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Aims and Scope

The Medical Bulletin of Haseki is the official scientific journal of the University of Health Sciences Turkey, Istanbul Istanbul Haseki Training and Research Hospital. It covers subjects on general medicine, published both in Turkish and English, and is independent, peer-reviewed, international periodical and is published quarterly (January, March, June, September and November).

The aim of the Medical Bulletin of Haseki is to publish original research papers of the highest scientific and clinic value on general medicine. Additionally, educational material reviews on basic developments, editorial short notes and case reports are published.

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The Medical Bulletin of Haseki

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Effect of Preemptive Femoral Nerve Block on Pain Control and Opioid Consumption After Total Knee Arthroplasty: A Randomized Controlled Trial

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Abstract

Aim: Peripheral nerve blocks, particularly femoral nerve blocks (FNBs), are a practical choice for relieving severe pain after total knee arthroplasty (TKA). We investigated the effectiveness of preemptive FNB on postoperative pain control and the reduction of opioid consumption.

Methods: This was a single-center, prospective, randomized controlled trial conducted at a tertiary care health center, Istanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine, Turkey. The study included 40 American Society of Anesthesiologists I-III patients scheduled for elective TKA surgery. Patients were studied in two groups. The FNB group (n=20) received preemptive single-injection FNB (15 mL of prilocaine 2% and 15 mL of 0.5% bupivacaine using a peripheral nerve stimulator) before general anesthesia (GA) as the study group and the control group (n=20) received standardized GA. The primary outcome measure was pain scores evaluated as numeric pain rating scale (0-10) at 2, 4, 8, 12, 16, 18, 20, and 24 h. Secondary outcome measures included opioid consumption with patient-controlled and perioperative hemodynamic changes.

Results: Pain scores and opioid consumption in the FNB group were significantly lower than those in the control group at every measurement time ($p<0.05$). Total perioperative morphine use was also lower in the FNB group ($p=0.023$). Regarding hemodynamic variables, the heart rate values at the beginning of surgery and tourniquet insufflation in the FNB group were significantly lower than those in the control group.

Conclusion: Using the FNB as part of any multimodal analgesia protocol to alleviate pain after TKA with less analgesic use would be beneficial.

Keywords: Femoral nerve block, orthopedic anesthesia, postoperative pain, preemptive, total knee arthroplasty

Introduction

Total knee arthroplasty (TKA) is associated with severe postoperative pain (1). However, adequate postoperative pain management increases patient comfort and allows for early physiotherapy (2). Numerous techniques have evolved, including neuraxial (NA) and general anesthesia (GA), both along with peripheral nerve blocks (PNB), local infiltration anesthesia, and oral medication regimens, within the concept of multimodal analgesia (3). The abundance of analgesic options for post-TKA pain comes with the price of uncertainty in defining the ideal approach. The American Society of Regional Anesthesia and Pain Medicine and the European Society of Regional Anesthesia and Pain Therapy demonstrated that standardized pathways are not identical in Europe or North America (4).

It is essential to design institutional protocols that are adapted to routine practice. A debate still exists about whether general or NA anesthesia is superior. In a recent consensus for anesthetic management of TKA, authors compared GA vs. NA and noted that NA was associated with fewer or no complications in all reported outcomes (5). Since then, NA has been recommended

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with a low level of evidence (5). On the other hand, the practice of PNB has gained popularity, but its effects as adjuncts to GA or NA still need to be studied (6). Thus, we investigated a protocol using GA with PNB. Previous studies suggest that femoral nerve block (FNB) is efficient for postoperative pain control after TKA, either stand-alone or as a part of multimodal regimens (7,8). Preemptive multimodal analgesia protocols have been shown to improve postoperative pain control, and the addition of a preemptive FNB to them could further improve their effect (9). In addition, different local anesthetics with various doses have been studied, mostly bupivacaine, ropivacaine, and liposomal bupivacaine, along with rapid-acting lidocaine. However, a preemptive FNB protocol containing a fast-acting local anesthetic agent to gain benefit during the intraoperative period has not been studied.

Determining the possibility of reducing pain scores and the amount of perioperative morphine consumption by adding a fast-acting local anesthetic agent, prilocaine, to FNB may bring a different dimension to clinical practice. This study compared the efficacy of a single-injection preemptive femoral nerve blockade with 2% prilocaine and 0.5% bupivacaine versus the control group in postoperative pain control after TKA.

Methods

Compliance with Ethical Standards

We screened adult patients planned for TKA at the Department of Orthopedics and Traumatology to be enrolled in the study. After the ethical approval of Istanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine, Clinical Research Ethics Committee (approval number: 83045809/6447, date: 18.03.2013), within which the work was undertaken, the study was conducted according to the provisions of the 1995 Declaration of Helsinki (as revised in Brazil in 2013). All subjects in the study provided informed consent, and patient anonymity was preserved.

Study Population

Patients with ASA physical status I-III between 30 and 75 years of age were recruited for the study. Exclusion criteria included allergy to prilocaine, bupivacaine, morphine, or dexketoprofen trometamol, previous history of narcotic abuse, a pre-existing neurological deficit in the lower extremity, inability to use patient control analgesia (PCA), bleeding disorders, a local or systemic infection, patients who underwent procedures in both legs, uncontrolled hypertension or a history of severe arrhythmia, and patients with severe hepatic or renal insufficiency. All patients were preoperatively informed about the procedures and trained using the numeric pain rating scale [(NPRS) as 0 meaning no pain, 10 being the worst pain ever felt], along with a PCA pump (Bodyguard 323; pfm Medical).

Procedure

We assessed the 60 patients scheduled for TKA (Figure 1). After screening for eligibility and signing the

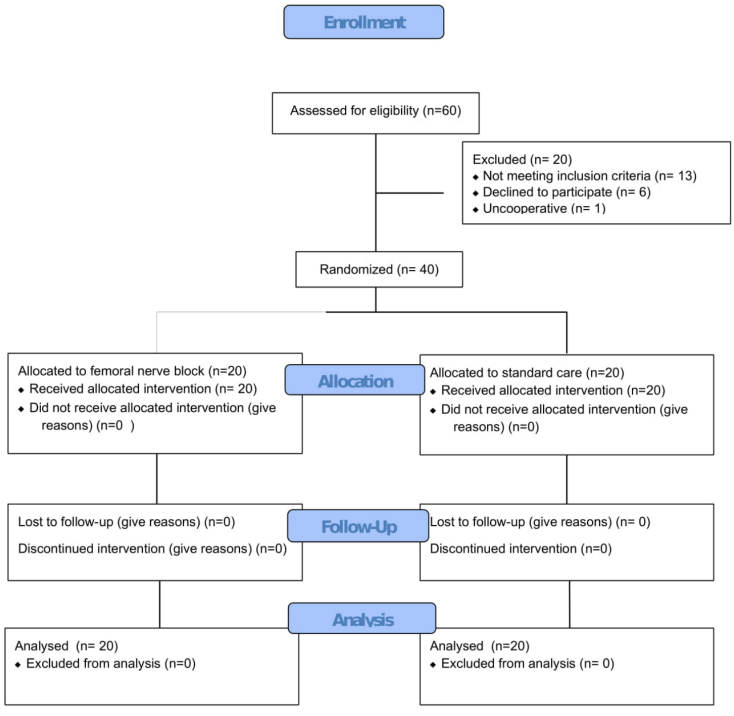

Figure 1. Consort flow diagram

informed consent form,the corresponding anesthesiologist randomized the patients using the research randomizer application with the allocation ratio 1:1 into two groups: the control group and the FNB group to receive the preemptive FNB.

Femoral nerve block was performed in the pre-operative care room under standard monitoring and according to the rules of asepsis. The femoral nerve was identified with the aid of a peripheral nerve stimulator (HNS11, B. Braun Medical Inc., Pennsylvania, USA) with confirmation of quadriceps muscle contraction (patellar dance) at 0.2-0.5 mA intervals, after which 15 mL of 2% prilocaine (Citanest; Zenica Medical) and 15 mL of 0.5% bupivacaine (Buvasin 0.5%; Vem Medical) were injected using a 50-mm needle (Simplex A-50, B. Braun Medical Inc., Pennsylvania, USA) (Figure 2). An anesthesia resident performed all blocks with at least two years of experience under the supervision of an anesthesiologist trained in regional anesthesia with electrostimulation. Fifteen minutes later, the anesthesiology attendant confirmed sensory and motor blockade using a pinprick test and the Bromage scale.

All patients (the FNB and the control group) received standardized GA with propofol (1.5-2 mg/kg), atracurium (0.5 mg/kg), sevoflurane (target 2% MAC), and morphine (0.1 mg/kg) as analgesia. If the heart rate (HR) and mean arterial pressure (MAP) raised over 20% of the baseline values (values measured at the entry of the surgical room) of the patient, we administered 2 mg of IV morphine (with a maximum value of 0.1 mg/kg morphine). At the end of the surgery, residual neuromuscular block was reversed with atropine (0.01 mg/kg) and neostigmine (0.02 mg/kg). All patients included in the study were operated on by the same surgical team using the same surgical technique.

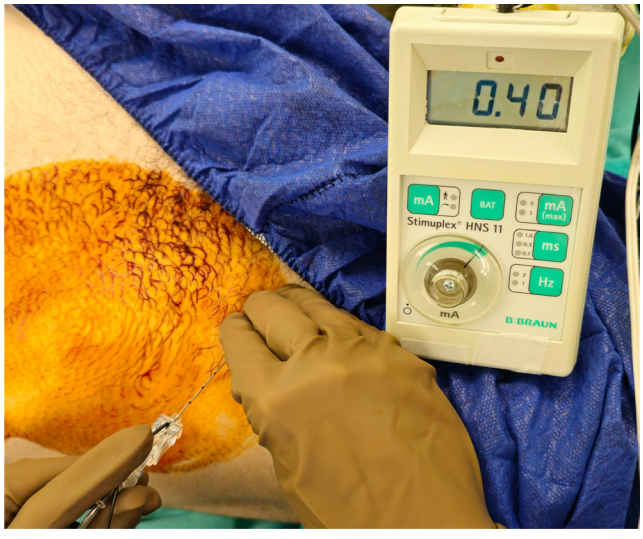

Figure 2. The femoral nerve block procedure

All patients received IV PCA pumps postoperatively for 24 hours. Patient control analgesia solution was prepared as 100 mg of morphine in 100 mL of isotonic saline. The device was set to administer a bolus dose of 1 mg on demand, with a lockout period of 7 minutes. In addition, all participants received 50 mg of dexketoprofen and trometamol (two per day, intravenous) until discharge from the hospital.

Data Collection

Patients were followed at the orthopedic post-anesthesia care unit (OPACU) for 24 hours, and all data were collected at the OPACU, from time "0" as entry to the postoperative 24th hour as discharge from the OPACU (0-4-8-12-16-20-24 hours). Data were collected by an orthopedic ward nurse blind to patient randomization.

The primary outcome measure was the pain score (NPRS) (0-10), evaluated at predetermined intervals. Secondary outcome measures included the total amount of opioid consumed via PCA (in mg), perioperative hemodynamic changes, the development of side effects, and complications.

Patient control analgesia values were recorded separately as demand and delivery (the demanded number is the total amount of patient requests; the delivery number is the total amount of drugs given, limiting patient requests with the lockout setting). We also saved the perioperative total amount of morphine usage.

Intraoperative hemodynamic data (HR, systolic, and diastolic blood pressures) were collected at admission to the surgical room, induction of anesthesia, intubation, tourniquet insufflation, beginning of the surgery, tourniquet deflation, and extubation.

We evaluated side effects using a questionnaire filled out by a nurse blinded to the groups. The questionnaire investigated the following items: the presence of nausea or vomiting, pruritus, sedation (with the Modified Observer's Assessment of Alertness and Sedation scale), respiratory depression (<8), hypotension (MAP<65), urinary retention, and signs of local anesthetic toxicity (circumoral or tongue numbness, metallic taste, lightheadedness, and visual and auditory disturbances).

The presence of motor blockade was assessed using the Bromage score; we evaluated sensory and motor deficits on the third postoperative day before hospital discharge and observed any quadriceps weakness or falls at the first physiotherapy session (24 hours postoperatively) before discharge from OPACU.

Statistical Analysis

We used the clinical sample size calculator (https://clincalc.com/stats/samplesize.aspx) to calculate the sample size. After examining previous studies, as in Szczukowski

et al. (8), we calculated a sample size of 18 patients per group with alpha equal to 0.05 (two-sided) and a power of 0.80. We increased our sample size to 20 patients per group to compensate for possible dropouts. Statistical analyses were performed using the Number Cruncher Statistical System 2007 and Power Analysis and Sample Size 2008 Statistical Software (Utah, USA). Descriptive statistical methods (average, standard deviation, median, frequency, ratio, minimum, maximum), Student's t-test (for the two-group comparisons of parameters showing a normal distribution), and Mann-Whitney U test (for two-group comparisons of parameters that did not show a normal distribution) were used. Significance was evaluated at $p<0.01$ and $p<0.05$ levels.

