com). (B) Samples pooled into 12 (4×3) tubes by 20 samples × 3 groups, each of 5 samples
CIN: Cervical intraepithelial neoplasia

a standardized preparation process involving the addition of a storage buffer, followed by centrifugation to remove cell debris. This process was critical for isolating a clear supernatant for subsequent analysis. The study meticulously measured the total protein concentration of each sample, acknowledging the inherent variability in biological materials. This step was essential in preparing the samples for the analytical phase, ensuring that each sample was handled with the utmost care to maintain its integrity for accurate analysis.

Detailed Liquid Chromatography and Tandem Mass Spectrometry Analysis Methodology

The analytical phase employed a label-free liquid chromatography and tandem mass spectrometry (LC-MS/MS) technique, emphasizing a pooling method (Figure 2B) to reduce individual sample variability. This phase was underpinned by a detailed protocol that began with the mixing of universal protein extraction solution with a protease inhibitor cocktail, followed by the application of heat to denature the proteins. The samples then underwent a series of reduction and alkylation reactions within protein low-bind tubes, culminating in a desalting and digestion process designed to release the peptides for analysis. This study leveraged advanced centrifugation techniques to prepare the sample lysate, ensure detergent depletion, and facilitate the isolation of peptides. Quantification of peptide concentration and optimization of loading volumes were critical steps, enabling precise analysis of tryptic peptides. The use of a Symmetry C18 column for peptide trapping and elution, followed by the application of an acetonitrile gradient, was pivotal in separating and fractionating peptides based on their hydrophobic characteristics. This detailed methodology underscores the study's commitment to achieving high-resolution peptide profiles, providing a robust foundation for subsequent statistical analysis.

Statistical Analysis

The statistical analysis was designed to rigorously evaluate the discriminative power of the identified biomarkers. By employing ANOVA tests and box plots, this study revealed and visualize the clinical performance of potential biomarkers. The use of MedCalc software facilitated a sophisticated analysis, allowing for the detailed examination of biomarker efficacy across different clinical groups. This analytical approach was instrumental in assessing the statistical significance of the findings, ensuring that the conclusions drawn from the study were both reliable and robust.

RESULTS

Overview of Sample Demographics and Classification

The study successfully analyzed 60 samples, which were meticulously categorized into three clinical groups based on their diagnostic criteria (see Figure 1B). The "control" group included samples from 20 individuals deemed healthy after rigorous screening. The "CIN-1" group comprised samples from 20 individuals diagnosed with mild dysplasia, indicating the initial stages of CIN. Furthermore, the "CIN-2&3" group was assembled from samples of 20 individuals, split evenly between moderate and severe dysplasia diagnoses, showcasing the study's commitment to covering a broad spectrum of the disease's progression. Each sample's corresponding colposcopic punch biopsy pathology report was meticulously collected and analyzed, adhering to the ethical guidelines set forth by the relevant committee.

Clinicopathological Characteristics

The clinicopathological profiles of the participants, which are vital for the comprehensive analysis, are detailed in Table 1. This included a broad range of data meticulously collected to ensure a robust understanding of each group's specific characteristics. Notably, the average age across all individuals from whom samples were collected was 34 years, highlighting a homogeneous age distribution that enhances the study's relevance to its target demographic.

Proteomic Analysis Findings

The proteomic exploration conducted through Nano LC-MS/MS analysis was a cornerstone of this study, yielding significant insights into the protein composition of the collected samples. A total of 244 protein groups were identified across the samples with high confidence, achieving a false discovery rate of less than 1%. This achievement underscores the precision and reliability of progenesis QIP software in parsing complex proteomic data to unveil proteins with potential relevance to the pathophysiology of CIN and its varying degrees of severity.

The identification of these protein groups marks a pivotal step toward understanding the molecular underpinnings of cervical dysplasia and its progression. The detailed analysis of these proteins, set against the backdrop of the clinical classifications of the samples, provides a rich dataset for further investigation into potential biomarkers for early detection, prognosis, and personalized treatment strategies for cervical dysplasia and cancer.

Table 1. Patient information

Sample chart (n=60)						
Age	**Protein (ug/mL)**	**Medical history**	**Infection**	**Cytology**	**Biopsy**	**Study group**
39	122.54	None	Acute vulvitis	Normal	Clear	Control
36	177.39	None	None	Normal	Clear	Control
38	5454.24	None	None	Normal	Clear	Control
34	428.38	None	Acute vaginitis, vaginal candidiasis	Normal	Clear	Control
43	1033.11	Conization	None	Normal	Clear	Control
33	631.22	None	None	Normal	Clear	Control
46	682.77	Ovarian cyst rupture	None	ASC-US	Clear	Control
25	666.46	None	Acute vaginitis	Normal	Clear	Control
32	1606.34	None	Vaginal candidiasis	Normal	Clear	Control
20	537.43	None	None	Normal	Clear	Control
32	507.60	None	None	Normal	Clear	Control
36	1132.90	None	None	Normal	Clear	Control
28	1322.01	None	None	Normal	Clear	Control
38	1092.81	None	Vaginal candidiasis	Normal	Clear	Control
43	990.53	Breast cancer	None	Normal	Clear	Control
27	1547.43	None	None	LSIL	Clear	Control
26	727.65	CIN-I	None	LSIL	Mucinous metaplasia	Control
40	1721.85	None	Cronic cervicitis	Normal	Squamous metaplasia	Control
38	366.30	None	Acute vaginitis	LSIL	Squamous metaplasia	Control
42	679.15	None	Chronic cervicitis	LSIL	Clear	Control
35	952.43	None	Acute vaginitis	HSIL	CIN-1	Mild dysplasia
39	21.80	None	None	ASC-US	CIN-1	Mild dysplasia
42	43.54	None	None	LSIL	CIN-1	Mild dysplasia
49	611.64	None	None	ASC-US	CIN-1	Mild dysplasia
27	509.82	None	Acute vaginitis	ASC-US	CIN-1	Mild dysplasia
32	610.09	None	None	LSIL	CIN-1	Mild dysplasia
33	276.17	LSIL	None	Normal	CIN-1	Mild dysplasia
39	262.22	LSIL	None	ASC-US	CIN-1	Mild dysplasia
30	605.67	None	None	ASC-H	CIN-1	Mild dysplasia
40	582.54	ASC-H	None	ASC-US	CIN-1	Mild dysplasia
39	580.23	None	None	ASC-H	CIN-1	Mild dysplasia
24	589.17	None	Acute vaginitis	HSIL	CIN-1	Mild dysplasia
43	101.86	ASC-US	None	LSIL	CIN-1	Mild dysplasia
37	598.36	None	None	-	CIN-1	Mild dysplasia
30	349.56	None	None	LSIL	CIN-1	Mild dysplasia
26	611.78	ASC-US	Acute vaginitis	ASC-US	CIN-1	Mild dysplasia
38	605.02	None	None	-	CIN-1	Mild dysplasia
30	587.50	None	None	LSIL	CIN-1	Mild dysplasia
46	560.42	None	None	ASC-US	CIN-1	Mild dysplasia
43	1849.82	Uterine polyps	Acute vaginitis	LSIL	CIN-1	Mild dysplasia
32	1253.50	ASC-H	None	ASC-H	CIN-2	Moderate dysplasia
28	749.86	None	Acute vaginitis	ASC-H	CIN-2	Moderate dysplasia

Table 1. Continued

Sample chart (n=60)						
Age	**Protein (ug/mL)**	**Medical history**	**Infection**	**Cytology**	**Biopsy**	**Study group**
23	1431.25	None	None	HSIL	CIN-2	Moderate dysplasia
35	821.40	None	None	Normal	CIN-2	Moderate dysplasia
29	656.61	None	None	LSIL	CIN-2	Moderate dysplasia
29	510.83	ASC-US	None	ASC-US	CIN-2	Moderate dysplasia
34	611.34	LSIL	None	LSIL	CIN-2	Moderate dysplasia
29	408.94	ASC-US	None	LSIL	CIN-2	Moderate dysplasia
32	522.59	None	None	LSIL	CIN-2	Moderate dysplasia
36	406.07	None	Acute vaginitis	HSIL	CIN-2	Moderate dysplasia
34	1440.49	ASC-US	None	ASC-US	CIN-3	Severe dysplasia
27	1063.41	None	None	ASC-H	CIN-3	Severe dysplasia
40	549.59	None	Acute vaginitis	LSIL	CIN-3	Severe dysplasia
36	638.98	HSIL	None	HSIL	CIN-3	Severe dysplasia
45	359.97	None	None	LSIL	CIN-3	Severe dysplasia
24	1332.13	None	None	LSIL	CIN-3	Severe dysplasia
29	425.82	None	Acute vaginitis	ASC-US	CIN-3	Severe dysplasia
43	377.74	LSIL	None	HSIL	CIN-3	Severe dysplasia
33	434.10	None	None	ASC-H	CIN-3	Severe dysplasia
32	451.30	None	Acute vaginitis	LSIL	CIN-3	Severe dysplasia

CIN: Cervical intraepithelial neoplasia, LSIL: Low-grade squamous intraepithelial lesions, ASC-US: Atypical squamous cells of undetermined significance, ASC-H: Atypical squamous cells, HSIL cannot be excluded, HSIL: High-grade squamous intraepithelial lesions

DISCUSSION

Considering the extensive research conducted over the past 15 years, as outlined in our review article (21), the investigation into the proteome of CVF has been a focal point in understanding gynecological health and disease. Previous studies, such as those by Van Ostade et al. (14), Zegels et al. (17), and Van Raemdonck et al. (22,23), Boylan et al. (24), Starodubtseva et al. (13), Ma et al. (25), and Gutiérrez et al. (26), have identified a varying number of proteins in CVF, reflecting the fluid's potential as a diagnostic tool for gynecological diseases. Despite differing methodologies across studies, the pursuit to delineate a "healthy core proteome" of CVF has been consistent, underscoring the fluid's variability and the challenges in using it for biomarker identification.

The pivotal discovery of our study was the identification of 244 protein groups with high confidence, highlighting the significant variability of the CVF proteome. Among these, three proteins -calmodulin-like protein-3 (CALL3, P27482), profilin-1 (PROF1, P07737), and annexin A3 (ANXA3, P12429)- were found to significantly differentiate between the clinical groups studied, with statistical significance shown in Figure 3B. This differentiation is crucial for understanding the molecular basis of cervical neoplasia and underscores the potential of these proteins as biomarkers for the disease.

Study Limitations

The study's methodology, while comprehensive, is not without its limitations. The variability inherent to CVF as a sample material introduces potential biases and uncertainties in protein identification. This variability, coupled with the diverse methods of sample collection and analysis used in previous studies, underscores the challenges in achieving a standardized approach to CVF proteomics. This study meticulously addressed these concerns through rigorous sample processing and advanced analytical techniques, but the potential for variability remains a critical consideration.

The differential protein expression profile analyzed in this study provides a nuanced understanding of cervical neoplasia at the molecular level. The significant proteins identified not only offer insights into the disease's pathophysiology but also align with findings from similar studies (23,26-28), reinforcing the relevance of these proteins in the context of cervical health. The careful interpretation of these results, considering the study's

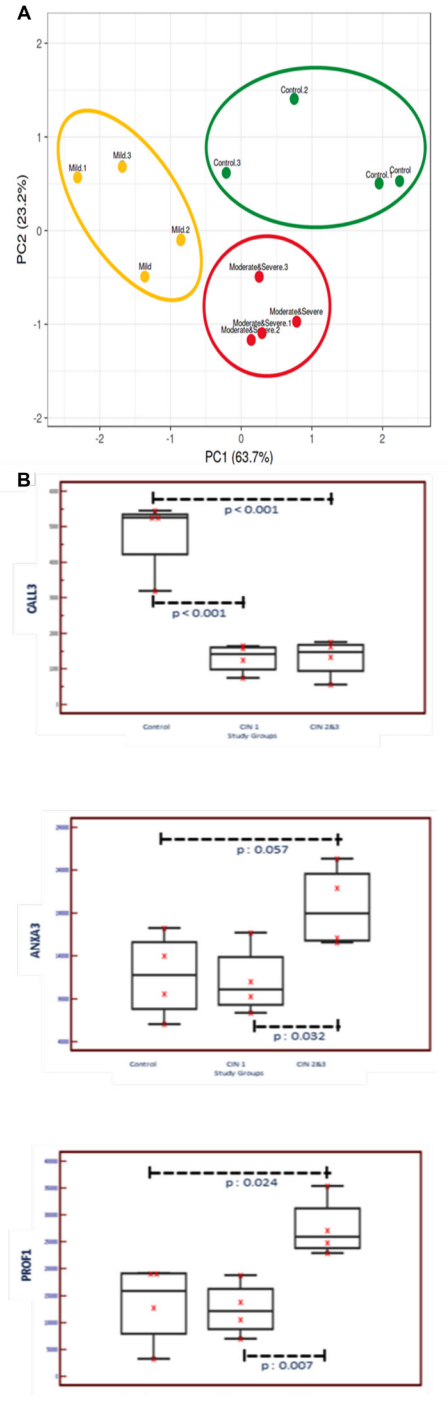

Figure 3. (A) Principal component analysis (PCA) plot with all identified proteins in the samples. (B) Box plot charts of the significant proteins for discrimination of the clinical groups
CIN: Cervical intraepithelial neoplasia

objectives and limitations, suggests a promising direction for future research in identifying reliable biomarkers for cervical neoplasia.

Before concluding, it is imperative to discuss the external validity of our findings. The study's results, while promising, are derived from a specific cohort, and their generalizability to broader population warrants careful consideration. The inherent variability of CVF (29,30) and the methodological differences across studies pose challenges in applying these findings universally. Nonetheless, the identified proteins provide a valuable foundation for further investigation into their roles in cervical neoplasia.

CONCLUSION

In summary, our study identified key proteins that significantly differ across various stages of cervical neoplasia, offering insights into the disease's molecular landscape. These findings highlight the potential of CVF proteomics in advancing the diagnosis and understanding of gynecological diseases. However, to confirm these findings and fully understand their implications, further randomized controlled trials are necessary.

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Ethics

Ethics Committee Approval: The study received approval from the Acıbadem Mehmet Ali Aydınlar University Medical Research Evaluation Board (ATADEK) (approval number: 2020-01/30, date: 09.01.2020).

Informed Consent: Informed written consent was obtained from all participants.

Authorship Contributions

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

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ORIGINAL ARTICLE

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Evaluating the Outcomes of Simultaneous Lung Resection and Cardiac Surgery: A Retrospective Cohort Study

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Abstract

Objective: The management of patients requiring both cardiac and pulmonary surgeries presents a unique challenge, given the rarity of coexisting conditions necessitating simultaneous interventions. This study aimed to evaluate the surgical outcomes of performing lung resection and cardiac surgery in a single operative session. The primary objective of this study was to assess the early and midterm outcomes of a combined surgical strategy for treating coexistent heart and lung diseases. Specifically, it seeks to understand the feasibility, safety, and efficacy of simultaneous operations compared with traditional staged approaches.

Methods: This retrospective analysis included 25 patients who underwent concurrent thoracic and cardiac surgery between 2012 and 2021. We examined the types of cardiac and pulmonary surgeries performed, the necessity of additional thoracotomy beyond median sternotomy, early postoperative outcomes, including operative mortality, the incidence of re-exploration due to complications, and pulmonary complications. Long-term outcomes were evaluated through direct outpatient visits or telephonic interviews.

Results: The average age was 62.6±9.4 years, with six females among the participants. Median sternotomy was the primary surgical approach for all patients, with one case requiring additional thoracotomy. Surgical interventions included 13 isolated coronary artery bypass grafting (CABG) procedures, 5 valve surgeries, 6 combined CABG and valve surgeries, and 1 Bentall procedure. Pulmonary interventions included 15 wedge resections and 10 lobectomies with lymph node dissection. There were no cases of operative mortality. Re-exploration was necessary in one patient because of bleeding ($p>0.05$). Post-extubation hypoxemia was not observed, and pulmonary complications occurred in two patients ($p>0.05$).

Conclusion: Simultaneous execution of thoracic and cardiac surgeries is feasible, demonstrating low rates of postoperative mortality and complications, thereby offering a viable alternative for patients with coexisting cardiac and pulmonary conditions. This study underscores the potential benefits of a simultaneous surgical approach in selected patients, suggesting that with appropriate preoperative planning and surgical expertise, combined operations can be safely conducted, minimizing the need for multiple hospitalizations and surgeries.

Keywords: Cardiac surgical procedures, pulmonary surgical procedures, wedge resection

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INTRODUCTION

Coexisting cardiac and pulmonary conditions that require surgical intervention are uncommon, yet they present significant clinical challenges (1). Incidental findings of lung masses during computed tomography (CT) scans for preoperative cardiac surgery evaluation are not unusual (2). The dual presence complicates surgical management because of the absence of a universally accepted protocol for simultaneously addressing both conditions (3). Historically, the preference was for a staged surgical approach, conducting cardiac surgery first and delaying pulmonary surgery by several weeks (4). However, emerging evidence, supported by findings from our research, suggests a shift toward simultaneous cardiac and pulmonary surgeries as a viable option, demonstrating promising surgical results (5-8).

The rationale behind this study stems from the complexity and intricacy of managing patients with concurrent cardiac and pulmonary surgical needs. Although the staged approach has its merits, it also prolongs the patient's recovery time and exposes them to the risks associated with multiple operations. The potential benefits of simultaneous surgery include reduced overall hospital stay, cost savings, and possibly a quicker return to normal activities for the patient. Despite these advantages, the decision to adopt a one-stage procedure must be carefully weighed against the increased complexity of performing two major surgeries simultaneously. The literature provides limited guidance on this matter, with studies offering varying outcomes and recommendations. This ambiguity underscores the necessity for further research to establish clearer guidelines and to explore the potential advantages of a one-stage surgical approach in this patient population. In addition, the evolution of surgical techniques and postoperative care has enabled more complex surgical procedures to be performed with improved safety profiles, suggesting that simultaneous surgeries could be more feasible than previously thought.

Therefore, this study was designed to evaluate the early and midterm outcomes of patients undergoing combined pulmonary resection and cardiac surgery at our specialized thoracic and cardiovascular surgery center. Our aim was to contribute to the body of evidence supporting the feasibility and safety of this approach, potentially offering a new perspective on optimal patient management. By comparing our results with those available in the literature, we sought to identify areas of convergence and divergence, thus providing insights into the relative benefits and challenges of simultaneous surgeries. The hypothesis of this study was that simultaneous pulmonary resection and cardiac surgery could achieve comparable, if not superior, outcomes to the traditional staged approach, thereby offering an effective alternative for patients with coexisting conditions.

METHODS

Study Setup and Data Collection

The scope of this study included patients who underwent simultaneous pulmonary resection and cardiac surgery at our institution from 2012 to 2021. The exclusion criteria were patients under 18 years of age and those who underwent emergency surgery. Preoperative demographic, echocardiographic, and laboratory data were systematically collected. Operation notes detailed the cardiac procedure type, use of cardiopulmonary bypass (CPB), durations of CPB and aortic cross-clamp, specifics of the pulmonary resection type, and need for thoracotomy alongside median sternotomy. Postoperative data encompassed operative mortality, cases requiring re-exploration because of bleeding or cardiac tamponade, pulmonary complications, and lengths of stays in the intensive care unit and hospital. Preoperative, operative, and postoperative outcomes were evaluated in two groups: patients undergoing wedge resection only and those undergoing lobectomy with lymph node dissection.

Definitions

Operative mortality was defined as death occurring either before discharge or within 30 days after surgery. Pulmonary complications included hypoxemia, air leakage necessitating drainage tubes for more than 3 days, pneumothorax, persistent pulmonary infiltrates on chest X-ray, pulmonary thromboembolism, pneumonia, reintubation, and tracheostomy.

Surgical Preparation and Technique

Pulmonary function tests and chest X-ray imaging were routinely performed before each cardiac surgery. All cardiac surgery patients were assessed by a pulmonologist during the preoperative period. Following the pulmonologist's recommendations, individuals with known lung masses or abnormalities on chest X-ray underwent further evaluation using tomography. In the context of concurrent pulmonary resection and cardiac surgery, procedures were performed with a low incidence of postoperative mortality and complications. The surgical approach for patients was determined collectively by a multidisciplinary team consisting of cardiovascular surgeons, thoracic surgeons, cardiologists, pulmonologist and radiologists. Conventional coronary angiography and transthoracic echocardiography were performed on all patients. The fine

needle aspiration procedure (FNAP) was not routinely performed preoperatively. Whole-body positron emission tomography/CT was used to evaluate preoperative cancer spread in cases focused on lung masses, while omitted for surgeries related to bullous lung disease. For off-pump surgeries, 80 U/kg heparin was administered, whereas on-pump surgeries received 400 U/kg heparin. CPB initiation was reserved for on-pump surgeries. Cold blood cardioplegia was employed in surgeries with arrested hearts. Following the completion of cardiac surgery, protamine was administered to counteract heparin. The choice between wedge resection or lobectomy, along with lymph node dissection, was made according to the pre-established surgical plan post-cardiac surgery. Direct lobectomy and lymph node dissection were performed in patients with a preoperative diagnosis of pulmonary malignancy using FNAP. In cases without a preoperative FNAP diagnosis, a frozen section in the form of wedge resection was obtained for mass lesions. If the frozen section revealed malignancy, the procedure was expanded to include lobectomy and lymph node dissection. All removed pulmonary masses were subjected to pathological examination.