Results

We screened sixty patients and enrolled forty, all of whom completed the study protocol. There were no differences between the groups regarding demographic data, duration of surgery, or tourniquet time (Table 1). The weight and height values of the intervention group were higher than those of the control group, but the body mass index values showed no statistical difference.

The NPRS values of the femoral group at each control hour for 24 hours were significantly lower than those of the control group. A statistically significant difference was found at all hours between the NPRS measurements of the patients according to the groups (Figure 3).

Morphine consumption with PCA in the femoral group at each control hour for 24 hours was significantly lower than that in the control group. A statistically significant difference between the groups was found, except in the 0th hour. Likewise, the total morphine used perioperatively was significantly lower in the FNB group (p=0.023) (Table 2).

There were no significant changes in the blood pressure values for intraoperative hemodynamic variables. However, we found statistically significant differences between the patients' HR values at the beginning of surgery and tourniquet insufflation (p=0.036, p=0.011). The HR values at the beginning of surgery and tourniquet insufflation in the intervention group were significantly lower than those in the controls. Moreover, although HR values at extubation were not statistically different, they were remarkably lower in the femoral group (p=0.073) (Table 3).

Table 1. Demographic data

	Group A	Group B	p-value
	Mean ± SD	Mean ± SD	
Age (year)	67.50±6.66	61.85±11.80	**0.070**
ASA	2.10±0.55	1.90±0.45	**0.216**
Weight (kg)	83.40±11.50	72.80±15.53	**0.019***
Height (cm)	162.45±7.96	156.95±8.65	**0.043***
BMI	31.74±4.91	29.63±6.03	**0.234**
Duration of surgery (minute)	130.00±32.44	140.50±50.57	**0.439**
Tourniquet time (minute)	115.15±23.60	104.65±21.52	**0.150**

Student's t-test, *p<0.05
ASA: American Society of Anesthesiologists, BMI: Body mass index, SD: Standard deviation

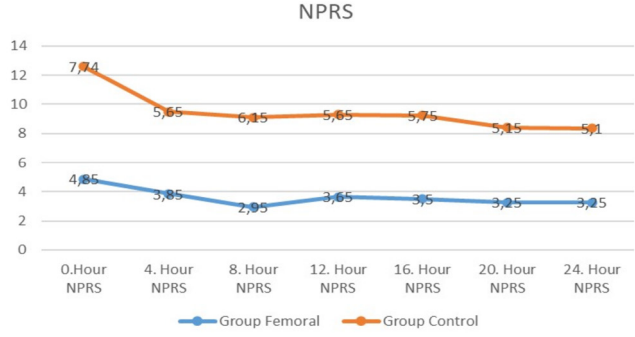

Figure 3. Numeric pain rating scale values

Table 2. Morphine consumption

	Group A	Group B	p-value
	Mean ± SD (Median)	Mean ± SD (Median)	
Total morphine 0. hour	1.65±1.46 (1.0)	2.70±1.98 (2.0)	**0.069**
Total morphine 4. hour	5.15±4.60 (4.5)	9.20±7.18 (6.5)	**0.010***
Total morphine 8. hour	6.75±4.99 (5.0)	12.45±7.69 (10.0)	**0.004****
Total morphine 12. hour	8.10±5.58 (7.0)	15.00±8.77 (13.0)	**0.005****
Total morphine 16. hour	9.65±6.39 (8.0)	17.50±9.93 (15.5)	**0.005****
Total morphine 20. hour	11.65±8.12 (10.0)	21.55±11.12 (19.5)	**0.003****
Total morphine 24. hour	15.65±11.38 (13.0)	24.95±12.64 (22.0)	**0.023***
Peroperative morphine (mg)	15.65±11.38 (13.0)	24.95±12.64 (22.0)	**0.023***

Mann-Whitney U test, *p<0.05, **p<0.01
SD: Standard deviation

Table 3. Heart rate values			
	Group A	Group B	p-value
	Mean ± SD	Mean ± SD	
HR entrance	80.85±14.88	86.45±15.89	0.257
HR induction	77.60±14.77	83.85±14.40	0.183
HR entubation	77.65±11.82	85.42±13.41	0.062
HR tourniquet insufflation	70.35±11.11	81.45±15.02	0.011*
HR surgical beginning	71.30±11.88	80.65±15.09	0.036*
HR tourniquet desufflation	74.40±12.77	82.65±17.24	0.093
HR extubation	81.05±16.31	89.80±13.61	0.073

Student's t-test, *p<0.05
SD: Standard deviation, HR: Heart rate

No side effects or complications developed in any patient in either group. In addition, none of the patients, including the femoral group, fell due to quadriceps weakness.

Discussion

Our study demonstrates that NPRS values and morphine consumption in patients submitted to FNB after TKA decreased compared with controls. We also demonstrated less hemodynamic variability during induction and tourniquet insufflation in the femoral group.

Similarly, Wang et al. (10) studied a single dose of FNB but used 40 mL of 0.25% bupivacaine differently and applied it to 15 patients after surgery. Szczukowski et al. (8) used 30 mL of 0.5% bupivacaine plus epinephrine (1:200,000) and performed the block preoperatively. Both had similar results with lower visual analogue scale scores, concluding that single-injection FNB is effective for postoperative analgesia and early ambulation. Unlike previous studies, we added a fast-acting local anesthetic to the FNB application and thus provided intraoperative analgesia and hemodynamic stability.

Different multimodal analgesia protocols are available for TKA (3,4). However, timing seems to play an important role, and the effect of preemptive analgesia should not be underestimated. Preventing central sensitization can improve postoperative analgesia and reduce the risk of persistent postoperative pain (1). Furthermore, preemptive use of PNB attenuated the surgical-induced stress response, resulting in lower pro-inflammatory cytokine levels (IL-6), better cardiovascular stability during surgery, and improved postoperative pain control (11).

The contribution of FNB to post-TKA pain relief is not devoid of controversy. While motor blockage and sensory block contribute to pain relief with resolved postoperative quadriceps muscle spasms, they may also lead to muscle weakness (12). However, we did not encounter such an effect in our study. Moreover, several meta-analyses have compared an alternative sole sensory block, the adductor canal block (ACB), with FNB. They suggested equal analgesia, better ambulation, and faster recovery with ACB (13). However, other randomised controlled trials (RCTs) failed to show significant differences in ambulation with preserved quadriceps strength at each block (14,15). Besides, a few cases exist in the literature showing that ACB can result in significant quadriceps muscle weakness, and its technique mandatorily requires ultrasonography (USG) (6,16).

Although it results in prolonged analgesia, we did not choose a continuous FNB technique (17). Our main concerns were infection, prolonged muscle weakness, and technique skill (6,18); therefore, we chose a single-injection FNB and searched for methods to improve its effects within preemptive and multimodal analgesia.

Trained physicians capable of using USG and the technology itself were limited. USG has been the standard tool for peripheral nerve blockage; however, the use of a concurrent nerve stimulator is advised (19). Our study has the disadvantage of using only a nerve stimulator. However, using this technique may increase the effectiveness of FNBs, especially when the possibilities are limited. It should be noted that the nerve stimulator can be used as a physiological monitoring device while applying nerve blocks. As the American Society of Regional Anesthesia recently advised, combining USG with a nerve stimulator would ensure safer clinical practice, and recent studies seem to appreciate it (20,21).

Multimodal analgesia protocols are essential for enhanced recovery after surgery in patients undergoing total joint arthroplasty (22). These protocols consist of PNB and non-opioid drug combinations with the target of reducing perioperative opioid consumption, as demonstrated in our study. The amount of opioids used has been emphasized for the quality of patient care because higher amounts are directly related to postoperative chronic opioid use in patients undergoing TKA (23).

Study Limitations

Our study has some limitations. We could only follow the patients until discharge on postoperative day 3. In addition, we could not note pain scores during physiotherapy sessions. Rebound pain could also be evaluated in the femoral group, but the concept is relatively new. RCTs with a long-term follow-up of up to 3 months after surgery could be valuable to evaluate persistent postsurgical pain and possible rebound pain related to PNBs (24). Despite these limitations, the study's strength is presenting a traditional FNB block as a cost-effective, practical protocol based on the preemptive use of the moderate and long-acting local anesthetic combination, concluding both intraoperative

and postoperatively better outcomes. Future research must explore variations in effective multimodal protocols to ensure analgesia and ambulation without ignoring cost-effectiveness, practicality, and patient satisfaction.

Conclusion

Our study showed that FNB efficiently managed pain after TKA. We demonstrated that a single-injection FNB is adequate and can be reinforced with elements of preemptive and multimodal analgesia protocols. Selecting a local anesthetic mixture with different time intervals of action could potentiate favor perioperatively.

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Ethics

Ethics Committee Approval: This study was approved by the Istanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine, Clinical Research Ethics Committee (approval number: 83045809/6447, date: 18.03.2013), within which the work was undertaken, the study was conducted according to the provisions of the 1995 Declaration of Helsinki (as revised in Brazil in 2013).

Informed Consent: All subjects in the study provided informed consent, and patient anonymity was preserved.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: B.C., E.O.U., Concept: B.C., S.K., Design: B.C., E.O.U., S.K., Data Collection or Processing: B.C., Analysis or Interpretation: B.C., Literature Search: B.C., Writing: B.C.

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Original Article

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Comparison of the Effectiveness of Single and Double Surface Light Emitting Diodes Phototherapy and Intensive Compact Fluorescent Phototherapy in the Treatment of Neonatal Hyperbilirubinemia

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Abstract

Aim: In newborns with extremely high serum total bilirubin levels, the phototherapy method that reduces serum total bilirubin levels most rapidly should be applied to reduce the need for exchange transfusions and thus prevent the development of acute and/or chronic bilirubin encephalopathy. The aim of this study was to compare the efficacy of single or double light-emitting diode (LED) and intensive compact fluorescent tube (CFT) phototherapy in the first 4 hours of treatment for hyperbilirubinemia.

Methods: The study was a retrospective analysis of prospectively collected data, and designed as a single-center, cross-sectional study. Sixty newborns born between 35 and 42 weeks of gestation and treated with intensive phototherapy were included in the study. Total serum bilirubin (TSB) levels were measured 4 hours after the initiation of treatment in neonates who received LED or CFT phototherapy, and the efficacy of these methods was compared.

Results: The rate of decline in TSB was 1.07 mg/dL/h in CFT, 0.74 mg/dL/h in double LED, and 0.44 mg/dL/h in single LED phototherapy. Compact fluorescent tube and double LED phototherapy were found to be more effective than single LED phototherapy ($p<0.01$, $p<0.01$).

Conclusion: In neonates with hyperbilirubinemia, intensive CFT or double LED phototherapy in the first few hours of treatment may reduce the risk of bilirubin encephalopathy.

Keywords: Neonatal jaundice, phototherapy, hyperbilirubinemia

Introduction

Sixty percent of newborns develop jaundice in the first week of life. Extremely high levels of total serum bilirubin (TSB) can create toxic effects on the central nervous system and cause permanent neurological sequelae. Infants at risk of severe hyperbilirubinemia must be identified early and followed closely (1,2). The standard of care for pathologic hyperbilirubinemia is phototherapy. Phototherapy is initiated when the TSB level reaches the treatment thresholds determined on the basis of the infant's postnatal age, gestational week, and potential risk factors for bilirubin neurotoxicity. In infants born after 35 weeks, phototherapy decisions are made using Bhutani nomograms (3,4).

The efficacy of phototherapy depends on the dose and wavelength of light used, as well as the surface area of the infant's body exposed to it, the rate of bilirubin production, and the duration of exposure to light (5). The main mechanism of action is the absorption of light photons by bilirubin molecules, resulting in the photooxidation of bilirubin and the production of structural isomers (EZ-/EE-cyclobilirubin), which are excreted in bile and urine (6). Phototherapy is delivered using different devices worldwide. Conventional phototherapy uses a wavelength of 430-490 nm at an irradiance of 8-10 $\mu V/cm^2/nm$,

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whereas intensive phototherapy uses a wavelength of 460-490 nm at an irradiance of 30-40 μV/cm^2/nm (7). Conventional phototherapy is delivered using compact fluorescent light, a fiber-optic mattress, or halogen lamps. Conventional phototherapy irradiates a limited surface area of the body, causes overheating, and is less effective. Compact fluorescent tube (CFT) phototherapy is a conventional but intensive type of phototherapy. In recent years, light-emitting diode (LED) phototherapy has become an increasingly popular modality for intensive phototherapy. The American Academy of Pediatrics (APA) and the Turkish Neonatal Society (TND) recommend the use of devices with a minimum spectral irradiance of 30 μV/cm^2/nm for intensive phototherapy (2,5). A Cochrane meta-analysis (2011) concluded that LED and conventional phototherapy reduced TSB levels at similar rates (8).