Postoperative Follow-up

The patients were transferred to the intensive care unit (ICU) with mechanical ventilator support. The invasive arterial pressure and central venous pressure were monitored. After extubation, the patients were mobilized. Arterial catheters were removed, and patients with stable hemodynamics were transferred to the cardiovascular service. Long-term treatment plans were developed on the basis of the pathology results. Patient follow-up was conducted long term either through in-person outpatient visits or telephone interviews.

This study was conducted in compliance with the Declaration of Helsinki. In this retrospective observational cohort study, patient data were collected following approval (approval number: 2022.02-13, date: 22.02.2022) from the İstanbul Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Training and Research Hospital Clinical Research Ethics Committee. A written informed consent was obtained from each patient.

Statistical Analysis

Statistical analyses were performed using R version 4.0.3 (R Foundation for Statistical Computing). The distributions of continuous variables were assessed using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Non-normally distributed continuous data were presented as medians and interquartile ranges and compared using the Mann-Whitney U test. Categorical data were presented as the number of patients with ratios and compared using Fisher's exact test. A p-value <0.05 was considered statistically significant.

RESULTS

The average age of the study participants was 62.6 years, with a standard deviation of 9.4 years. Of these, six participants (24%) were female. A total of nine patients (36%) had been diagnosed with diabetes mellitus, all of whom were on insulin or oral antidiabetic drugs. Most cohort, 21 individuals (84%), reported a history of smoking, whereas only four (16%) reported never having smoked. Chronic renal failure was not reported in any participant's history. The median value for preoperative serum creatinine was recorded at 0.89 mg/dL, with an interquartile range of 0.73-0.96 mg/dL. Comprehensive preoperative demographic and clinical details are provided in Table 1.

Table 1. Comparison of preoperative demographic and clinical data

	All patients (n=25)	Only wedge resection (n=15)	Lobectomy and lymph node dissection (n=10)	p-value*
Age (years)	65 (54-72)	65 (54-72)	64 (54-67)	0.70
Male	76	73	80	1.00
Hypertension	76	80	70	0.65
NYHA stage 3-4	20	33	0	-
Diabetes mellitus	36	27	50	0.40
COPD	32	33	30	1.00
Smoker	84	80	90	0.63
Serum creatinine (mg/dL)	0.89 (0.73-0.96)	0.89 (0.83-0.93)	0.85 (0.73-0.96)	0.89
Ejection fraction (%)	50 (35-60)	50 (35-55)	55 (45-60)	0.38

Data are given as percentage or median (interquartile range) as appropriate.
COPD: Chronic obstructive pulmonary disease, NYHA: New York Heart Association
*Comparison of wedge resection, lobectomy, and lymph node dissection

Operative Details

Median sternotomy was used for all surgical procedures, with an additional thoracotomy required for one patient because of a malignant mass in the left lower lobe of the lung. Surgical procedures varied among the patients; isolated coronary artery bypass grafting (CABG) was performed on 13 patients, two of whom employed the beating heart technique. Isolated aortic valve replacements were performed in three patients, whereas single instances of mitral valve replacement, tricuspid valve repair, combined aortic and mitral valve replacement, and the Bentall procedure were performed. Six patients underwent combined CABG and valve surgeries. The median times for CPB and aortic cross-clamp were 95 and 53 min, respectively.

Isolated wedge resections were performed on 15 patients, with six of these proceeding to lobectomy based on the frozen section results. Lobectomy and lymph node dissection were performed in 10 patients (40%) following heart surgery, predominantly in the right upper lobe, as observed in nine patients (36%). The operative details are summarized in Table 2.

Operative mortality was not reported in the cohort. Re-exploration because of hemorrhagic complications was necessary for only one patient (4%), and none experienced cardiac tamponade. Post-extubation, hypoxemia was not observed in any patient, eliminating the need for non-invasive mechanical ventilation or reintubation.

Pulmonary complications were noted in two patients (8%), with pneumonic infiltration detected on X-ray within four days post-surgery, leading to the initiation of antibiotic treatment, which resolved the condition within five days. In these cases, *Klebsiella pneumoniae* was identified in sputum cultures before antibiotic administration. One patient experienced persistent air leakage, which resolved spontaneously within eight days post-operation without the need for further invasive procedures. No significant statistical differences were noted in intubation duration, ICU stay length, and total hospital stay between patients undergoing wedge resection only and those receiving lobectomy with lymph node dissection ($p>0.05$). The postoperative outcomes are detailed in Table 3.

Pathological examinations revealed non-small-cell lung cancer in nine patients, including adenocarcinoma in four, squamous cell carcinoma in two, large cell carcinoma in one, atypical carcinoid in one, and undifferentiated round cell carcinoma in another. One patient was diagnosed with small cell lung cancer. In addition, benign lung tumors were diagnosed in 12 patients, including six hamartomas, three adenomas, and three papillomas. Pathology reports for three patients operated on for high-risk bullous lung disease showed emphysematous changes.

Table 2. Comparison of operational data

	All patients (n=25)	Only wedge resection (n=15)	Lobectomy and lymph node dissection (n=10)	p-value*
Cardiac surgery data				
On pump CABG	44	40	50	0.70
Off-pump CABG	8	7	10	1.00
Aortic valve surgery	12	13	10	1.00
Mitral and tricuspid valve surgeries	4	7	0	-
Aortic and mitral valve surgery	4	7	0	-
Combined CABG and valve surgery	24	20	30	0.65
Bentall procedure	4	7	0	-
CPB time (min)	95 (63-137)	95 (83-132)	91 (77-138)	0.82
ACC time (min)	53 (36-94)	52 (35-92)	56 (40-95)	0.89
Pulmonary surgery data				
Right upper lobe	36	33	40	1.00
Right middle lobe	4	7	0	-
Right lower lobe	28	27	30	1.00
Left upper lobe	28	33	20	0.70
Left lower lobe	4	0	10	-

Data are given as percent or median (interquartile range) as appropriate. ACC: Aortic cross clamp, CABG: Coronary artery bypass grafting, CPB: Cardiopulmonary bypass, min: Minutes

*Comparison of only wedge resection, lobectomy, and lymph node dissection

Table 3. Comparison of postoperative data				
	All patients (n=25)	**Only wedge resection (n=15)**	**Lobectomy and lymph node dissection (n=10)**	**p-value***
Need for re-exploration	4	0	10	-
Pulmonary complications	8	7	10	1.00
Intubation time (hours)	19 (12-39)	13 (12-30)	19 (13-43)	0.33
ICU stay (hours)	37 (25-78)	27 (24-61)	37 (27-86)	0.27
Hospital stay (days)	7 (5-12)	6 (5-10)	7 (5-13)	0.31
Data are given as percentage or median (interquartile range) as appropriate. ICU: Intensive care unit *Comparison of only wedge resection, lobectomy, and lymph node dissection				

Long-term follow-up ranged from 1 to 9 years, during which nine patients died; three from lung cancer and six from cardiac causes. No reoperations for cardiac or thoracic conditions were reported. Among those who died of lung cancer, recurrence and metastasis were identified, with all three succumbing to the disease within one year of recurrence diagnosis. Coronary angiography was performed in two patients with recurrent chest pain, although no coronary stents were placed. Permanent pacemakers were implanted in two patients who had undergone combined CABG and valve surgery.

DISCUSSION

Chest X-ray is instrumental in the preoperative assessment of cardiac surgeries, often leading to additional imaging to closely examine areas of concern. Occasionally, these evaluations reveal unexpected pathologies that necessitate pulmonary resection; however, a standardized surgical approach for such scenarios remains undefined (3). The literature describes two principal strategies: a staged approach in which lung surgery follows cardiac surgery according to the original plan (4,9) and a simultaneous procedure that combines pulmonary resection and cardiac surgery (5-8,10). The choice between a staged and simultaneous approach lacks direction from prospective studies. Simultaneous operations provide the benefits of prompt lung cancer resection, decreased overall costs, and reduced length of hospital stays but introduce challenges such as managing two critical organs at once, increased risk of postoperative bleeding, and the intricacies involved in extensive lymph node dissection (11-13). Extra incisions alongside median sternotomy increase surgical risks (14). In our practice, the simultaneous approach has been the standard for the last decade, primarily through median sternotomy to diminish surgical risks. Among 24 patients treated, only one required an additional thoracotomy for extensive lymph node dissection.

Despite the majority of cardiac surgeries being performed on-pump (92%), the need for re-exploration due to bleeding was rare, occurring in just one patient, and pulmonary complications were observed in only two patients during the initial postoperative phase. While off-pump CABG is linked to fewer bleeding and pulmonary complications, our outcomes indicate that on-pump procedures can be safely integrated into simultaneous operations (15-17). Preferring to complete cardiac surgery before pulmonary resection typically reduces cardiac-related risks during concurrent surgeries (1). We believe that addressing the cardiac condition first not only decreases the potential for cardiac issues during combined surgeries but also paves the way for a smoother recovery. Moreover, starting with pulmonary surgery could result in increased bleeding and edema at the lung incision sites because of the administration of heparin during cardiac procedures. For these reasons, lung surgeries were conducted after cardiac interventions in all cases.

A comprehensive meta-analysis of 29 retrospective observational studies encompassing 536 patients revealed an operative mortality rate of 0.01 and a postoperative complication rate of 0.40 for individuals undergoing combined cardiothoracic surgeries (18). Our study's initial postoperative results are consistent with these findings, demonstrating that combined pulmonary resection and cardiac surgeries can be performed with a relatively minimal surgical risk. Pathology outcomes from our cohort revealed malignancies in 10 patients. Not pursuing simultaneous surgeries might delay scheduling lung operations due to the need for antiplatelet or anticoagulant therapy and extended recuperation after cardiac procedures, potentially worsening malignant growths. Despite the need for longer anesthesia times during combined surgeries, these can be performed with low rates of postoperative mortality and complications.

In summary, our findings suggest that simultaneous pulmonary resection and cardiac surgery are feasible with low rates of postoperative mortality and complications.

Study Limitations

This investigation is not without its limitations, including a small cohort size, the inclusion of varied surgical pathologies, and differences in surgical approaches, especially regarding on-pump versus off-pump CABG.

CONCLUSION

In conclusion, our study demonstrates that simultaneous pulmonary resection and cardiac surgery can be performed with minimal postoperative mortality and complication rates. To validate these results, further randomized controlled trials are necessary.

Ethics

Ethics Committee Approval: In this retrospective observational cohort study, patient data were collected following approval (approval number: 2022.02-13, date: 22.02.2022) from the İstanbul Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Training and Research Hospital Clinical Research Ethics Committee.

Informed Consent: A written informed consent was obtained from each patient.

Authorship Contributions

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

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A Single-center Study Comparing Volumetric and Morphometric Measurements of Chiari Malformation in the Turkish Population

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Abstract

Objective: This study aimed to determine the values of volumetric and morphological parameters in Chiari malformation type 1 (CM1) patients in the Turkish population.

Methods: This retrospective study was conducted at a single center and included patients diagnosed with CM1 between 2013 and 2023. The patients were separated into two groups: the group CM1 and the control group comprising healthy individuals (group control). The morphometric measurements were clivus length, supraocciput length, foramen magnum diameters, distance between the midbrain-pons junction and midbrain-medullospinal junction, cerebellar hemisphere height, tentorium angle, clivus angle, clivus-tentorium angle, posterior fossa volume (PFV), and cerebellar tonsillar morphology.

Results: The cerebellar tonsillar herniation was 11.43±2.09 mm in group CM1 and -2.64±2.37 mm in the control group. The mean clivus and supraocciput length were 34.26±4.76 mm and 41.26±4.33 mm in group CM1 and 36.85±3.23 mm and 42.21±2.86 mm in the control group, respectively. The mean foramen magnum diameters were 31.41±3.28 mm in group CM1 and 35.64±2.32 mm in the control group ($p<0.05$). The mean PFV was 153.91±5.02 mL in group CM1 and 180.70±11.62 mL in the control group ($p<0.05$).

Conclusion: Two parameters were statistically significantly decreased in CM1 patients (PFV and foramen magnum diameters), indicating the main morphometric change that guides diagnosis and treatment in CM1 patients. All other parameters examined in this study were deemed unnecessary because there was no significant difference between CM1 and the average population.

Keywords: Chiari malformation, morphometric, volumetric, Turkish population

INTRODUCTION

Chiari malformation type 1 (CM1) is a congenital disorder described by Chiari (1) in the late 19th century that can disrupt the circulation of cerebrospinal fluid (CSF) at the level of the foramen magnum by displacing the cerebellar tonsils from the foramen magnum into the spinal canal.

The exact reason for the caudal location of the cerebellar tonsils remains unknown; however, a smaller posterior fossa than usual and geometric mismatches relative to the healthy population are believed to contribute. Despite the uncertain etiology, the migration of cerebellar tonsils into the spinal canal in CM1 results in compression of the tracts at this level, disrupting CSF circulation and leading to neurological symptoms and complications. Several theories have been developed in the literature, including caudal traction theory, hydrodynamic theory, overgrowth theory, small posterior fossa theory, dysraphic theory, and developmental arrest theory. These theories explain various phenomena and have been extensively studied in academic research. It is important to consider each theory impartially and objectively before drawing conclusions (2).

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Studies analyzing radiological measurements of anatomical variances in these patients relative to the healthy population are still inadequate (3). Magnetic resonance imaging (MRI) examinations in current radiological analyses of the posterior cranial fossa (PCF) offer highly detailed anatomical data (4). MRI is an exceptional radiological diagnostic instrument for visualizing the craniovertebral junction and describing associated pathologies of the cerebellum, brainstem, and spinal cord (5).

Many parameters are used for radiological measurements in CM1 (6). These radiographic measurement parameters include clivus length, supraoccipital length, foramen magnum diameter, distance between the midbrain-pons junction and midbrain-medullospinal junction, height of the cerebellar hemisphere, tentorium angle, clivus angle, clivus-tentorium angle, volume of posterior fossa, cerebellar tonsillar morphology (pegged, intermediate, rounded), and other parameters related to the posterior fossa and craniovertebral junction (7,8). This study aimed to determine the values of volumetric and morphological parameters in CM1 patients in the Turkish population. This single-center, retrospective, observational study comprehensively included and compared different anatomical parameters that were previously considered significant (3-8). The statistical significance of the data obtained for the parameters studied helps to reveal important anatomical features in the pathophysiology of CM1. These clinical studies may advance decision making for CM1 by improving our understanding of its pathophysiology.

METHODS

Study Design

This retrospective study was conducted at a single center and included individuals diagnosed with CM1 and cerebellar tonsillar ectopia of at least 5 mm on cranial MRI between 2013 and 2023, as well as healthy individuals without neurological pathology on cranial MRI. Cranial and cervical MRI exams conducted during the last preoperative period standardized the examination protocol for neurosurgical patients with CM1. Inclusion and exclusion criteria limited the study to individuals 18 years or older, without consideration for gender differences. All cases of CM1 were included in the study, irrespective of the presence of a syrinx. Patients with syrinx in the control group, including healthy individuals, were excluded from the study. Informed consent of the patients was obtained from all cases. Morphometric measurements were conducted using MRI examinations of the craniovertebral junction on subjects separated into two groups: the group CM1 and the control group comprising healthy individuals (group C) (see Table 1 and Table 2). Morphometric measurements compared among the groups were restricted to clivus length, supraocciput length,

Table 1. Descriptive analysis of group CM1 and group control

	Group CM1	Group control
NoC	78	75
Gender (F/M)	49/29	45/30
Age	36.8±11.3	37.8±11.6
Mean tonsillar herniation (mm)	11.43±2.09	-2.64±2.37
Tonsillar morphology		
Pegged	22/78 (28%)	
Intermediate	43/78 (55%)	
Rounded	13/78 (17%)	
Syringomyelia	26/78 (33%)	
Myelomalacia	7/78 (9%)	
Platybasia	1/78 (1%)	
4th ventricule enlargement	1/78 (1%)	

CM1: Chiari malformation type 1, NoC: Number of cases, F/M: Female/Male, mm: Millimeters

Table 2. Comparison of the radiological measurements of the two groups

Parameters	Group CM1	Group control	p-value
Mean length of the clivus	34.26±4.76	36.85±3.23	>0.05
Mean length of the supraocciput	41.26±4.33	42.21±2.86	>0.05
Mean foramen magnum diameters	31.41±3.28	35.64±2.32	<0.05
Mean distance between the midbrain-pons junction and midbrain-medullospinal junction	48.01±3.14	45.08±3.02	>0.05
Mean cerebellar hemisphere height	52.96±4.03	54.11±2.24	>0.05
Mean angle of the tentorium	89.21°±8.79	92.85°±6.83	>0.05
Mean angle of the clivus	121.55°±7.13	122.21°±8.76	>0.05
Mean clivus-tentorium angle	8.1°±4.49	8.2°±3.95	>0.05
Mean posterior fossa volume	153.91±5.02	180.70±11.6	<0.05

CM1: Chiari malformation type 1

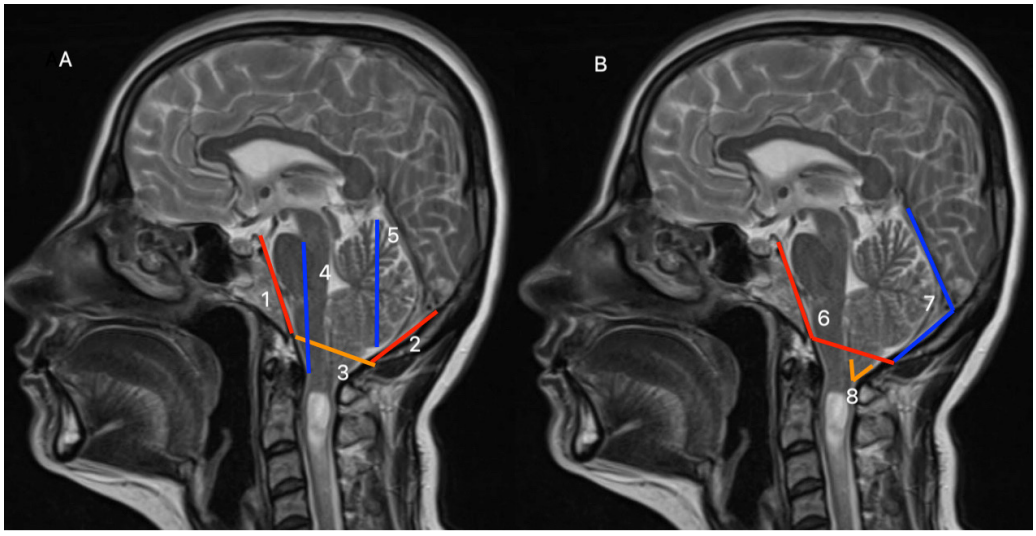

Figure 1. Morphometric analyses in T1-weighted sagittal magnetic resonance imaging of a Chiari malformation-type 1 diagnosed patient. A: 1; Length of clivus, 2; Length of supraocciput, 3; Foramen magnum diameters, 4; Distance between midbrain-pons junction and midbrain-medullospinal junction, 5; Cerebellar hemisphere height, B: 6; Angle of clivus, 7; Angle of tentorium, 8; Tonsillar morphology

foramen magnum diameters, distance between the midbrain-pons junction and midbrain-medullospinal junction, cerebellar hemisphere height, tentorium angle, clivus angle, clivus-tentorium angle, posterior fossa volume (PFV), and cerebellar tonsillar morphology (pegged, intermediate, rounded) (3) (see Figure 1 and Figure 2).

MRI Analysis and Measurement Techniques

MRI was conducted at a single institution using a 1.5-Tesla system (Magnetom Avanto, Siemens Medical Systems, Erlangen, Germany). The imaging comprised sagittal T1 and T2, coronal T2, axial T1, T2, and fluid-attenuated inversion recovery sequences. Examination was performed using sagittal T1-weighted images. Parameters for sagittal T1 sequences were as follows: TR/TE: 346/13, FOV: 270, slice thickness 5 mm, matrix 320x60.

Volumetric Measurements

The contours of the posterior fossa were manually delineated on each sagittal T1-weighted image by a single radiologist, and the volume was calculated using ExtremePACS software tools (Ekstrem Bir Bilgisayar, Ankara, Turkey) by summation of each voxel in the selected region of interest.