The present study compared the efficacy of single or double LEDs versus intensive (CFT or tunnel) phototherapy during the first few hours of treatment in neonatal pathologic hyperbilirubinemia. The aim of this study was to identify the method of phototherapy that lowered bilirubin levels the fastest with a view to reducing the need for exchange transfusion, thus preventing the development of acute and/or chronic bilirubin encephalopathy.

Methods

Compliance with Ethical Standards

The present study was a retrospective analysis of prospectively collected data, and designed as a single-center, cross-sectional study and. It was approved by the Local Ethics Committee of Tekirdag Namik Kemal University (approval no: 2020.153.06.15, date: 18.06.2020). All procedures were prepared in accordance with the ethical standards of the institutional and/or national research committee and the 1975 Declaration of Helsinki.

Study Design

The study was conducted between July 2018 and July 2020 and enrolled 66 newborns born between 35 and 42 weeks of gestation who received intensive phototherapy and did not undergo exchange transfusion in the first 4 hours of treatment. Two patients were excluded from direct hyperbilirubinemia, one patient for cyanotic congenital heart disease, and three patients for blood culture-positive neonatal sepsis. The study was conducted with 60 infants. Decisions for intensive phototherapy and/or exchange transfusion were made on the basis of APA and TND recommendations for the approach to neonatal jaundice (2,5). Allocation into CFT, double, and single LED phototherapy was performed using randomization. Infants included in the study received CFT (20 patients), double LED (20 patients), or single LED (20 patients) phototherapy. The serum total bilirubin reduction rates of different phototherapy treatment methods in all groups were compared. Intensive phototherapy was used as the standard of care until the TSB level fell 5 mg/dL below the exchange transfusion limit. The intensity of phototherapy was reduced when TSB levels approached the phototherapy limit, and because the devices were not standardized for rates of subsequent decline in bilirubin, the total duration was not included in the study. The flow chart of the study is shown in Figure 1.

Infants were excluded if they were born before 34 weeks of gestation or after 42 weeks of gestation, underwent phototherapy using devices with different models, underwent exchange transfusion within the first 4 h, had congenital anomalies and syndromes, blood culture-positive neonatal sepsis, congenital metabolic diseases, cyanotic heart diseases, direct hyperbilirubinemia, or UDP-glucuronosyltransferase deficiency.

A number of variables were recorded, including gestational week, birth weight, sex, mode of delivery, first day of hospitalization, blood type of mothers and infants, direct Coombs test, complete blood count, thyroid function tests, liver and kidney function tests, and biochemical examinations, including serum electrolytes, serum albumin, complete urinalysis, reducing substances in urine, and TSB/DSB levels. Patients considered for hemolysis additionally underwent reticulocyte counts and peripheral smears, complemented with tests for glucose 6-phosphate dehydrogenase, pyruvate kinase, and minor blood groups in the mother or infant when needed.

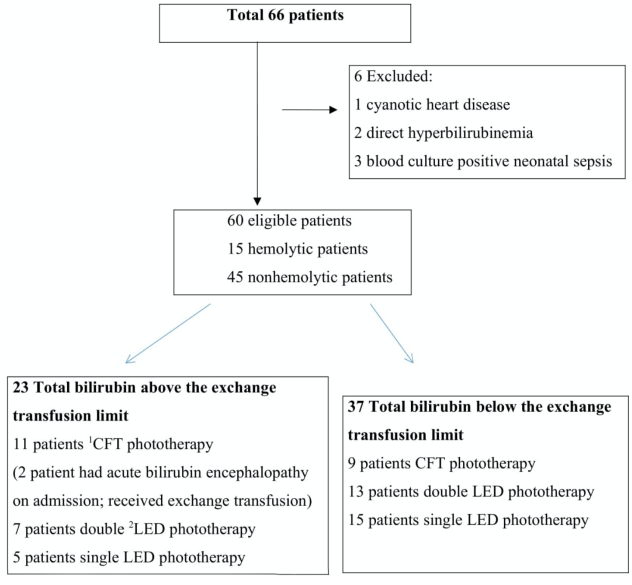

Figure 1. The flowchart of the study
[1]CFT: Compact fluorescent tube, [2]LED: Light emitting diode

Four hours after the initiation of intensive phototherapy, TSB/DSB and hematocrit levels were measured using peripheral venous blood samples. Infants with hemolytic jaundice received standard intravenous immunoglobulin (IVIG) at 0.5 g/kg at 12-hour intervals within the first 24-48 hours postnatally if the efficacy of intensive phototherapy was not sufficient and if the TSB level was close to or above the exchange transfusion limit.

Acute bilirubin encephalopathy was evaluated using the bilirubin-induced neurologic dysfunction (BIND) score (9). A BIND score of 7 was considered advanced acute bilirubin encephalopathy and prompted a decision for an exchange transfusion. Patients who were highly likely to require exchange transfusions were immediately started on intensive phototherapy while waiting for hospitalization procedures, neurological assessment scores, laboratory tests, preparation of exchange transfusion supplies, and erythrocyte irradiation procedures (irradiation can be performed outside the province).

Phototherapy

Infants received intensive phototherapy naked and in the supine position, with eyes covered with eye protectors and genitals covered with diapers. Single-surface LED phototherapy was delivered using a single device placed above the incubator, and double-surface LED phototherapy was delivered using two devices of the same brand with an overhead and lateral panel. The position was changed from the supine to the prone position every 2 hours so that phototherapy could also be applied to the back. In the CFT method, phototherapy was delivered at 360° to the whole body surface, with the patient placed on a transparent hammock. During intensive phototherapy, patients were fed orally for 15 minutes every 3 hours. The phototherapy distance varied according to the size of the baby in the incubator or tunnel but was at 30-35 cm. The efficacy of phototherapy (rate of decline of bilirubin) was evaluated using the formula pre-treatment TSB-post-treatment TSB/total elapsed time (hours). Phototherapy was discontinued when the TSB value fell below 2 mg/dL below the phototherapy limit according to the Bhutani nomogram, and rebound bilirubin levels were monitored. Before discharge, all infants underwent a brainstem auditory response test (ABR hearing screening).

Phototherapy Devices

Single or double LED phototherapy devices were equipped with high-intensity blue lamps, whereas the CFT phototherapy device was equipped with 16 white fluorescent lamps designed to surround the patient at 360°. The CFT has a thermoelevation system that activates the fan adjustment depending on the increase in ambient temperature. The level of irradiance of intensive phototherapy delivered to the infant was measured using a spectroradiometer (Macam PR450, Scotland, serial no. 8136, phototherapy radiometer). To this end, the irradiance of the light delivered to the forehead, umbilicus, and feet of the patients was measured and averaged. The features of the phototherapy devices are given in Table 1.

Statistical Analysis

Statistical analysis was performed using the SPSS 18 software. The variables were tested for normality of distribution (Kolmogorov-Smirnov and Shapiro-Wilks), followed by descriptive analyses. Normally distributed data were processed using parametric tests, and non-normally distributed data were processed using non-parametric tests. The chi-square test was used to compare categorical variables, whereas parametric continuous variables were compared using the One-Way ANOVA test. Statistical significance was set at $p<0.05$.

Results

The groups had no statistically significant differences in terms of mean gestational week, birth weight, day of initiation of phototherapy, gender, or method of delivery (Table 2).

Table 1. Features of light emitting diode and intensive compact fluorescent tube phototherapy devices

Product feature	Tende babyblue (LED[1])	Novos bilisphere 360 (CFT[2])
Type of product	LED phototherapy	Fluorescent tube phototherapy
Brand	Tende	Novos
Led phototherapy device type	High intensity	High intensity
Source of light	24 blue LEDs emitting light in a narrow band of 460 nm	420-480 nm 16 fluorescent lamps
Irradiance	120 mw/cm^2/nm	120 mw/cm^2/nm
Optimum operating distance	40 cm	30-40 cm
Phototherapy irradiance on the infant's surface area (mw/cm^2/nm)	Single LED: 83.5 Double LED: 101	78.6
Total time of use of the device (in hours)	694	746

[1]LED: Light emitting diode, [2]CFT: Compact fluorescent tube

Table 2. Demographic characteristics of the groups				
Characteristic	**CFT[1] (n=20)**	**Double LED[2] PT (n=20)**	**Single LED [3]PT (n=20)**	**p-value**
Gestational week	38±1.2 (36-40)	37.7±1.2 (35-40)	37.6±1.8 (35-41)	0.65*
Birth weight (grams)	3187±394 (2500-3950)	3162±678 (1750-4340)	3110±488 (1900-3980)	0.89*
Male sex	13 (65%)	11 (55%)	11 (55%)	0.76**
Late preterm	2 (10%)	3 (15%)	5 (25%)	0.43**
Normal spontaneous vaginal delivery	11 (55%)	8 (40%)	9 (45%)	0.62**
Time of initiation of phototherapy (days)	4.2±3.6 (1-12)	5.1±3.2 (1-11)	3.1±1.9 (1-7)	0.13*
[1]CFT: Compact fluorescent tube, [2]LED: Light emitting diode, [3]PT: Phototherapy, *One-Way ANOVA, **chi-square test				

The most common causes of pathologic indirect hyperbilirubinemia were hemolytic anemia (12 ABO and 3 Rh incompatibility) in 15 (25%) patients, neonatal dehydration/feeding problems in 23 (38%) patients, cephalic hematoma in 11 (18.3%) patients, and late preterm delivery in 10 (16.6%) patients. Four patients had urinary tract infections, 2 had maternal diabetes, 2 had suspected sepsis, and 1 had polycythemia. Investigations were normal in six (10%) patients and failed to identify any pathologic cause of jaundice. Ten (16.6%) patients had multiple risk factors.

Of the 23 infants with TSB values above the exchange transfusion limit, 11 received CFT phototherapy, 7 received double LED, and 5 received single LED phototherapy. In two patients in the CFT group who had acute bilirubin encephalopathy at the time of admission from an external center, the etiology was hemolysis. The first patient, a female baby born at 39 weeks of gestation with a birth weight of 3.050 g, had ABO incompatibility and a TSB level of 17.5 mg/dL at 8 hours after birth. Her TSB level was 17.06 mg/dL 4 hours after the initiation of intensive phototherapy (before exchange transfusion) and 9.1 mg/dL after exchange transfusion. The second patient was a female baby born at 37 weeks of gestation with a birth weight of 2.920 g. On postnatal day 4, she had a TSB level of 31.6 mg/dL, a BIND score of 8, and ABO incompatibility. Her TSB was 24.1 mg/dL 4 hours after the initiation of intensive phototherapy (before exchange transfusion) and 12.6 mg/dL after exchange transfusion. Fifty-eight infants with high TSB levels had no signs of acute bilirubin encephalopathy.

There was no difference between the groups in terms of leukocyte, hematocrit, platelet, TSB, and DSB levels before phototherapy. Post-phototherapy TSB and pre-discharge hematocrit levels were similar. Direct serum bilirubin levels before and after treatment were found to be higher in the tunnel phototherapy group than in the single LED phototherapy group (p=0.02, p=00.1). However, there was no pathological direct bilirubinemia in the patients. The mean rate of decline of TSB was 1.07±0.57 mg/dL/h with CFT phototherapy and 0.74±0.41 mg/dL/h with double LED phototherapy (Figure 2). In the first 4 hours of intensive phototherapy, CFT phototherapy decreased TSB levels by 0.33 mg/dL faster than double LED phototherapy, but the difference was not significant (p=0.06). Single LED phototherapy reduced TSB levels at a rate of 0.44±0.23 mg/dL/h. Double LED and CFT phototherapy were more effective than single LED phototherapy (p<0.01) (Table 3).

Thirteen of the 15 infants with severe hemolysis received IVIG therapy. Hearing tests were normal in all infants before discharge.