Clivus Length

The length of the clivus is the length of the line from the apex of the dorsum sella to the basion (Figure 1). Anatomical reference point: the apex of the dorsum sella and the basion (3).

Supraocciput Length

The measurement of supraocciput length describes the distance between the center of the internal occipital protuberance and the opisthion (Figure 1). The anatomical reference points are from the internal occipital protuberance to the opisthion (3).

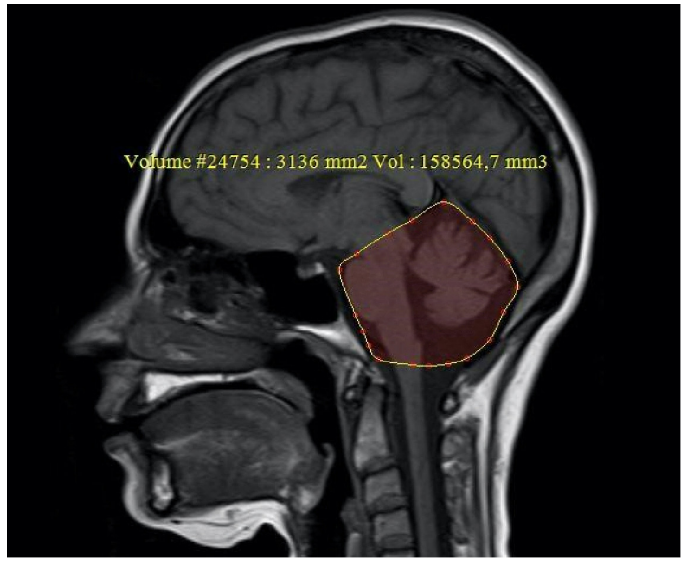

Figure 2. Volumetric measurement using the manual delineation method by ExtremePACS software tools

Diameter of the Foramen Magnum

The length of the line between the basion and the opisthion determines the diameter of the foramen magnum (Figure 1). Basion and opisthion serve as anatomical reference points (3).

Distance Between the Midbrain Pons and Medullospinal Junctions

This measurement denotes the length of the line between the junction of the midbrain (mesencephalon) and pons and the junction of medullospinal (Figure 1). The anatomical reference

points are the midbrain to pons junction and the medullospinal junction (4).

Cerebellar Hemisphere Height

The length of the line descending from the closest point of the cerebellum to the splenium of the corpus callosum to the closest point to the opisthion in the plane of the foramen magnum is defined as the height of the cerebellar hemisphere (Figure 1). Anatomical reference point: the point closest to the splenium of the corpus callosum and the opisthion in the plane of the foramen magnum of the cerebellum (4).

Tentorium Angle

The tentorium angle refers to the angle formed by the line between the tentorium and the internal occipital protuberance and opisthion (Figure 1). This anatomical reference point is formed by the line between the tentorium, internal occipital protuberance, and opisthion (5).

Clivus Angle

The clivus angle is the angle of the clivus relative to the plane of the foramen magnum (Figure 1). Anatomical reference point: the angle at which the clivus line intersects the plane of the foramen magnum (6).

Clivus-Tentorium Angle

This measurement refers to the angle between the clivus and tentorium (Figure 1). Anatomical reference point: the point where the clivus and tentorium lines meet.

Posterior Fossa Volume

The PFV refers to the total volume of the space between the tentorium, dorsum sella, basion, opisthion, and internal occipital protuberance (Figure 2). Anatomical reference point: tentorium, dorsum sella, basion, opisthion, and internal occipital protuberance.

Cerebellar Tonsillar Morphology

This assessment refers to the shape of the cerebellar tonsils descending from the foramen magnum (Figure 1). "Pegged" means pointed. "Intermediate" means moderately prominent. "Rounded" means rounded. Anatomical reference point: cerebellar tonsils and foramen magnum (8).

Inclusion Criteria

- All adults over 18 years of age
- Without discrimination of the male or female gender
- I have MRI scans of the brain
- Patients with CM1 or no other neurological pathology

Exclusion Criteria

- Patients with a history of surgery for neurologic pathology
- Patients diagnosed with any neurological pathology other than CM1

Statistical Analysis

SPSS 15.0 for Windows was used for statistical analysis. Descriptive statistics were reported as number and percentage for categorical variables and mean, standard deviation, minimum, and maximum for numerical variables. Two independent group comparisons of numerical variables were made using Student's t-test when the normal distribution condition was met and Mann-Whitney U test when it was not. Independent group comparisons of numerical variables were performed with one-way ANOVA when the numerical variables met the normal distribution condition in the groups and with Kruskal-Wallis test when they did not. Subgroup analyses were performed using the Mann-Whitney U test, a nonparametric test, and interpreted with Bonferroni correction. The relationships between numerical variables were analyzed with Pearson correlation analysis when the parametric test condition was met and with Spearman correlation analysis when the condition was not met. Alpha level was set as $p<0.05$ for statistical significance.

In this study, the investigators obtained the necessary approval from the İstanbul Prof. Dr. Cemil Taşcıoğlu City Hospital Clinical Research Ethics Committee (approval number: E-48670771-514.99-208874893, date: 08.02.2023), and the study was conducted in accordance with the Declaration of Helsinki. The article was written in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.

RESULTS

One hundred and forty-three participants (94 females, 59 males) had a mean age of 36.3±9.2 years (min: 18, max: 64) (Table 1).

Group control: the study comprised 75 patients, including 45 females and 30 males, aged between 21 and 56 years with a mean age of 37.8±11.6 years. The mean tonsillar herniation was -2.64±2.37 mm, ranging between -7 and 2 mm (Table 1).

Group CM1: comprised 78 patients, including 49 females and 29 males, aged between 18 and 63 years with a mean age of 36.8±11.3 years. The mean tonsillar herniation was 11.43 mm ±2.09 ranging between 9-16 mm. The classification of cerebellar tonsils was pegged in 22 cases, intermediate in 43 cases, and rounded in 13 cases. Apart from tonsillar herniation,

syringomyelia was present in 26 patients, focal myelomalacia in 7 patients, platybasia in 1 patient, and fourth ventricular enlargement in 1 patient (Table 1).

The mean clivus and supraocciput length were found to be 34.26±4.76 mm and 41.26±4.33 mm in group CM1 and 36.85±3.23 mm and 42.21±2.86 mm in the control group, respectively. No significant differences were observed in both parameters with $p>0.05$. Additionally, the mean foramen magnum diameters were measured to be 31.41±3.28 mm in group CM1 and 35.64±2.32 mm in group control, with a significant decrease observed in group CM1 ($p<0.05$). The average distance between the midbrain pons and medullospinal junction in the control group was 45.08±3.02 mm, and in group CM1 was 48.01±3.14 mm ($p>0.05$).

The median height of the cerebellar hemisphere was 54.11±2.24 mm in the control group and 52.96±4.03 mm in group CM1 ($p>0.05$).

The average tentorium, clivus, and clivus-tentorium angles were 92.85°±6.83, 122.21°±8.76, and 8.2°±3.95 degrees, respectively, in the control group and 89.21°±8.79, 121.55°±7.13, and 8.1°±4.49 degrees, respectively, in group CM1 ($p>0.05$ in all three parameters).

The mean PFV was 153.91±5.02 mL in group CM1 and 180.70±11.62 mL in group control ($p<0.05$). Statistical analysis indicated that the mean PFV significantly decreased in the CM1 group. Other parameters did not exhibit significant differences between the two groups, except for the mean PFV and foramen magnum diameters (Table 2).

DISCUSSION

Many parameters are used for radiological measurements in individuals with CM1. However, it is still not fully understood which of these radiological parameters holds more significance. Comparing the radiological measurements with those of a healthy population may prove crucial in determining significant differences, ultimately leading to a better understanding of the pathophysiology of the disease. In this study, we measured and compared various parameters in the posterior fossa and craniovertebral junction of individuals with CM1 and a healthy control group.

CM1 is a congenital malformation characterized by placement of the cerebellar tonsils below the foramen magnum (9). Because clinical progression occurs over time, the disease is not solely a congenital malformation but a dynamic process. Therefore, radiological follow-up is performed in addition to clinical follow-up and evaluation of CM1. MRI is the standard radiological examination used for CM1 because of its ability to clearly display the anatomy at the craniocervical junction. Meadows et al. (10) highlighted the dynamic nature of CM1 and the need for static examinations, such as morphometric measurements obtained through MRI, to fully comprehend this condition. Some measurements obtained on MRI for the posterior fossa and craniocervical junction are important in evaluating the clinical diagnosis, follow-up, and treatment outcome of CM1 (11). These measurements are linked to a reduction in PFV and an augmentation in cerebellar volume. Vurdem et al. (12) used stereological methods to measure posterior fossa and cerebellar volumes and emphasized the potential of these measurements in the evaluation of CM1 cases. Morphometric measurements of CM1 using MRI remain an interesting field of study that warrants further exploration. Notably, Urbizu et al. (13) undertook a morphometric analysis using MRI to examine the oropharynx and oral cavity in CM1 patients, explicitly highlighting the significance of morphometric evaluations in comprehending the anatomical disparities associated with this condition. In their study of surgically treated CM1 cases, Marianayagam et al. (14) analyzed pre- and postoperative morphometric features to evaluate clinical outcomes and emphasized the significance of morphometric measurements in CM1 management.

Thus, volumetric and morphometric measurements constitute a crucial component of the comprehensive evaluation, classification, and management of CM1. These measurements provide important insights into the pathophysiology, clinical outcomes, and dynamic nature of CM1, thus guiding clinical decision-making and treatment strategies.

The study compared various parameters between groups concerning the craniovertebral junction and posterior fossa, including clivus length, supraocciput length, foramen magnum diameters, distance between the midbrain-pons junction and midbrain-medullospinal junction, cerebellar hemisphere height, tentorium angle, clivus angle, clivus-tentorium angle, PFV, and cerebellar tonsillar morphology. It was noted that the PFV and foramen magnum diameter were smaller in the CM1 group than in the control group, exhibiting statistically significant differences among these parameters.

Nishikawa et al. (15) conducted a morphometric study indicating a potential relationship between the overcrowding of the PCF in patients with adult Chiari malformation and their PFV. Roller et al. (16) conducted a study that showed a significant decrease in PFV and posterior fossa linear dimensions in symptomatic pediatric and adult patients with CM1 compared with control subjects.

This finding supports the relationship between Chiari malformation and PFV. Hage et al. (17) presented further evidence on the significance of PFV in the pathogenesis of Chiari malformations, highlighting the correlation between volume reduction in the PCF and CM1. In contrast, Halvorson et al. (18) discovered no variation in PFV between the groups. Given the inconsistent results, further investigation is warranted. In this study, the mean PFV was significantly smaller in the CM1 group than in the control group.

Additionally, the research implies that the foramen magnum diameter in CM1 cases is significantly smaller than that in the control group. While there is no definitive evidence in the literature that indicates a significant variation in the diameter of the foramen magnum between CM1 patients and the healthy population, Furtado et al. (19) highlighted the irregular shape of the foramen magnum in Chiari malformation and demonstrated the potential role of foramen magnum dimensions in the pathophysiology of CM1. Sarvaiya et al. (20) conducted a morphometric analysis of the dimensions of the foramen magnum to comprehend the anatomical variations linked to Chiari malformations. These observations highlight the importance of the foramen magnum diameter in the context of Chiari malformations.

Consistent with the literature, this study demonstrates a substantial connection between reduced PFV and Chiari malformations, suggesting that the role of foramen magnum dimensions is a topic of ongoing investigation and discussion. Additional research is necessary to elucidate the exact morphometric characteristics that contribute to the development of CM1.

Previous studies have used different radiological parameters for morphometric and volumetric examinations of the posterior fossa in CM1 cases, as discussed above. However, this study comprehensively designed the study method and examined multiple radiological parameters together, resulting in findings consistent with those reported in the literature. The study concludes that in cases of CM1, the PFV and the diameter of the foramen magnum are reduced, whereas other radiographic parameters do not show statistical significance. Radiological measurements, especially volumetric measurements, are difficult to obtain and are unlikely to be used in the diagnostic phase. However, they seem to be used to make treatment decisions before surgery and to evaluate treatment effectiveness after surgery. The standard surgical approach for CM1 involves posterior fossa decompression and extensive duraplasty. However, there is currently much discussion in neurosurgery about craniovertebral junction stabilization and fusion surgeries. This study emphasizes the importance of PFV in the pathophysiology of CM1 and suggests that posterior fossa decompression is the main component of CM1 treatment.

Study Limitations

Although the study relied on prolonged case follow-up, its single-center design can be seen as a limitation.

To enhance generalizability, larger population cohorts with long-term follow-up should be incorporated into multicenter studies.

CONCLUSION

This morphologic study aimed to rule out unnecessary volumetric measurements in the preoperative planning of CM1 patients. Only two parameters were statistically significantly decreased in CM1 patients (PFV and foramen magnum diameters) and may help us identify actual CM1 patients during outpatient clinics. In contrast, measuring these two parameters may help the surgeon during the preoperative planning period. However, all other parameters examined in this study were found to be unnecessary because there were no significant differences between CM1 and the average population. Because these measurements are generally time-consuming and require trained personnel, unnecessary parameters may be negligible.

Ethics

Ethics Committee Approval: In this study, the investigators obtained the necessary approval from the İstanbul Prof. Dr. Cemil Taşcıoğlu City Hospital Clinical Research Ethics Committee (approval number: E-48670771-514.99-208874893, date: 08.02.2023), and the study was conducted in accordance with the Declaration of Helsinki.

Informed Consent: Consent was received from the patients who participated in this study.

Authorship Contributions

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

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

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ORIGINAL ARTICLE

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Predicting Postoperative Complications and Mortality in Total Joint Arthroplasty: The Role of the Geriatric Nutritional Risk Index

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Abstract

Objective: Total joint arthroplasty (TJA) significantly improves the quality of life of individuals with severe arthritis. Despite its success, postoperative complications can affect outcomes and increase healthcare costs. Malnutrition has been identified as a key predictor of adverse surgical outcomes, including increased risk of infection and impaired wound healing. This study aimed to assess the predictive value of the geriatric nutritional risk index (GNRI) for 90-day postoperative complications and one-year mortality in patients undergoing TJA. This study investigates whether lower GNRI scores are associated with higher incidences of complications and mortality.

Methods: A retrospective analysis was conducted on patients over 65 years of age who underwent elective hip or knee arthroplasty between 2013 and 2022. GNRI was calculated using postoperative serum albumin levels and the ratio of current body weight to ideal body weight. Patients were categorized on the basis of GNRI scores to evaluate their risk of postoperative complications and mortality.

Results: The study included 723 patients, with a mean age of 70.4±2.7 years and a mean body mass index of 26.31±0.98. Postoperative GNRI identified 55.7% (n=403) of patients as having normal nutritional status, 41.5% (n=300) as low risk, and 2.8% (n=20) as moderate/severe risk. Complications within the 90-day postoperative period were observed in 4.7% (n=34) of patients, and the 1-year mortality rate was 2.1%. Patients in the moderate/severe malnutrition category had significantly higher rates of complications and mortality ($p<0.001$).

Conclusion: Lower postoperative GNRI values are significantly associated with increased rates of 90-day complications and 1-year mortality in patients with TJA, highlighting the importance of nutritional status in surgical outcomes. GNRI is a valuable tool for identifying patients at risk of postoperative complications and mortality following TJA. Addressing nutritional deficiencies preoperatively could enhance recovery and reduce adverse outcomes, emphasizing the need for nutritional assessments in the surgical management of elderly patients.

Keywords: Total knee arthroplasty, total hip arthroplasty, total joint arthroplasty, geriatric nutritional risk index, malnutrition

INTRODUCTION

Total joint arthroplasty (TJA) is recognized as a highly successful intervention for alleviating pain and improving the quality of life in patients with severe arthritis. Among orthopedic procedures, hip and knee replacements are notably prevalent, particularly in the United States, with projections indicating a surge in demand, largely attributed to an increasingly aged population (1-3). Despite the overall success of these surgeries, complications although infrequent, can impose significant financial burdens on both patients and the healthcare system (4). Considering this, preoperative patient factors have been extensively studied to predict adverse surgical outcomes, with malnutrition emerging as a critical determinant of such outcomes, affecting wound healing and increasing the risk of infections (5,6).

In the elderly, malnutrition is a critical issue, worsening morbidity and mortality rates, diminishing functional capacities, and lowering the quality of life. This condition, which is both preventable and manageable, becomes particularly concerning when combined with the catabolic effects of surgery, leading to muscle wasting and adversely affecting post-surgical recovery.

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These effects can lead to longer hospital stays, higher complication rates, and increased mortality, underscoring the importance of addressing nutritional deficiencies to improve surgical outcomes and patient recovery (7-10).

The geriatric nutritional risk index (GNRI) is an effective metric for evaluating the nutritional status of older adults, incorporating serum albumin levels and the ratio of current to ideal body weight to identify malnutrition risks. GNRI has proven useful in the early detection of malnutrition, facilitating appropriate interventions to mitigate its impact. Furthermore, this index has been applied to predict postoperative complications and mortality risks, offering valuable insights for patient management, particularly in patients undergoing dialysis or those with existing cardiovascular conditions (11-13).

Therefore, this study was designed to explore the predictive value of GNRI for assessing the risk of 90-day postoperative complications and 1-year mortality following TJA. We aimed to determine whether lower postoperative GNRI scores correlate with increased incidences of complications and mortality. We hypothesized that patients demonstrating diminished GNRI values post-surgery would experience higher rates of adverse outcomes, emphasizing the importance of nutritional status in surgical recovery and long-term health.

METHODS

Study Approval and Ethical Considerations

The study received approval from the Clinical Research Ethics Committee of the University of Health Sciences Turkey, Prof. Dr. Cemil Taşcıoğlu City Hospital (approval number: E-48670771-514.99-226507389, date: 11.10.2023) and adhered to the ethical guidelines of the Declaration of Helsinki. Written informed consent was obtained from all participants prior to their inclusion. This retrospective study focused on patients aged 65 years and older who underwent total elective knee or hip arthroplasty from 2013 to 2022. The exclusion criteria included patients younger than 65 years, those undergoing nonelective and emergency procedures, and individuals lacking comprehensive demographic data such as albumin levels, height, and weight.

Participant Selection and Data Collection

Eligible patients were those aged 65 years and above who had undergone elective knee or hip arthroplasty within the specified period. Comprehensive demographic and clinical information was gathered, including age, sex, body mass index (BMI), American Society of Anesthesiologists classification, Charlson comorbidity index (CCI), preoperative and postoperative albumin levels, smoking status, type of surgical procedure, and a detailed history of comorbid conditions such as diabetes, congestive heart failure, hypertension, chronic obstructive pulmonary disease, dyspnea, anemia, preoperative dialysis, disseminated cancer, significant weight loss, chronic steroid use, and osteoarthritis.

Nutritional Status Assessment

The GNRI formula was employed to assess nutritional status: GNRI = [1.489× albumin (g/L)] + [41.7× (body weight/ideal weight)] (14). The ideal body weight was calculated on the basis of a BMI of 22 kg/m^2 (15). For patients whose actual body weight exceeded their ideal weight, the ratio was adjusted to 1, considering the possibility of undernutrition in obese individuals (16). GNRI scores >98 indicated normal nutritional status, scores between 92 and 98 suggested low risk, and scores <92 were categorized as moderate to severe risk (17).

Outcome Measures

Early complications, including surgical site infections and periprosthetic joint infections within the first 90 days after surgery, were documented. In addition, all-cause mortality within the first year following surgery was recorded.

Statistical Analysis

Data analysis was conducted using the SPSS software version 25.0. Descriptive statistics are presented as percentages, means, and standard deviations. The normal distribution of variables was assessed using histogram plots and the Kolmogorov-Smirnov test. For normally distributed variables, one-way ANOVA was applied to compare groups. Categorical data analysis used the Pearson chi-square test. Binary logistic regression analysis was performed to identify risk factors associated with complications and mortality, with p-values <0.05 as indicative of statistical significance.

RESULTS

In this study, 723 patients who underwent TJA were analyzed. Of these, 77.4% (n=560) were women. The procedures consisted of 65.4% (n=473) total knee arthroplasties and 34.6% (n=250) total hip arthroplasties. The average age of participants was 70.4±2.7 years, with a mean CCI of 5.13±0.89 and a BMI of 26.31±0.98 (Table 1). Initial assessment of the GNRI based on preoperative albumin levels indicated that all patients had a normal nutritional status (GNRI >98).

Postoperative GNRI evaluation revealed that 55.7% (n=403) of patients maintained normal nutritional status, 41.5% (n=300)

were categorized as having low nutritional status, and 2.8% (n=20) were in moderate to severe nutritional status. Within the 90-day postoperative period, 4.7% (n=34) of the cohort experienced infection-related complications. The study observed a one-year mortality rate of 2.1%. A significant association was found between postoperative GNRI categories and the incidence of complications and mortality rates, with those in the moderate/severe malnutrition category exhibiting significantly higher rates ($p<0.001$ for both comparisons). No significant differences were observed when comparing postoperative GNRI with patient age, BMI, and CCI scores (Table 2).