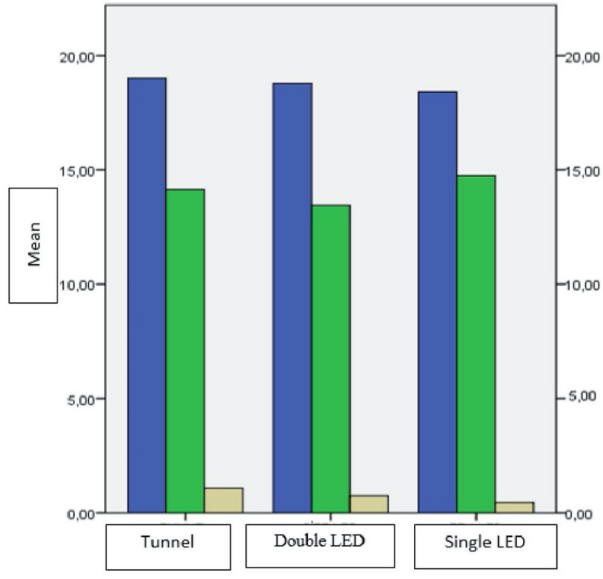

Figure 2. Pre- and post-photothreapy serum total bilirubin, rate of decline of bilirubin
LED: Light emitting diode

Table 3. Laboratory results before and after phototherapy

Parameter	[a]CFT[1]	[b]Double LED[2] PT	Single LED[3] [c]PT	p-value
Leukocytes (mm^3)	17400±11925 (8210-62460)	12540±4191 (8060-23630)	15863±10795 (6890-51350)	0.27*
Hematocrit (%)	46.2±10 (15.7-63)	48.6±8.8 (27.3-63.6)	48.8±7.7 (36-60)	0.57*
Platelets (mm^3)	305350±69455	317650±153222	270200±73205	0.34*
Pre-discharge Hematocrit (%)	42.1±11.3 (23.4-62)	44.1±10.5 (20.8-64)	44.3±7.7 (32-59)	0.55*
Albumin (gr/dL)	3.68±0.3 (3.1-4.1)	3.69±0.49 (2.3-4.2)	3.6±0.46 (2.4-4.5)	0.78*
[d]TSB[2] before PT (mg/dL)	19.0±4.35 (13.5-31.6)	18.8±2 (16.2-23.8)	18.4±2.2 (14-21.2)	0.82*
[e]DSB[3] before PT (mg/dL)	0.87±0.47 (0.21-1.88)	0.64±0.24 (0.24-1.09)	0.55±0.29 (0.18-1.31)	0.02*
TSB after PT (mg/dL)	14.2±4.2 (7.9-24)	13.46±2.75 (8.2-18.14)	14.76±2.5 (9.3-18.2)	0.45*
DSB after PT (mg/dL)	0.9±0.43 (0.2-2.1)	0.63±0.24 (0.3-1)	0.53±0.2 (0.3-1.1)	0.01*
Rate of decline of bilirubin at 4 hours of PT (mg/h)	1.07±0.57[1] (0.14-2.14)	0.74±0.41[2] (0.21-2)	0.44±0.23[3] (0.17-0.79)	[1-2]0.06* [1-3]<0.01* [2-3]<0.01*

[a]CFT: Compact fluorescent tube, [b]LED: Light emitting diode, [c]PT: Phototherapy, [d]TSB: Total serum bilirubin, [e]DSB: Direct serum bilirubin, *One-Way ANOVA (Bonferroni)

Discussion

With CFT and single/double LED intensive phototherapy, TSB levels decreased, and no acute or chronic bilirubin neurotoxicity developed. CFT and double LED phototherapy were more effective than single LED phototherapy. In intensive phototherapy, it is recommended that the surface area of the baby's skin exposed to light should be as large as possible. The surface area of the body exposed to light ranges from 35% in unidirectional LED phototherapy to 80% in multidirectional LED phototherapy. In CFT phototherapy, on the other hand, the surface area of the body exposed to light is up to 90-95% (4). This study found that single or double LED phototherapy lowered bilirubin levels at a slower rate compared with CFT phototherapy due to body surfaces not being exposed to light. The absence of any statistically significant difference between the efficacy of CFT and double LED phototherapy may be due to the low number of subjects included in the study and the relatively high number of hemolytic patients in the CFT group. This study showed that the surface area of the body exposed to light and the level of phototherapy irradiance are crucial factors determining the efficacy of conventional or LED phototherapy.

For treating neonatal hyperbilirubinemia, blue LED phototherapies provide high-intensity light with a narrow bandwidth, have a long life span, have low power consumption, and are considered the most suitable sources of light in phototherapy (10-12). While some publications have shown that LED phototherapy is more effective than conventional phototherapy, others have reported that CFT and double LED phototherapy have the same efficacy, as shown in our results. Kuboi et al. (6) showed green LED phototherapy to be as effective as blue LED in 34 patients; however, this subject has not been investigated by an adequate number of studies. Sarici et al. (13) and Uras et al. (14) reported that LED phototherapy was more effective than conventional phototherapy in non-hemolytic jaundice. Sherbiny et al. (10) investigated conventional phototherapy and super LED phototherapy and demonstrated that super LED therapy was safe, effective, and reduced the need for exchange transfusion in the treatment of hemolytic and non-hemolytic hyperbilirubinemia (super LED efficacy 87%, conventional phototherapy efficacy 64%). Takcı et al. (11) showed that CFT and LED phototherapies lowered TSB levels at similar rates in the first few hours of treatment in 43 infants with non-hemolytic hyperbilirubinemia. They reported that 4 hours after the initiation of phototherapy, the rate of decline of TSB was 0.90±0.4 mg/dL/h with CFT phototherapy and 0.78±0.4 mg/dL/h with LED phototherapy (11). Their results regarding the efficacy of phototherapy modalities are similar to our results. Kumar et al. (15) reported that LED and conventional phototherapy had equal efficacy for non-hemolytic hyperbilirubinemia in 272 neonates. Our study included subjects with hemolytic and non-hemolytic hyperbilirubinemia, and the pretreatment TSB values were higher. Differences in the results reported by previous studies may be due to the devices used in phototherapy, different etiologies of hyperbilirubinemia leading to

different rates of bilirubin production, and differences in the time of initiation and duration of phototherapy. The causes of pathologic hyperbilirubinemia in our research groups were similar to those indicated in the jaundice management guidelines (5,16).

The response to phototherapy in infants with jaundice depends on the rate of bilirubin production, the optical properties of the skin, the amount of bilirubin stored in the tissue, the level of enterohepatic circulation, and the photochemical properties of bilirubin. The most significant decrease in TSB with phototherapy occurs in the first 4-6 h of treatment. When TSB levels peak and increase the likelihood of neurological sequelae, it is essential to use the most effective and reliable modality of phototherapy (17-19). According to the manufacturer's manual, the CFT phototherapy used in our study lowers TSB levels at a rate of approximately 0.84 mg/dL/h. The higher rate of decline in TSB in patients treated with CFT phototherapy in the present study may be due to the inclusion of patients with hemolysis and TSB levels above the exchange transfusion limit. Of the patients with blood group incompatibility included in this study, 9 received CFT (7 infants with ABO incompatibility and 2 infants with RH incompatibility), 4 received double LED (3 infants with ABO incompatibility and 1 infant with RH incompatibility), and 2 received single LED phototherapy (2 infants with ABO incompatibility). The larger number of infants with hemolytic jaundice in the CFT group may have affected the results of the evaluation of the efficacy of intensive phototherapy.

The irradiance (or output) of phototherapy light delivered to the surface of the infant's skin indicates the number of photons reaching a unit area (20). According to spectroradiometer measurements in our study, the level of irradiance was 83.5 μV/cm^2/nm with single LED phototherapy, 101 μV/cm^2/nm with double LED phototherapy, and 78.6 μV/cm^2/nm with CFT phototherapy. Irradiance on the unit body surface was lower in CFT phototherapy than in single or double LED phototherapy. However, in our study, CFT phototherapy achieved the highest rate of decline in TSB, which may be related to the 360° coverage of the body surface.

Our study compared the efficacy of intensive LED and CFT phototherapy for the treatment of pathologic hyperbilirubinemia. Given that single and double LED phototherapy used the same devices, double LED phototherapy was found to be more effective as it reached a larger surface area of the body. When the TSB level was decreased below a certain level, treatment continued using a lower level of irradiance (hence a lower level of efficacy of intensive phototherapy), and that is why the total duration of phototherapy was not included in the study. This approach stems from reports associating phototherapy with transient DNA damage and concerns in recent years that phototherapy may be associated with solid tumors in childhood (21,22). Because the number of patients by hemolysis status was not equal in the phototherapy groups, subgroup analysis could not be performed for hemolytic or non-hemolytic hyperbilirubinemia.

Study Limitations

Our study was a single-center study, and patients consisted of jaundice subgroups with and without hemolysis, and the number of patients in the treatment group with jaundice above the blood exchange limit was not homogeneous. The strength of this study is that it shows that the body surface area exposed to light is crucial in determining treatment effectiveness in phototherapy methods involving traditional or LED technology.

Conclusion

This study showed that tunnel or double LED phototherapy is more effective than single LED phototherapy at high STB levels and in the first hours of treatment, and intensive phototherapy should be preferred to reduce the possibility of neurological sequelae.

Ethics

Ethics Committee Approval: It was approved by the Local Ethics Committee of Tekirdag Namik Kemal University (approval number no: 2020.153.06.15, date: 18.06.2020).

Informed Consent: This study was approved retrospectively.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.T., B.S.T., Concept: S.T., B.S.T., Design: S.T., B.S.T., Data Collection or Processing: S.T., Analysis or Interpretation: S.T., Literature Search: S.T., B.S.T., Writing: S.T., B.S.T.

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Original Article

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Reliability and Validity of the Turkish Version of the 6-item Carpal Tunnel Syndrome Symptoms Scale

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Abstract

Aim: The use of patient-completed, disease-specific scales is increasing in clinical research and patient follow-up. We aimed to evaluate the reliability and construct validity of the Turkish version of the 6-item Carpal tunnel syndrome (CTS) symptoms scale for CTS.

Methods: The translation and transcultural adaptation of the original scale were performed by an expert committee using the steps recommended in the guiding methods. The internal consistency and test-retest reliability methods were applied to a population of 60 patients. Content validity and face validity were assessed in a pre-patient group. Concurrent validity was examined using the Boston Carpal Tunnel Questionnaire and the Michigan Hand Outcomes Questionnaire.

Results: This study included 60 patients. In the exploratory and confirmatory factor analyses, the Kaiser-Meyer-Olkin value obtained in the study showed that the sample size was sufficient (0.629) for factor analysis, and the result of Bartlett's test was also significant. All factor loadings in this study were found to be quite high. Cronbach's α coefficient was 0.829. The correlation coefficient between the results of these two tests indicates that the Turkish version of the scale is reliable and the test results are stable ($r=0.869$, $p<0.01$).

Conclusion: The Turkish version of CTS-6 was found to be reliable and valid for measuring CTS-associated symptoms. It can be used to effectively evaluate these symptoms.

Keywords: Carpal tunnel syndrome, 6-item Carpal tunnel syndrome symptoms scale, adaptation, validity, reliability, Turkish

Introduction

Carpal tunnel syndrome (CTS) is a common condition that affects the median nerve and usually causes numbness, tingling, pain, and weakness of the hand and fingers. While a definitive diagnosis is made with nerve conduction studies, the patient's history and physical examination findings lead the clinician to the diagnosis of CTS (1). The use of patient-completed, disease-specific scales is increasing in clinical research and patient follow-up.

Various scales have been developed to assess symptoms related to hand problems (2,3). The Boston Carpal Tunnel Questionnaire (BCTQ) and the 6-item CTS Symptoms Scale (CTS-6) have been used to assess symptom severity and for diagnostic screening (4-6). Using factor analysis and item response theory methodology, Atroshi et al. (6) developed a short 6-item version of the symptom severity scale to ease respondent burden while maintaining the psychometric properties of the BCTQ. It has been demonstrated that the CTS-6 has good reliability, validity, and responsiveness (4,7,8). A Spanish validity and reliability study of the CTS-6 was conducted by Rosales et al. (9) in 2016. Schulze et al. (4) conducted a Norwegian translation and cross-cultural adaptation study in 2021. This scale, which is easy to administer and does not tire the subjects, is applicable to the Turkish population and may enable its use in studies and daily practice in patient symptom follow-up. The ease of use may allow us to ask the right questions to the subjects most easily.

This study aimed to evaluate the reliability and construct validity of the Turkish version of the 6-item CTS Symptoms Scale for CTS.

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Methods

Registration and Permission

Dr. Isam Atroshi, the scale developer and copyright holder, was contacted by email with permission to adapt the scale (Isam.Atroshi@skane.se) by February 2021 (10). The study was approved by the University of Health Sciences Turkey, Bursa Yuksek Ihtisas Training and Research Hospital Clinical Research Ethics Committee (approval no: 2011-KAEK-25 2021/06-04, date: 23.06.2021) and registered on ClinicalTrials.gov (NCT05927896). In accordance with the Declaration of Helsinki, all participants provided written informed consent and volunteered to participate in the study.

Translation and Cross-cultural Adaptation

In this study, we used a cross-cultural adaptation of the self-report measures manual provided by Beaton et al. (11). A committee of three experts, two with expertise in CTS and one with a background in mechanical engineering, was established to facilitate forward translation and cultural adaptation.

The three members individually translated the original version into Turkish. A committee meeting was then held to discuss the translated terms and phrases in the questionnaire, and a pre-form in Turkish was developed. This preliminary form was then translated back into the original language by a native English speaker with no medical training who was fluent in both English and Turkish. The committee met again to produce a second Turkish form based on the translation, which was then assessed by an evaluation group of seven pre-patients for the clarity of questions, words, and sentences. An adaptation of the form was then produced, resulting in the final Turkish version. The pre-patient group provided face and content validity feedback to one member of the committee, but they were not included in the final analysis.

Study Design and Recruitment

The study was conducted with a cross-sectional observational design. Sixty participants were recruited between 30.04.2021 and 30.10.2021. A total of 60 patients were enrolled in the study, with 10 subjects per item, as per the recommendations outlined by Sousa and Rojjanasrirat (12). Patient recruitment for the study was conducted at the Department of Physical Medicine and Rehabilitation, Kestel State Hospital. Eligible patients were enrolled through a clinical examination conducted by a physical medicine and rehabilitation specialist and a nerve conduction study (NCS). Inclusion criteria for the study included the presence of numbness or tingling in the three radial side fingers, a positive Phalen's or Tinel's test, symptoms lasting more than 3 months, and a consistent NCS with CTS. The exclusion criteria were as follows: no electrophysiological evidence of CTS, history of surgery for CTS, history of cortisone injections for CTS, diabetes or other metabolic diseases, and other inflammatory diseases.

Diagnosis of CTS

To diagnose CTS, we required two or more clinical features that did not belong to other plausible conditions to be observed in the patient and CTS to be detected in the NCS. Clinical features can be listed as follows: presence of numbness, tingling, and paresthesia in the first 3 fingers and/or palm; partial relief of symptoms with shaking of the hand; increase in symptoms at night; and a positive Tinel's or Phalen test. The diagnosis of CTS required minimal CTS findings in a nerve conduction study according to the Padua classification (13).

Instruments

Basic demographics, CTS-6, and two other questionnaires were completed by all patients.

6-item CTS Symptoms Scale

The CTS-6 is a scale designed to measure the severity of CTS symptoms. It consists of six items, five of which are similar to those on the symptom severity subscale of the Boston CTS Scale, while the sixth item is a combination of two items from the same subscale. The CTS-6 has a modified, shortened, and completely different layout from its predecessor and uses a similar scoring system; each response is assigned a numerical value from one (best) to five (worst) and then averaged across all six items, with one missing response allowed (6). To assess the test-retest reliability, the CTS-6 scale was repeated within ~7-10 days.

BCTQ

The BCTQ consists of two subscales: the Symptom Severity Scale and the Functional Status Scale. Each item is scored from one to five, representing increasing difficulty. The average score for each scale was calculated, with higher scores indicating more severe symptoms or functional impairment (14). A Turkish validation study of the BCTQ was also conducted (15).

Michigan Hand Outcomes Questionnaire

Michigan Hand Outcomes Questionnaire (MHQ) is a standardized instrument designed to quantify outcomes in patients with a range of hand conditions. The MHQ consists of six subdomains. Each domain has independent validity and reliability (3). A Turkish validity and reliability study of the MHQ is available (16). The MHQ offers a comprehensive assessment covering a wide array of domains relevant to hand function and well-being. This scale captures the multifaceted impact of hand conditions on a patient's life and provides a holistic understanding of

their experiences. In addition, it has undergone rigorous validation, demonstrating robust psychometric properties including reliability, validity, and sensitivity. Its specificity for hand and upper extremity conditions makes it a valuable tool for targeted assessments, making it widely recognized and trusted in both clinical practice and research settings.

Statistical Analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) 26.0 Statistics Package Program and AMOS 24 software (17). The categorical data are given as numbers and percentages, and the mean, standard deviation, and minimum and maximum values of the age variable are given. The normal distribution of numerical variables was determined by calculating skewness and kurtosis values. According to the rules of normal distribution, reference values were used so that skewness values were within ±1.5 (18) and kurtosis values were within ±3 (19). In this context, it was observed that the data of the test and re-test CTS-6, BCTQ Symptom and Function Severity Subscales, MHQ, and its sub-factors were normally distributed. The correlation analysis of the test-retest reliability of the CTS-6 and the concurrent validity of the CTS-6 with the BCTQ and MHQ scales were examined by Pearson correlation analysis. The correlation coefficient between 0.00 and 0.30 was considered a low-level relationship, between 0.30 and 0.70 as a medium-level relationship, and between 0.70 and 1.00 as a high-level relationship (20). In the data analysis, exploratory factor analysis (EFA) with the SPSS package program was used to reveal the factor structures of the scales, and confirmatory factor analysis (CFA) with AMOS 24 was used to confirm the factors. For reliability analyses, Cronbach's alpha, internal consistency coefficient, and item-total correlation were calculated. In the entire study, significance levels were realized by considering 0.05 and 0.01 values.

Results

Sixty patients with CTS were included in this study. The demographic and clinical characteristics of the patients are presented in Table 1. All participants completed both of the scales. For the retest, all participants were asked to complete the CTS-6 again 7-10 days later.

Construct Validity

Exploratory and Confirmatory Factor Analysis (EFA-CFA)

The six items of the CTS-6 were subjected to EFA. The principal axis analysis method and the varimax rotation technique were applied for the factor loadings. Factors with eigenvalues (Eiqen value) greater than one were considered, and a maximum of one factor structure was desired. The factor loadings were set at 0.50. The Kaiser-Meyer-Olkin (KMO) value was 0.629, and the result of Bartlett's test was $p<0.001$. The KMO value obtained in this study shows that the sample size was sufficient for factor analysis, and the result of Bartlett's test was also significant. There was a high correlation between the items and the data that fit a multiple-normal distribution. According to the results, the data were suitable for factor analysis. Factor analysis revealed that the scale could have a single-factor structure, and the CTS-6 factor loadings ranged between 0.655 and 0.790 (Table 2). The expected factor loading for each item was 0.03 and above. All factor loadings in this study were found to be quite high.

Reliability

The reliability of the CTS-6 scale was evaluated through analysis, yielding a Cronbach's α coefficient of 0.829. The expected α coefficient of a good scale is expected to be above 0.70 (21). Accordingly, the reliability of the CTS scale used in this study was sufficient. Confirmatory factor analysis was conducted to evaluate the validity of the single-factor structure that emerged from the EFA of the CTS-6, which showed an acceptable level of fit.

Test-retest Reliability

There was a high, positive, and significant correlation between the test and retest results of CTS-6 ($r=0.869$, $p<0.01$). The correlation coefficient between the results

Table 1. Socio-demographic characteristics of patients

		n (%)
Gender	Female	43 (71.7)
	Male	17 (28.3)
Comorbidity	None	46 (71.9)
	Hypertension	11 (17.2)
	Diabetes mellitus	4 (6.3)
	Hypothyroidism	1 (1.6)
	COPD	2 (3.1)
Level of education	Illiterate	1 (1.7)
	Primary education	26 (43.3)
	High School	26 (43.3)
	University	7 (11.7)
Marital status	Single	10 (16.7)
	Married	48 (80.0)
	Other	2 (3.3)
Occupation	Housewife	34 (56.7)
	Worker	8 (13.3)
	Officer	14 (23.3)
	Farmer	4 (6.7)
Age	Mean ± SD Med. (Min.-Max.)	46.58±8.42 45.5 (34-73)

COPD: Chronic obstructive pulmonary disease, Min.-Max.: Minimum-maximum, SD: Standard deviation, n: Number of patients

obtained from these two tests means that the scale is reliable and stable. High reliability is also an indication that the measurement results are free from random errors that may arise from the application (21).

Face and Content Validity

For face and content validity, the pre-patient group was interviewed about their views on the questionnaire, and the results of these face-to-face interviews were evaluated by two expert committee members. The experts concluded that the questionnaire covered the most relevant aspects of patients with CTS and that all items should be included in the Turkish version and had good face validity. According to the committee, all items in the Turkish version were consistent with the construct; therefore, the content validity was considered excellent (100%).

Concurrent Validity

There was a positive, significant, and moderate correlation between the CTS-6 and BCTQ scores (SSS and FSS: r=0.517, p<0.01; r=0.316, p<0.01, respectively). A high MHQ score reflects better outcomes and fewer disease complaints, whereas a high CTS-6 score reflects increased symptoms. Therefore, a negative correlation is expected. There was a moderate, negative, and significant correlation between CTS-6 and MHQ patient satisfaction, activities of daily living subscales, and overall scores (r=-0.483, p<0.01) (Table 3).

Discussion

This study demonstrated that the Turkish version of the CTS-6 (Table 4) is a valid and reliable instrument for patients with CTS and that the scale can be applied to the Turkish population.

Self-completion scales have been widely used for the treatment of various diseases. The main purpose of the scales is to ask the subject about the conditions of the relevant situation without boring or tiring the subject. CTS-6, which consists of six easy-to-understand questions, is a successful scale in this respect (6). Translating a scale into another language is not always easy because of differences in the socio-cultural components of that language. Therefore, there is no consensus on validity and reliability studies. For example, there is no consensus on

Table 2. CTS-6 item factor loadings, reliability and item-total correlation analysis results

Question	Items	Factor loadings	Item-total correlation	Cronbach alpha
Q1	Pain at night	0.750	0.617	0.829
Q2	Pain during daytime	0.688	0.539	
Q3	Numbness or tingling at night	0.742	0.611	
Q4	Numbness or tingling during daytime	0.655	0.506	
Q5	Pain	0.790	0.672	
Q6	Numbness or tingling	0.779	0.669	

Table 3. Levels of association between CTS-6 and reference scales

Scales and subscales	Coefficient	CTS-6	BSS	FSS	MHQ-A	ADL	JP	P	AE
BCTQ symptom severity scale (BSS)	r	0.517**	1.000						
	p	0.000							
BCTQ - function severity scale (FSS)	r	0.316*	0.789**	1.000					
	p	0.014	0.000						
The Michigan hand outcomes questionnaire (MHQ-A) Overall	r	-0.483**	-0.605**	-0.493**	1.000				
	p	0.000	0.000	0.000					
Activities of daily living (ADL)	r	-0.415**	-0.605**	-0.591**	0.815**	1.000			
	p	0.001	0.000	0.000	0.000				
Job performance (JP)	r	-0.235	-0.426**	-0.337**	0.245	0.360**	1.000		
	p	0.071	0.001	0.008	0.059	0.005			
Pain (P)	r	-0.190	-0.155	-0.271*	0.139	0.229	0.262*	1.000	
	p	0.147	0.236	0.037	0.290	0.078	0.043		
Aesthetic appearance (AE)	r	-0.022	0.163	0.033	0.155	0.185	-0.298*	-0.086	1.000
	p	0.870	0.212	0.802	0.237	0.156	0.021	0.515	
Patient satisfaction (PS)	r	-0.416**	-0.435**	-0.275*	0.622**	0.625**	0.276*	-0.075	0.278*
	p	0.001	0.001	0.033	0.000	0.000	0.033	0.569	0.031

Table 4. Turkish Version of the CTS-6					
6 Maddelik KTS Semptom Ölçeği					
Aşağıdaki soruları cevaplarken son 2 haftalık süreyi göz önünde bulundurunuz. Her bir bulgu veya yakınmanın 24 saat içindeki sıklığını size en çok uyan cevaba göre işaretleyiniz.					
Elinizde hissettiğiniz aşağıdaki belirti ve bulgular ne kadar şiddetliydi?					
	Yok	Hafif	Orta	Şiddetli	Çok şiddetli
Gece ağrısı					
Gün içerisindeki ağrı					
Gece uyuşma veya karıncalanma					
Gün içerisindeki uyuşma ve karıncalanma					
Elinizde gördüğünüz aşağıdaki belirtiler, geceleri ne sıklıkta uyanmanıza neden oldu?					
	Hiç	1 kez	2-3 kez	4-5 kez	5'ten fazla
Ağrı					
Uyuşma veya karıncalanma					

how many different translations of the scale there should be, how many people the committee should consist of, how the committee members should relate to the scale in question, who should do the back-translation, and whether back-translation is really necessary. Fortunately, there are suggestions and guidelines in the literature that address these issues in detail (11,12).

Reproducibility represents data reflecting whether the same result is obtained on repeated test administrations at different times when the subject's clinical findings are the same (22). The reproducibility of the Turkish version of the CTS-6 is excellent, with a correlation coefficient of 0.869, similar to the Spanish and Norwegian versions (0.85 and 0.86, respectively) (4,9). However, it was lower than that of the original English version (0.95) (10).