Detailed logistic regression analysis identifying risk factors for complications and mortality among the study participants is presented in Table 3 and Table 4.

Table 1. Demographic data of patients included in the study

Age (years)	**70.4±2.7**
Gender n (%) Female Male	 560 (77.4%) 163 (22.6%)
Body mass index (kg/m²)	26.31±0.98
Surgical procedure (n, %) Total knee arthroplasty Total hip arthroplasty	 473 (65.4%) 250 (34.6%)
ASA class (n, %) 1 2 3 4	 25 (3.4%) 357 (49.4%) 324 (44.8%) 17 (2.4%)
Charlson comorbidity index	5.13±0.89
Complication (n, %)	34 (4.7%)
Mortality (n, %)	15 (2.1%)

ASA: American Society of Anesthesiologists

DISCUSSION

A crucial discovery from this research is the correlation between postoperative serum markers and the GNRI, highlighting that a GNRI less than 92 is significantly associated with increased risks of early postoperative complications and mortality. This finding aligns with those of prior studies that have evaluated the prognostic value of preoperative nutritional assessments (1,15,18).

Table 2. Comparison of the patients included in the study according to the GNRI groups after surgery

	Normal risk (n=403)	Low risk (n=300)	Moderate/Severe risk (n=20)	p-value
Age (years)	70.39±2.72	70.4±2.69	70.55±2.31	0.967*
Body mass index (kg/m²)	26.35±1	26.23±0.94	26.63±0.98	0.089*
Charlson comorbidity index	5.11±0.87	5.17±0.93	5.05±0.73	0.619*
Complication (n, %)	1 (0.3%)	23 (7.7%)	10 (50%)	<0.001**
Mortality (n, %)	5 (1.24%)	5 (1.66%)	5 (25%)	<0.001**

GNRI: Geriatric nutritional risk index
* One-way ANOVA test
** Pearson chi-square test

Table 3. Binary logistic regression analysis of complications in patients included in the study

Risk factors	B	Exp(B)	p-value	95% confidence interval Lower-Upper
Age (years)	-0.029	0.972	0.713	0.834-1.133
Body mass index (kg/m²)	0.230	1.259	0.294	0.819-1.937
Charlson comorbidity index	-0.032	0.969	0.897	0.601-1.562
Postoperative GNRI	-0.505	0.603	<0.001	0.516-0.706

GNRI: Geriatric nutritional risk index, B: Estimated coefficient, Exp(B): Exponential value of B

Table 4. Binary logistic regression analysis of mortality in the patients included in the study

Risk factors	B	Exp(B)	p-value	95% confidence interval Lower-Upper
Age (years)	0.052	1.053	0.629	0.853-1.300
Body mass index (kg/m²)	0.251	1.285	0.377	0.737-2.242
Charlson comorbidity index	1.168	3.216	0.001	1.613-6.414
Postoperative GNRI	-0.116	0.018	0.018	0.808-0.980

GNRI: Geriatric nutritional risk index, B: Estimated coefficient, Exp(B): Exponential value of B

This implication suggests a potential strategy to mitigate postoperative complications and mortality by preventing the decline from normal nutritional status to malnutrition in the geriatric population undergoing surgery.

The literature has consistently documented the link between preoperative hypoalbuminemia and the heightened risk of adverse postoperative outcomes (19-21). In this study, all participants had normal preoperative albumin levels; however, a 4.7% incidence of early postoperative infections was observed, indicating that postoperative albumin levels might offer a predictive value for such complications when used in GNRI calculations.

The phenomenon of malnutrition in obese patients, though less apparent, is a significant concern (22). Huang et al. (23) identified malnutrition in 8.3% of obese individuals based on specific biochemical markers, noting that these patients faced a higher rate of complications compared with their well-nourished obese counterparts. Considering that the average BMI of participants in this study places them in the overweight category, the risk of overlooking malnutrition in patients with higher than ideal body weight is evident.

The GNRI formula adjustment for individuals with body weight exceeding their ideal weight suggests that albumin levels below specific thresholds could inaccurately represent patients as being at lower nutritional risk than they actually are. This study's data showed that early complications predominantly occurred in those classified within the low nutrition group based on postoperative GNRI values.

Study Limitations

This study's retrospective nature, variability in surgical practitioners, and relatively modest sample size compared with the broader literature constitute its primary limitations. Nonetheless, it represents one of the initial attempts to leverage postoperative nutritional assessments, through GNRI, to predict outcomes following TJA. Future research with a prospective design and larger cohorts, encompassing a comprehensive range of risk factors, is essential to validate and expand upon these findings.

CONCLUSION

The transition from normal to malnourished status post-surgery, as indicated by hypoalbuminemia, significantly impacts the risk of complications and mortality within the first year after TJA. The outcomes of this study underscore the importance of considering postoperative albumin levels in nutritional risk assessments. Consequently, further randomized controlled trials are required to confirm these insights and guide clinical practice toward improved postoperative care and nutritional management.

Ethics

Ethics Committee Approval: This study was approved by the Clinical Research Ethics Committee of the University of Health Sciences Turkey, Prof. Dr. Cemil Taşcıoğlu City Hospital (approval number: E-48670771-514.99-226507389, date: 11.10.2023).

Informed Consent: Informed consent was obtained from all participants.

Authorship Contributions

Surgical and Medical Practices: M.Y., A.Y., N.E., M.S.S., T.O.B., H.G., Concept: M.Y., A.Y., N.E., M.S.S., T.O.B., H.G., Design: M.Y., A.Y., N.E., M.S.S., T.O.B., H.G., Data Collection or Processing: M.Y., A.Y., N.E., M.S.S., T.O.B., Analysis or Interpretation: M.Y., A.Y., N.E., M.S.S., T.O.B., H.G., Literature Search: M.Y., A.Y., N.E., M.S.S., T.O.B., H.G., Writing: M.Y., A.Y., N.E., M.S.S., T.O.B.

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CASE REPORT

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Rapid Recurrence of Glioblastoma After 12 Days Despite Gross Total Resection

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Abstract

To present a unique case of rapid recurrence of glioblastoma after 12 days despite gross total resection. Glioblastomas are highly mortal and aggressive tumors. Despite advancements in therapy, gross total resection, radiotherapy, and chemotherapy, the recurrence rate is high and overall survival is short. We report a unique case of a patient with recurrence of glioblastoma in just 12 days despite gross total resection, which has not been previously reported in the literature. A 65-year-old woman complained of headaches and disturbance of speech for three days. On magnetic resonance imaging (MRI), a 5x4.5 cm diffuse contrast-enhanced mass lesion was detected. The patient underwent elective surgery in which the lesion was completely removed. Postoperative MRI scans revealed that the tumor was completely removed. She was released from the hospital on her postoperative 6th day. On the postoperative 12th day the patient was brought to our hospital with seizures and somnolence. On radiological images, a mass lesion in the same surgical area was detected. She underwent surgery in which the recurrent mass lesion was completely removed. Biopsy results correlated with those of the previous surgery. The reason why glioblastomas are such mortal tumors is their high recurrence rate. Overall recurrence occurs between 32-36 weeks after surgery. Serial neuroimaging should be performed to monitor potential relapse. Early recurrence before 3 months is very rare. A case like ours in which the tumor re-occurred just 12 days after total resection shows that there is still research to be done to understand the recurrence characteristics of glioblastoma.

Keywords: Glioblastoma, recurrence, brain tumors, neuro-oncology

INTRODUCTION

Glioblastomas represent 15% of all brain tumors and are the most common malignant tumor of the central nervous system in adults (1). Previously known as glioblastoma multiforme, according to the World Health Organization (WHO) 2016 classification of central nervous system tumors, they are now situated in the subgroup of diffuse astrocytic and oligodendroglial tumors and are divided into isocitrate dehydrogenase (IDH) mutant and wild-type glioblastoma (2). IDH-wildtype represents approximately 90% of all glioblastomas and occurs mainly in patients over 55 years of age. The IDH-mutant type arises primarily from prior lower grade diffuse gliomas and is mostly seen in younger patients (3). The term "not otherwise specified" is used for tumors in which the IDH evaluation could not be performed (2). Development and risk factors remain unclear, but patients with genetic disorders such as neurofibromatosis and Li-Fraumeni syndrome and radiation exposure are shown to have a higher risk of developing glioblastoma (4). Symptoms may change due to the size and location of the mass and may vary from simple headaches to seizures, motor deficits, or coma. The treatment goal is maximum safe resection followed

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by radiotherapy and in some cases chemotherapy. Despite good surgical outcomes, the common length of survival is 12 to 15 months. Only 3-7% of all patients survive for more than 5 years. People who have not undergone any treatment usually die within 3 months (5). The reason for the high mortality of glioblastoma is the high recurrence rate. Most patients show relapse of the tumor 8 months after surgery. Recurrence before 3 months, especially after removal of more than 98% of the tumor and adjuvant radiotherapy or chemotherapy, is very rare (6). Patients with a high Karnofsky performance score (KPS) before surgery usually have a longer survival time. Biopsies showing O-6-methylguanine-DNA methyltransferase (MGMT) translation have a higher suitability to temozolomide (TMZ), thus showing a better long-time survival (7). Also, an IDH1 mutation or adjuvant use of the antiangiogenic agent bevacizumab might lead to a more favorable prognosis (8). To summarize, patients with the IDH1 mutation and the MGMT methylation combined have the longest survival, the ones with either one of them intermediate survival, and patients with none of them the shortest (9). We report a unique case of a patient with recurrence of glioblastoma in just 12 days despite gross total resection, which has not been previously reported in the literature.

CASE PRESENTATION

We present the case of a 65-year-old woman complaining of headaches and disturbance of speech for three days. Glasgow Coma Scale (GCS) score was 15. The general condition was good, but she had problems with articulation. Cranial magnetic resonance imaging (MRI) was scheduled in which a 5x4.5 cm diffuse contrast-enhanced mass lesion was detected (Figure 1). The patient was informed about the pathology, and informed consent documents were obtained. She underwent elective surgery, and the postoperative images showed that the lesion was completely removed (Figure 2). The biopsy was reported as glioblastoma [WHO grade IV, IDH wild-type, GFAP (+), ki67 (+), SMA (-)] (Figure 3). She was released from the hospital on her postoperative 6th day without any deficits and scheduled for radiochemotherapy 10 days later. On the postoperative 12th day the patient was brought to our hospital with seizures and somnolence. GCS on admission was 10 (E3V3M4). On MRI, a mass lesion in the same operation area was detected (Figure 4). She underwent surgery in which the recurrent mass lesion was completely removed. The biopsy results correlated with the same as the previous surgery (Figure 5). The patient was transferred to the radiation oncology department for radiotherapy and chemotherapy after 10 days without any neurological deficits.