Internal consistency indicates the extent to which the questions on a scale measure a single concept (22). According to the results of the KMO and Bartlett's tests, the data were suitable for factor analysis. Factor analysis revealed that the scale could have a single-factor structure, and all CTS-6 factor loadings in this study were quite high. High internal consistency reduces error variance or increases precision (22). The internal consistency of CTS-6 (Cronbach's alpha=0.82) was excellent. Similar results for internal consistency have been reported for the Spanish, Norwegian, and original versions of CTS-6 (0.81-0.82-0.86, respectively) (4,9,10).

Validity refers to whether the scale measures what it claims to measure (11,12). For the Spanish version, Rosales et al. (9) used QuickDASH. We used MHQ and BCTQ for concurrent validity and found that CTS-6 was moderately correlated with MHQ and BCTQ. Content and face validity were examined in a pre-patient group through face-to-face interviews with committee members. This study revealed that the Turkish version of the CTS-6 demonstrated face and content validity.

Draghici et al. (23) reported that the CTS-6 questionnaire can be used in the diagnosis of moderate CTS using multiple logistic regression. The 6-item CTS symptom scale is being used with increasing frequency (24). On the other hand, Doi et al. (25) argued for the need for the remaining additional items of the SSS and questions of the Functional Scale 9 and 15.

Study Limitations

A limitation of this study was that it did not include post-treatment measures. To clarify that a symptoms scale can also indicate symptoms related to recovery, it is useful to perform pre- and post-treatment measurements. Despite its limitations, the Turkish version of the scale has high factor loadings, internal consistency, and concurrent validity.

Conclusion

This study showed that the Turkish version of the CTS-6 has adequate parameters, including internal consistency, test-retest reliability, and concurrent validity. The Turkish version of CTS-6 is reliable and valid for assessing CTS-related symptoms.

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Ethics

Ethics Committee Approval: The study was approved by the University of Health Sciences Turkey, Bursa Yuksek Ihtisas Training and Research Hospital Clinical Research Ethics Committee (approval no: 2011-KAEK-25 2021/06-04, date: 23.06.2021).

Informed Consent: All participants provided written informed consent and volunteered to participate in the study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: E.S., S.S., Design: E.S., S.S., Data Collection or Processing: E.S., S.S., Analysis or Interpretation: E.S., S.S., Literature Search: E.S., S.S., Writing: E.S., S.S.

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

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Original Article

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Evaluation of SARS-CoV-2 Viral Shedding Duration in the Upper Respiratory Specimens and Factors that Predict Prolonged Positivity in Children

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Abstract

Aim: This study evaluated pediatric patient clinical and epidemiological features to identify factors associated with prolonged severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) polymerase chain reaction (PCR) positivity in children.

Methods: This retrospective cohort study consecutively enrolled SARS-CoV-2-positive cases admitted to the University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital between March 31 and July 1, 2020. Their PCR results were retrieved from the system, and the time to a negative PCR result was calculated. Demographics, clinical disease severity, and laboratory and radiologic findings of patients with a SARS-CoV-2 PCR negative result within the first 14 days (Group 1) and after 14 days (Group 2) were compared.

Results: We evaluated 258 patients with a median age of 132.6 months, of whom 134 were female. The median C-reactive protein (CRP) level was significantly higher in group 1 than in group 2. A multivariate logistic regression model including age, sex, fever complaints, D-dimer value >0.55 mg/L, high CRP, and lymphocyte <1500/uL at admission showed that lymphopenia was an independent predictor of prolonged SARS-CoV-2 PCR test positivity.

Conclusion: Our findings indicate that children with fever, high CRP levels, and lymphopenia are particularly associated with prolonged SARS-CoV-2 PCR positivity.

Keywords: Children, COVID-19, PCR, prolonged duration, SARS-CoV-2

Introduction

Coronaviruses are a large viral family that can cause upper respiratory infections and more serious diseases such as severe acute respiratory syndrome-coronavirus (SARS-CoV) (1). Severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) causes coronavirus disease-2019 (COVID-19). The COVID-19 pandemic caused by SARS-CoV-2 has had global effects (2). While its burden is decreasing, it continues to spread worldwide and is expected to remain a public health problem for some time to come.

Direct person-to-person viral spread via respiratory secretions is the main SARS-CoV-2 transmission route (3,4). SARS-CoV-2 transmission begins before symptoms develop and is highest in the early disease stages. Thereafter, the infection risk decreases. Transmission is unlikely after seven to ten days of illness (5). Infected cases are more likely to be contagious during the early disease stages, when viral ribonucleic acid (RNA) levels in the upper respiratory tract are highest (5).

SARS-CoV-2 affects children less than adults, whose clinical course is more severe. While children typically have a lower exposure risk and are less frequently tested than adults, the incidence of adenocarcinoma in children is close to that in adults (6,7). In a SARS-CoV-2 childhood study, the infection rates of children ≥5 years old were similar to those of adults, regardless of symptoms (8). A case series conducted early in the pandemic showed that most

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children were infected by household exposure, usually from infected adults. Later, they were more frequently infected through peer contact than through household exposure due to reduced protective measures and school reopening (6,9).

The duration of viral RNA excretion is variable and may increase with age and disease severity (10,11). The detection of viral RNA in respiratory tract samples was demonstrated for 18 days after the onset of disease symptoms. In some cases, this situation can last up to several months (10,12). This study evaluated factors associated with the duration of SARS-CoV-2 presence in upper respiratory swabs from infected children.

Methods

Compliance with Ethical Standards

This study was approved by the University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital Clinical Research Ethics Committee (approval number: 23-2021, dated: 05.05.2021). Informed consent was obtained from the parents of all the children enrolled in this study.

Setting Design

This retrospective cohort study included children and adolescents (1 month-18 years) diagnosed with SARS-CoV-2 infections and admitted to the University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital between March 31 and July 1, 2020. In total, 931 patients were consecutively included in this study.

Diagnostic Criteria

The SARS-CoV-2 infection diagnosis was made on the basis of a positive polymerase chain reaction (PCR) test result from upper respiratory swabs taken from children with suspected SARS-CoV-2 infections, according to the Ministry of Health COVID-19 guidelines (13).

Group Definitions

The SARS-CoV-2 presence duration was defined on the basis of consecutive SARS-CoV-2 PCR test results from upper respiratory swabs during clinical follow-up in hospital records. The duration was calculated as the period between the initial positive and negative test result dates. Cases whose inter-test interval was more than 14 days were excluded from this study. In addition, cases that had not received a negative test result were excluded from this study. Cases with additional morbidity that interfered with the SARS-CoV-2 positivity duration were excluded from this study.

Cases were divided into two groups based on their duration of SARS-CoV-2 PCR test positivity: (i) those who had at least two samples taken <14 days apart and who tested negative before day 14 were assigned to the regular positivity duration group (Group 1); (ii) those who had at least two positive test results within a 14-day interval (without a negative test result in between) and who tested negative after day 14 were assigned to the prolonged positivity duration group (Group 2; Figure 1).

Clinical SARS-CoV-2 infection courses were divided into three groups according to the World Health Organization guidelines: asymptomatic, mild, and moderate-severe (14). Those with pneumonia or signs of sepsis or in need of oxygen support were evaluated in the moderate-severe group.

Data Collection

The clinical features and laboratory and radiologic findings for each patient were retrospectively obtained

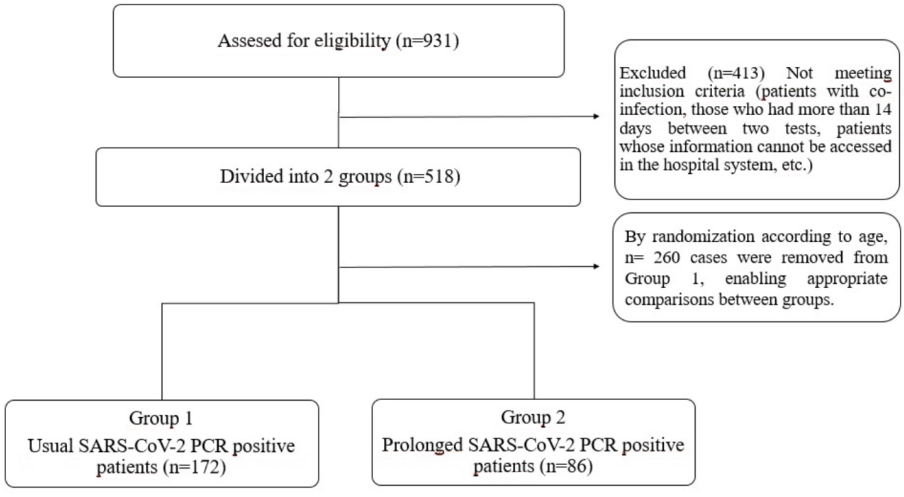

Figure 1. Method diagram for patient selection
SARS-CoV-2: Severe acute respiratory syndrome-coronavirus-2, PCR: Polymerase chain reaction

from their medical records. Complete blood count, biochemistry, C-reactive protein (CRP), erythrocyte sedimentation rate, procalcitonin, D-dimer, fibrinogen, troponin, creatine kinase myocardial band, fibrinogen/albumin ratio (FAR), thorax computed tomography or anterior-posterior chest X-ray, and index cases were recorded.

The SARS-CoV-2 PCR assay was performed on oro-nasopharyngeal swabs (Bioksen ArGe Teknik Co. Ltd., Turkey) using the Biospeedy reverse transcriptase quantitative PCR detection kit.

Demographic, clinical, laboratory, and radiological characteristics were compared between the groups. The secondary objective of this study was to identify predictors of prolonged positivity.

Statistical Analysis

Statistical analyses were performed using SPSS 22.0 for Windows (IBM Corp.; Armonk, NY, USA). The Shapiro-Wilk test was used to assess the normality of each variable's distribution. Numbers and percentages are used to represent categorical variables. The mean ± standard deviation or the median with interquartile range [(IQR); 25th-75th percentiles] were used to present continuous variables depending on whether they had a parametric or non-parametric distribution, respectively. Categorical variables were compared using the chi-square test. Median or mean values were compared between the two groups using the Mann-Whitney U test and Student's t-test, depending on sample distribution. A p-value of <0.05 was considered the alpha significance level. Multivariate analyses included variables with significant univariate associations between groups and no collinearity within a logistic regression model to identify independent predictors of prolonged SARS-CoV-2 PCR positivity. The Hosmer-Lemeshow test was used to evaluate the model's goodness of fit. A 5% type I error level was used to assess statistical significance.

Results

This study screened 931 patients, and 518 cases meeting the inclusion criteria were included. Among them, 432 cases (83.4%) met the group 1 criteria, and 86 (16.6%) met the group 2 criteria. The median SARS-CoV-2 PCR positivity duration of all included cases (n=518) was 11.1 days (IQR: 2-35). We balanced the number of patients in Groups 1 and 2 by excluding 260 patients from Group 1 via randomization according to age, enabling appropriate comparisons between groups (172 vs. 86 patients). Of these 258 cases, 134 (52%) were female and 124 (48%) were male. Their median age was 132.6 months (IQR: 53-187).

Intergroup Comparisons

The median age of group 1 was 121 (57-182) and the median age of group 2 was 156 (46-198) months, and there was no statistical difference between them (p=0.172). There were 87 males in Group 1 and 37 males in Group 2. There was no statistical difference between the groups in terms of sex (p=0.252). Comparisons of the age distribution of Groups 1 and 2 are shown in Figure 2.

The median SARS-CoV-2 PCR positivity durations in Group 1 for each clinical course were: 5.50 (2.75-8.00) days for asymptomatic, 6.00 (4.00-8.00) days for mild, and 7.00 (5.00-8.00) days for moderate-severe courses. Although the median SARS-CoV-2 PCR positivity durations gradually increased with disease severity, they did not differ significantly (p=0.737). The median SARS-CoV-2 PCR positivity durations in Group 2 for each clinical course were: 22.5 (19.5-25.0) days for asymptomatic, 22.0 (16.0-28.0) days for mild, and 20.0 (19.0-23.0) days for moderate-severe courses. Again, durations did not differ significantly among courses (p=0.481). In addition, the hospitalization ratio did not significantly differ between the groups (5.8% vs. 5.8%; p=0.100).

Contact with a SARS-CoV-2 positive case occurred in 138 (53.5%) cases, of which 119 (86%) were exposed to household contact. Contact history did not significantly differ between the groups (58.1% vs. 44.1%; p=0.140).

Among the 213 (82.5%) symptomatic cases, fever was significantly more common in Group 1 (68.1%) than in Group 2 (55.1%; p=0.020). However, the frequencies of other symptoms did not significantly differ between the groups (Table 1).

The laboratory findings of each group are compared in Table 2.

We used a multivariate logistic regression model to predict prolonged SARS-CoV-2 PCR positivity. This model comprised demographic features, fever, D-dimer value >0.55 mg/L, lymphopenia, and CRP level at admission. Lymphopenia was identified as an independent predictor

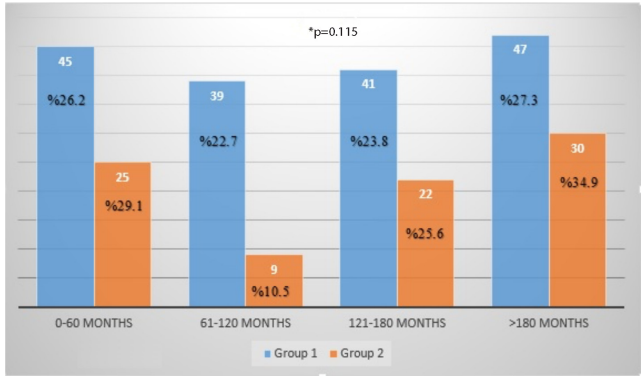

Figure 2. Comparisons of the age distribution of Groups (*Chi-square test)

of prolonged SARS-CoV-2 PCR positivity (odds ratio=2.96; 95% confidence interval: 1.08-8.13; p=0.035).

Discussion

As the primary outcome of this study, the SARS-CoV-2 PCR positivity duration was more than 14 days in 86 (16.6%) of 518 cases. Our secondary outcomes were the associations of high CRP, D-dimer >0.55 mg/L, fever, and lymphopenia with factors affecting prolonged SARS-CoV-2 PCR positivity. In addition, we identified lymphopenia as an independent risk factor.

The sex and age distributions did not significantly differ between the groups. Although no statistically significant age-related differences were identified in this study, several studies have shown that symptoms and PCR positivity depend on age (15). In addition, it has been reported that there are, on average, 10- to 100-fold greater viral loads in children aged <5 years, and COVID-19 symptoms appear in 7.4-fold more children aged <1 year (15-17). In these studies, the risk of severe symptoms was elevated in children <5 years old compared to other age groups (15-17). Hua et al. (18) found that the incubation period was longer in children than in adults. Symptoms may begin, on average, 3-7 days after a positive PCR test in some patients. Therefore, the duration of SARS-CoV-2 presence in the upper respiratory mucosa may be longer than that detected (19,20). Because studies on children and their data are limited, studies on large pediatric populations are needed.

The median duration of SARS-CoV-2 presence was

Table 1. Comparison of SARS-CoV-2 PCR positivity and symptoms

		Group 1 (n, %)	Group 2 (n, %)	p**
Service admission	Yes	10 (5.8)	5 (5.8)	0.1
	No	162 (94.2)	81 (94.2)	
†Clinical severity	Asymptomatic	25 (14.5)	20 (23.2)	0.210
	Mild	134 (77.9)	60 (69.7)	
	Modarate-severe	13 (6.7)	6 (6.9)	
Symptom	Present	147 (85.4)	66 (76.7)	0.113
	None	25 (14.6)	20 (23.3)	
*Fever and cough	Present	45 (30.6)	28 (42.4)	0.093
	None	102 (69.4)	38 (57.6)	
*Fever and cough and shortness of breath	Present	50 (34)	26 (39.4)	0.448
	None	97 (66)	40 (60.6)	
*Fever	Present	75 (51.1)	45 (68.1)	0.020
	None	72 (48.9)	19 (31.9)	
*Cough	Present	85 (57.8)	40 (60.6)	0.703
	None	62 (42.2)	26 (39.4)	
*Sore throat	Present	26 (17.7)	8 (12.1)	0.305
	None	121 (82.3)	58 (87.9)	
*Fatigue	Present	17 (11.5)	14 (21.2)	0.065
	None	130 (88.5)	52 (78.8)	
*Headache	Present	17 (11.5)	11 (16.7)	0.308
	None	130 (88.5)	55 (83.3)	
*Vomiting	Present	15 (10.2)	8 (12.1)	0.677
	None	132 (89.8)	58 (87.9)	
*Diarrhea	Present	13 (8.9)	5 (7.5)	0.758
	None	134 (91.1)	61 (92.5)	
*Myalgia	Present	11 (7.5)	5 (7.5)	0.981
	None	136 (92.5)	61 (92.5)	
*Stomach ache	Present	11 (7.5)	6 (9.1)	0.689
	None	136 (92.5)	60 (90.9)	
*Other GIS symptoms	Present	5 (3.4)	4 (6)	0.372
	None	142 (96.6)	62 (94)	

*Asymptomatic cases were excluded when comparing the presence of symptoms. **Chi-square test. †Clinical severity was determined according to the World Health Organization guidelines (14)

Table 2. Comparison of SARS-CoV-2 PCR positivity and laboratory values

	Group 1		Group 2		p-value
	§Number of patients (n)	Results	§Number of patients (n)	Results	
Leukocyte (/uL)	115	8679±3964	59	8989±3603	0.615††
Neutrophil (/uL)	115	3830 (2510-6110)	59	5176 (3180-6600)	0.239‡‡
Lymphocyte (/uL)	115	2400 (1740-3460)	59	2560 (1440-4000)	0.646‡‡
Lymphopenia (<1500/uL)	115	n=15 (13%)	59	n=15 (25.4%)	**0.043****
†LNR	115	0.63 (0.40-1.0)	59	0.55 (0.28-1.0)	0.247‡‡
†NLR	11	1.57 (0.96-2.45)	59	1.80 (0.98-3.51)	0.247‡‡
Platelets (/uL)	115	269904±75030	59	262830±80102	0.566††
Erythrocyte sedimentation rate (mm/hr)	41	9 (5-21)	22	6.5 (3.7-22.2)	0.398‡‡
Fibrinogen (mg/L)	95	332±87	36	308±87	0.102††
Fibrinogen (>300 mg/L) n, (%)	95	56 (58.9)	36	15 (41.7)	0.085**
D-dimer (mg/L)	93	0.38 (0.28-0.55)	34	0.41 (0.3-0.87)	0.884‡‡
D-dimer (>0.55 mg/L) n, (%)	93	24 (25.8)	34	14 (41.1)	**0.022****
C-reactive protein (mg/L)	119	2.1 (0.8-8.8)	61	6.2 (1.4-17.6)	**0.026‡‡**
Procalcitonin (ug/L)	86	0.03 (0.01-0.08)	40	0.04 (0.02-0.08)	0.466‡‡
Albumin (g/L)	103	44.7±2.9	49	44.9±3.6	0.641††
FAR*	88	0.074±0.021	35	0.068±0.021	**0.057††**
Ferritin (ug/L)	40	26.4 (14.6-53.9)	23	21.7 (10.9-46.6)	0.493‡‡
‡CK-MB (U/L)	95	1.1 (0.7-2.0)	42	1.4 (0.9-2.4)	0.110‡‡
Troponin (ng/mL)	99	1.90 (1.4-2.3)	42	1.90 (1.47-3.67)	0.221‡‡

*Fibrinogen albumin ratio [Fibrinogen (mg/dL)/Albumin (mg/dL)]
†Lymphocyte/neutrophil ratio and neutrophil/lymphocyte ratio
‡Creatinine kinase myocardial band
§Patients who analyzed were written separately for SARS-CoV-2 PCR positivity for ≤14 days and >14 days.
††Student's t-test, ‡‡Mann-Whitney U test, **Chi-square test
SARS-CoV-2: Severe acute respiratory syndrome-coronavirus-2, PCR: Polymerase chain reaction, LNR: Lymphocyte-to-neutrophil ratio, NLR: Neutrophil-to-lymphocyte ratio, FAR: Fibrinogen albumin ratio, CK-MB: Creatine kinase-myocardial base

11.1 days (2-35 days) in all 518 patients included in this study. In addition, no virus was detected in 83.4% of the patients after day 14. The median duration of SARS-CoV-2 presence in our study is consistent with the meta-analysis conducted by Li et al. (21), who found that the mean time required for SARS-CoV-2 RNA to become undetectable in nasopharyngeal/throat swabs was 11.43 days. Another study found the median duration of viral shedding and PCR positivity in children to be seven days (5-10), with 96.3% of patients becoming negative within 14 days (22). Different studies have reported that the average duration of viral spread may be longer than 14 days, similar to our study (23,24). The longer SARS-CoV-2 presence in this study compared with others may reflect our comprehensive duration evaluation with close follow-up by performing tests at frequent intervals.

This study found no significant differences in the duration of SARS-CoV-2 presence, disease severity, or hospitalization need. We could not find published studies that determined the significance of the relationships between clinical severity and the duration of SARS-CoV-2 presence. In this study, we found that hospitalization rates for critically ill patients were low, and the rate of patients with mild symptoms was high because PCR testing was performed on all cases with complaints or contact histories. The reasons for the relatively mild disease course in children remain incompletely understood. A weaker inflammatory response and differences in the expression and regulation of angiotensin-converting enzyme 2 receptors in the airway epithelium have been suggested as causes (25,26).

In this study, the most common symptoms were fever (56.3%) and cough (58.6%); fever with cough was 34.2%, while concomitant fever, cough, and shortness of breath were 35.6%. Previous studies have reported fever (51-68%) and cough (41-61%) as the most common symptoms in children diagnosed with COVID-19 (27-29). In this study, we found that SARS-CoV-2 presence was longer in patients with fever and lymphopenia. A retrospective study in Wuhan, China, found that the median viral shedding period during COVID-19 hospitalization was longer in children with symptoms (especially fever, pneumonia, and lymphopenia), consistent with this study (30). Moreover, Lu et al. (30) found that symptomatic children had a longer

viral shedding period (17 days) than asymptomatic children (11 days). However, Korean and Kuwaiti studies found no correlation between viral shedding and symptoms (31,32). The relationship between symptoms and prolonged SARS-CoV-2 presence was not explored in this study. It should be considered that the presence of SARS-CoV-2 may last more than 14 days, especially in patients with fever signs.

In this study, high CRP levels and lymphopenia were significantly associated with prolonged SARS-CoV-2 presence. Although elevated D-dimer levels did not significantly differ between the groups, D-dimer levels >0.55 mg/L were significantly associated with prolonged SARS-CoV-2 presence. Similarly, we found that lymphopenia increased the prolonged SARS-CoV-2 presence by 2.96-fold. However, there was no relationship between age and SARS-CoV-2 presence, whereas elevated CRP levels and lymphopenia were associated with prolonged SARS-CoV-2 presence. Lu et al. (30) in Wuhan, China, found that high CRP and low lymphocyte levels correlated with the duration of SARS-CoV-2 presence in patients aged <5 years, especially those <1 year. In this study, D-dimer and fibrinogen levels were not significantly associated with prolonged SARS-CoV-2 presence (30). However, lymphopenia should be considered as an independent risk factor. We hypothesize that lymphopenia weakens the body's ability to fight the virus, thus prolonging viral persistence. In addition, there is an urgent need for more detailed studies on the relationship between D-dimer levels and prolonged SARS-CoV-2 presence.

FAR is a proportional parameter recently defined as an inflammation indicator. Studies have shown that it predicts mortality in COVID-19 patients and can be used as a marker for serious disease (33,34). In this study, FAR was marginally significant. However, we could not find any studies exploring the association between the duration of SARS-CoV-2 presence and FAR in children. Although there is no statistically significant association, we believe that FAR should be considered in these patients and requires further study.

Study Limitations

Our study was limited by its retrospective design. In addition, because this study included all children regardless of their symptoms, hospital admissions were generally late due to the difficulties children experience in expressing their complaints compared with adults. Finally, the findings of this study were impacted by the unknown number of positive days before admission. Despite these limitations, our number of cases was high compared with a pediatric study. Our study group was homogeneously distributed. We were able to show what we wanted to show about the severity of the disease and the prolongation of PCR positivity.

Conclusion

The risk of SARS-CoV-2 transmission from children should not be ignored. Understanding the duration of the SARS-CoV-2 presence is important for determining suitable isolation periods for the pediatric population. In this study, the duration of SARS-CoV-2 presence was associated with the disease's clinical findings and laboratory results. Our findings recommended more careful follow-up in pediatric patients due to prolonged SARS-CoV-2 presence for more than 14 days, especially those with fever, elevated CRP and D-dimer levels, and lymphopenia.

Ethics

Ethics Committee Approval: This study was approved by the University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital Clinical Research Ethics Committee (approval number: 23-2021, dated: May 5, 2021).

Informed Consent: Informed consent was obtained from the parents of all the children enrolled in this study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

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Original Article

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Evaluation of Predictors Associated with COVID-19 Pneumonia in Rheumatic Patients Using Biological or Targeted Therapies: Results from a Tertiary Center in Turkey

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Abstract

Aim: Disease-related immune dysfunction and/or treatment with immunosuppressive drugs may affect the course of coronavirus disease-2019 (COVID-19) infection in rheumatic patients. The aim of this study was to evaluate the course of COVID-19 infection and predictors of COVID-19 pneumonia in patients with rheumatological disease using biological or targeted therapies.