DISCUSSION

Glioblastomas are the most aggressive primary brain tumor. Despite advancements in therapy standards, gross total resection, radiotherapy, and chemotherapy, the recurrence rate is high and overall survival is short. Survival for longer than 2 years is only 2.2% (10). Only a few single cases survive for longer, but potentially wrong pathology results must be taken notice. The reason why glioblastomas are such mortal tumors is their high recurrence rate. Overall recurrence occurs between 32-36

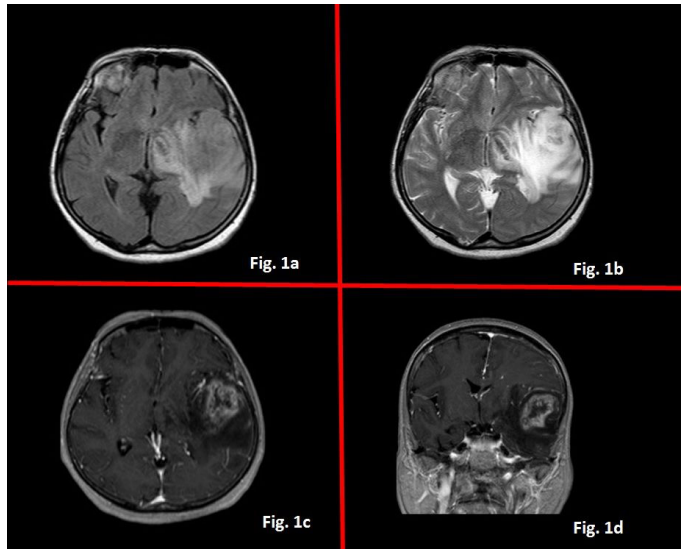

Figure 1. Cranial MRI of the patient before the first surgery. T1 axial (1a), T2 axial (1b), contrast-enhanced T1 axial (1c), and contrast-enhanced T1 coronal (1d) views. A 5x4.5 cm diffuse mass lesion in the temporal area was detected
MRI: Magnetic resonance imaging

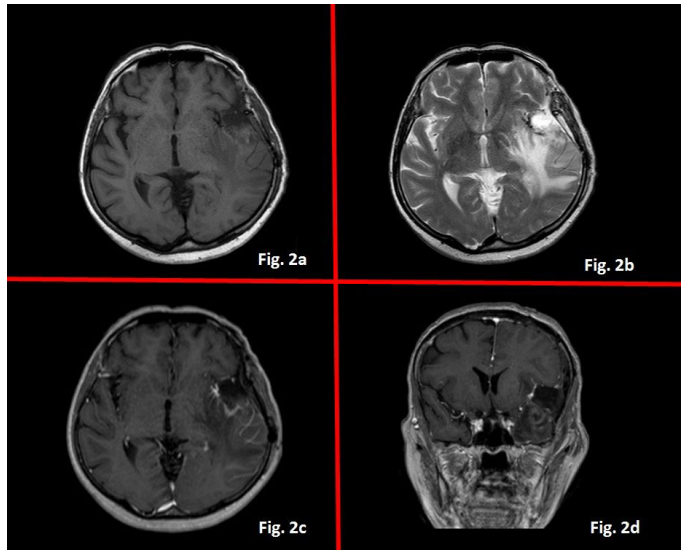

Figure 2. Cranial MRI of the patient after the first surgery. T1 axial (2a), T2 axial (2b), contrast-enhanced T1 axial (2c), and contrast-enhanced T1 coronal (2d) views. Gross total resection of the entire tumor is observed
MRI: Magnetic resonance imaging

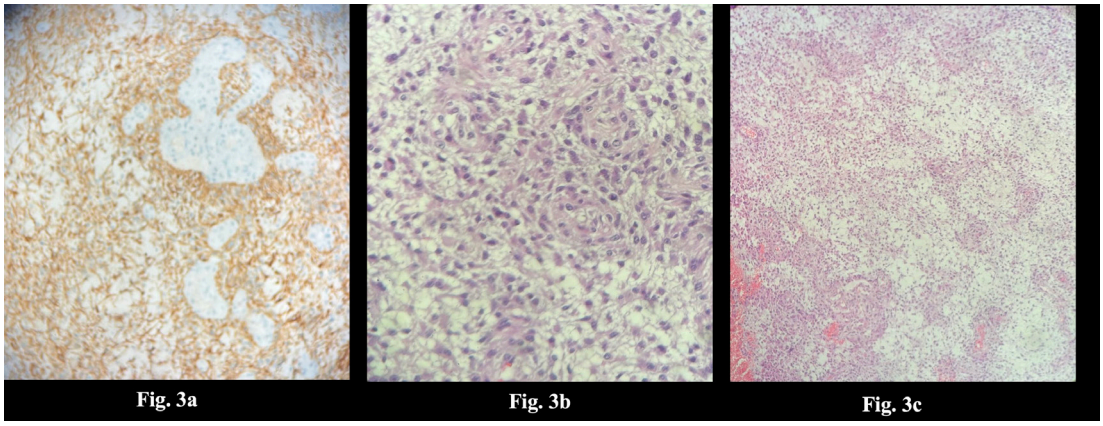

Figure 3. Images of the pathology slices after the first surgery. (3a) Positive immunohistological GFAP positivity and microvascular proliferation areas (IHKx200), (3b) Cellularity of tumoral cells and nuclear atypical proliferations (HEx400), (3c) Crest imaging and cellularity (HEx200). All findings indicate glioblastoma (WHO Grade IV)

WHO: World Health Organization, GFAP: Glial fibrillary acidic protein

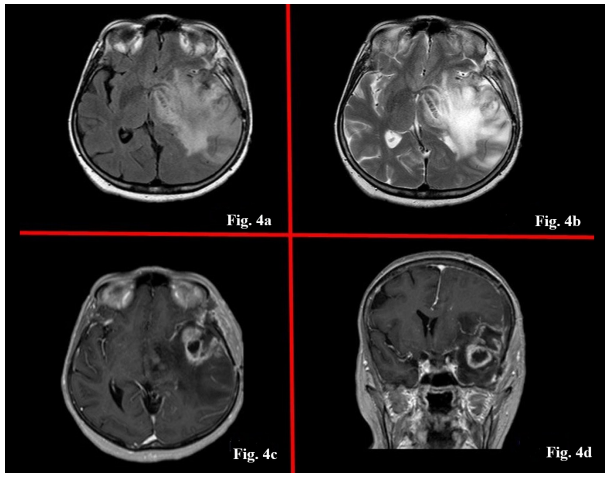

Figure 4. Cranial MRI of the patient 12 days after surgery. T1 axial (3a), T2 axial (3b), contrast-enhanced T1 axial (3c), and contrast-enhanced T1 coronal (3d) views. A recurrent mass lesion in the same surgical area is detected

MRI: Magnetic resonance imaging

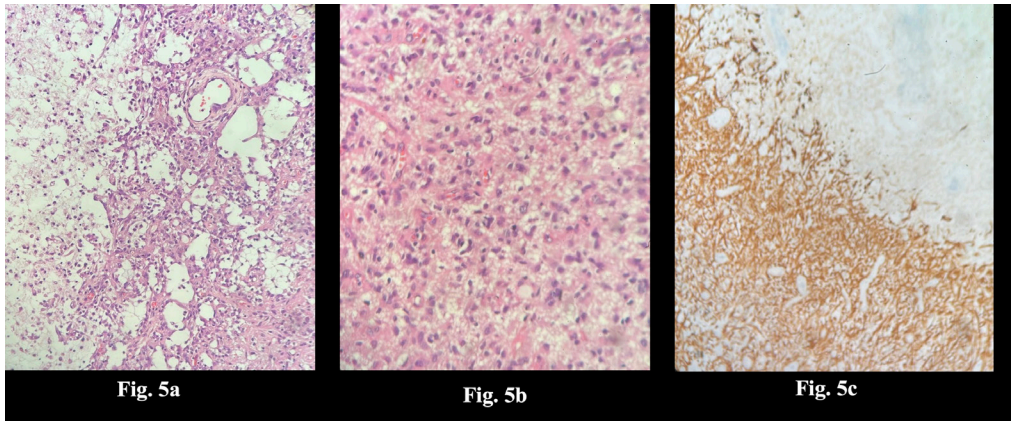

Figure 5. Images of the pathology slices after the second surgery. (4a) Necrosis area (HEx200), (4b) Cellularity and atypical proliferation (HEx400), (4c) GFAP positivity and tumor necrosis area (IHKx200). All findings indicate recurrent glioblastoma (WHO Grade IV)

WHO: World Health Organization, GFAP: Glial fibrillary acidic protein

weeks after surgery and increases 90% of the original tumor location (6). Some are thought to develop in the form of new lesions due to continuous growth patterns or dissemination (11). Serial neuroimaging should be performed to monitor potential recurrence, but differentiating from pseudoprogression or radionecrosis may be difficult. Especially after radiation and TMZ treatment, pseudoprogression can occur in 20-30% of cases (12). Additional imaging modalities such as diffusion-weighted imaging and perfusion MRI with contrast MRI might be necessary to make this differentiation. The management of recurrent gliobastomas remains controversial. Overall KPS, involvement of eloquent areas, and size of the lesion must be taken notice. Reoperation, reradiation, and systemic chemotherapy or a combination of these are the options (13). Because our patient developed new symptoms after the post-operative 12th day and did not receive any radiotherapy or chemotherapy, we did not suspect any pseudoprogression or radionecrosis in such a short time frame and suspected a relapse of the tumor, which was later confirmed by the pathology results.

CONCLUSION

Glioblastomas are highly mortal and aggressive tumors with a high recurrence rate. Even gross total resection in combination with radiochemotherapy is not sufficient to avoid relapse. Early recurrence before 3 months is rare. A case like ours in which the tumor re-occurred just 12 days after total resection shows that there is still research to be done to understand the recurrence characteristics of glioblastoma.

Ethics

Informed Consent: Informed consent form was obtained from the patient.

Authorship Contributions

Surgical and Medical Practices: M.A.Ç., Concept: O.B., Design: S.Ş., Data Collection or Processing: Y.K., Analysis or Interpretation: Y.K., Literature Search: O.B., Writing: İ.A.

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

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