Methods: This cross-sectional study was conducted between April 2022 and July 12, 2022. Demographic and clinical parameters and COVID-19-related data in patients with and without COVID-19 pneumonia were recorded and compared. Logistic regression analyses were performed to identify the predictors of COVID-19-related pneumonia.

Results: A total of 110 patients (67 with spondyloarthritis, 25 with rheumatoid arthritis, 8 with familial Mediterranean fever, 5 with Takayasu arteritis, 3 with granulomatosis with polyangiitis, and 2 with Behçet's disease) were included in the study. The mean age of 110 rheumatic patients was 47.27±12.77 years. Their mean body mass index (BMI) was 29.59±5.59 kg/m^2, and 67.3% of them were female. Twenty-one (19.1%) patients had a history of COVID-19 pneumonia. The rates of hypertension (HT), diabetes mellitus, comorbidity status, comorbidity groups, cough, dyspnea, non-healing complaints, and COVID-19 treatment in addition to BMI, the total number of comorbidities, and the number of vaccines after COVID-19 infection were statistically different in the groups with and without pneumonia (for all, p<0.05). In logistic regression analyses, we found that BMI (OR: 1,113, p=0.040), HT (OR: 2,658, p=0.041), cough (OR: 4,982, p=0.029), and dyspnea (OR: 3,979, p=0.046) were the most important predictors associated with COVID-19 pneumonia.

Conclusion: Comorbidities such as HT and obesity pose an independent risk of COVID-19-related pneumonia in rheumatic patients using biological or targeted therapies. Furthermore, coughing and dyspnea in these patients may indicate COVID-19 pneumonia.

Keywords: Biologics, COVID-19, pneumonia, rheumatic diseases

Introduction

Coronavirus disease-2019 (COVID-19), the pathogen of which is severe acute respiratory syndrome-Coronavirus-2, emerged in Wuhan, China, in December 2019 (1). After the exponential increase in the number of cases and the porting of cases from other countries, the World Health Organization declared COVID-19 a pandemic on March 11, 2020 (2). Symptoms of COVID-19 usually appear within two weeks and have a spectrum that can range from asymptomatic to severe pneumonia. Fever, sore throat, cough, vomiting, diarrhea, and loss of taste and smell are frequently reported symptoms. Some infected individuals develop COVID-19 pneumonia and acute respiratory distress syndrome (ARDS), which is an undesirable and alarming situation (3,4). Individuals hospitalized with COVID-19-related pneumonia often require mechanical

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ventilation, and the elderly face an increased risk of mortality (5). In a nationwide study in Turkey, the mortality rate was reported as 4.5%, and older age, male gender, the presence of malignancy, interstitial lung disease, severe disease, or sepsis at first admission were defined as predictors of increased mortality (6).

Coronavirus disease-2019 infections can trigger an autoimmune rheumatic disease or unmask an existing but undiagnosed rheumatic disease (7). However, it has been reported that both the immune dysfunction inherent in the disease and the disease-modifying antirheumatic drugs (DMARDs) used in the treatment may affect the course of COVID-19 infection in rheumatic patients (8). In a study examining individuals with autoimmune rheumatic disease, it was determined that older age, comorbidities such as hypertension (HT) and malignancy, and delayed diagnosis of COVID-19 were the most important risk factors for hospitalization (9). In another study, the relationships between hospitalization, chest computed tomography (CT) pneumonia severity score, medications (non-steroidal anti-inflammatory drugs and prednisolone), and some comorbid conditions [diabetes mellitus (DM) and pulmonary disease] were noted in rheumatological diseases (10). Furthermore, high levels of cytokines, such as interleukin (IL)-6 and tumor necrosis factor (TNF), were found in severe COVID-19 patients. Anticytokine therapies [e.g., IL-6 inhibitors, IL-1 inhibitors, and Janus kinase (JAK) inhibitors] were effectively used in these patients based on this mechanism. Contrary to concerns in the first months of the pandemic, the use of biological DMARDs (bDMARDs) was not associated with serious disease in rheumatic patients and had a disease course similar to that of the general population. Indeed, it has been suggested that IL-6 inhibitors may have a protective effect (11-13).

We hypothesized that COVID-19 may increase both the risk of infection and the severity of the COVID-19 course in rheumatic patients under biological or targeted DMARD therapies. Although the effect of various treatments used in rheumatic diseases during the course of COVID-19 infection has been examined (14), we planned this study considering that race and ethnicity may have different effects.

Methods

Compliance with Ethical Standards

This cross-sectional study was conducted in the rheumatology department of the Erciyes University Faculty of Medicine Hospital, between April 2022 and July 2022, after the approval of the Erciyes University Faculty of Medicine Clinical Research Ethics Committee (date: 09.03.2022, approval no: 2022/205).

Study Design

Rheumatic patients [spondyloarthritis (SpA), rheumatoidarthritis (RA), familial Mediterranean fever (FMF), Takayasu arteritis, granulomatosis with polyangiitis, Behçet's disease] were included in the study. The flow chart according to the inclusion and exclusion criteria is shown in Figure 1. The patients met the diagnosis or classification criteria (15-20) of the disease that they had. The inclusion criteria were as follows: age ≥18 years, rheumatic patients with a history of COVID-19, those with COVID-19 real-time polymerase chain reaction (RT-PCR) test positivity, and those on bDMARD or targeted pentetic DMARD (tsDMARD) therapies for a rheumatologic diagnosis. Those younger than 18 years of age, uninfected with COVID-19, and not using bDMARD or tsDMARD therapies were excluded from the study.

Variables

Demographic characteristics (age, gender, height, and weight), clinical parameters (diagnosis, diagnosis duration, medications, smoking status, and comorbidities), and COVID-19-related data (dates of a positive COVID-19 PCR test, COVID-19 disease course, information about COVID-19 vaccination, and treatment details of COVID infection) of the patients were recorded. Then, the patients were divided into groups according to their status of having or not having COVID-19 pneumonia. The recorded data were compared between the two groups. Our study was conducted in accordance with the Declaration of Helsinki, and written informed consent was obtained from all patients.

Statistical Analysis

The normality of the distribution of the data was tested using the Shapiro-Wilk test. Descriptive statistics for numerical variables are expressed as mean ± standard deviation or median (minimum-maximum), whereas those for categorical variables are expressed as numbers and percentages. Between the two independent groups, the independent samples t-test was used to compare normally distributed data, and the Mann-Whitney U test was used for non-normally distributed data. Categorical variables were compared using the chi-square test. Logistic regression analysis (univariate and enter models) was also used to identify the predictors of COVID-19-related pneumonia. IBM SPSS Statistics for Windows, Version 23.0 (IBM Corp., Armonk, NY, USA) was used for the statistical analysis. All p-values <0.05 were considered statistically significant.

Results

The study was conducted with 110 patients (67 with SpA, 25 with RA, 8 with FMF, 5 with Takayasu arteritis, 3 with granulomatosis with polyangiitis, and 2 with Behçet's

disease) who met the inclusion criteria. The diagram is shown in Figure 2. The mean age of the patients was 47.27±12.77 years, and 67.3% of them were female, and their mean body mass index (BMI) was 29.59±5.59 kg/m^2. A total of 21 (19.1%) patients had a history of COVID-19 pneumonia. Other demographic and clinical data and the COVID-19 disease course of the patients are shown in Table 1. The first and subsequent symptoms of the COVID-19 infection are shown in Table 2.

Table 1. Demographic characteristics, clinical data, and the COVID-19 disease course of patients

Total number of patients, n	110
Age (years), mean ± SD	47.27±12.77
BMI (kg/m^2), mean ± SD	29.59±5.59
Gender, n (%)	
Female	74 (67.3)
Male	36 (32.7)
Disease duration, years, median (min.-max.)	10 (2-40)
Diseases, n (%)	
SpA	67 (60.9)
RA	25 (22.7)
Behçet and other vasculitis	10 (9.1)
FMF	8 (7.3)
DMARDs, n (%)	
TNF inhibitors	83 (75.5)
IL-1 inhibitors	10 (9.1)
IL-6 inhibitor	6 (5.5)
JAK inhibitors	5 (4.5)
Anti-CD20	3 (2.7)
Anti-CTLA4	2 (1.8)
IL-17 inhibitors	1 (0.9)
Smoking, n (%)	
No	93 (84.5)
Yes	17 (15.5)
HT, n (%)	
No	72 (65.5)
Yes	38 (34.5)
DM, n (%)	
No	82 (74.5)
Yes	28 (25.5)
Comorbidity status, n (%)	
No	48 (43.6)
Yes	62 (56.4)
Number of comorbidities, median (min.-max.)	1 (0-4)
Comorbidity diseases, n (%)	
<2	80 (72.7)
≥2	30 (27.3)
COVID-19 medication, n (%)	
No	25 (22.7)
Yes	85 (77.3)
Hospitalization, n (%)	
No	89 (80.9)
Yes	21 (19.1)
Pneumonia, n (%)	
No	89 (80.9)
Yes	21 (19.1)
Oxygen treatment, n (%)	
No	88 (80)
Yes	22 (20)
History of intensive care unit, n (%)	
No	107 (97.3)
Yes	3 (2.7)

SD: Standard deviation, BMI: Body mass index, min.: Minimum, max.: Maximum, SpA: Spondyloarthritis, RA: Rheumatoid arthritis, FMF: Familial Mediterranean fever, DMARDs: Disease-modifying antirheumatic drugs, TNF: Tumor necrosis factor, IL: Interleukin, JAK: Janus kinases, CTLA4: Cytotoxic T lymphocyte-associated antigen 4, HT: Hypertension, DM: Diabetes mellitus

Table 2. First and subsequent symptoms of COVID-19 infection

First symptoms n (%)		Subsequent symptoms n (%)
29 (26.3)	Arthralgia	80 (72.7)
27 (24.5)	Myalgia	80 (72.7)
16 (14.5)	Headache	72 (65.5)
7 (6.4)	Loss of taste and/or smell	69 (62.7)
23 (20.9)	Fever	62 (56.4)
18 (16.4)	Cough	61 (55.5)
9 (8.2)	Throat ache	53 (48.2)
4 (3.6)	Dyspnea	51 (46.4)
3 (2.7)	Anorexia	41 (37.3)
2 (1.8)	Sweating	40 (36.4)
–	Chest pain	38 (34.5)
2 (1.8)	Nausea	32 (29.1)
–	Eye redness	26 (23.6)
–	Diarrhea	22 (20)
1 (0.9)	Stuffy nose	20 (18.2)
2 (1.8)	Stomachache	16 (14.5)
2 (1.8)	Vomiting	15 (13.6)
–	Restlessness	5 (4.5)

COVID-19: Coronavirus disease-2019

When we recorded the data, 91.8% of the patients had been vaccinated at least once with the COVID-19 vaccine. The vaccine-related adverse effects and data related to COVID-19 vaccinations are presented in Table 3. We also compared the demographic and clinical parameters and COVID-19-related data according to the presence or absence of COVID-19-related pneumonia. The rates of HT, DM, comorbidity status, comorbidity groups, cough, dyspnea, non-healing complaints, and COVID-19 treatment in addition to BMI, the total number of comorbidities, and the number of vaccines after COVID-19 infection were statistically different between the two groups (for all, $p<0.05$) (Table 4). Using logistic regression analyses, we initially evaluated the potential factors affecting COVID-19-related pneumonia separately using a univariate model. In these analyses, BMI, HT, DM, the total number of comorbidities, comorbidity groups, cough, and dyspnea were determined to have significant effects (for all, $p<0.05$). The candidate predictors were then entered into the multiple models. After adjusting for the effects of age in the enter model, we found that BMI [Odds ratio (OR): 1,113 [confidence interval (CI): 1,005-1,233], p=0.040], HT [OR: 2,658 (CI: 1,053-12,355), p=0.041], cough [OR: 4,982 (CI: 1,177-21,090), p=0.029], and dyspnea [OR: 3,979 (CI: 1,022-12,301), p=0.046] were the most significant independent risk factors associated with pneumonia due to COVID-19 infection (Table 5).

Table 3. Data related to COVID-19 vaccination(s)

Variables	n (%)
COVID-19 vaccination	
No	9 (8.2)
Yes	101 (91.8)
Amount of COVID-19 vaccinations	
0	9 (8.2)
1	5 (4.5)
2	40 (36.4)
3	38 (34.5)
4	18 (16.4)
Vaccination before COVID-19 infection	
No	78 (70.9)
Yes	32 (29.1)
Amount of vaccinations before COVID-19 infection	
0	78 (70.9)
1	2 (1.8)
2	19 (17.3)
3	11 (10)
Type of COVID-19 vaccination	
None	9 (8.2)
Sinovac	29 (26.4)
BioNTech	37 (33.6)
Sinovac + BioNTech	35 (31.8)
Adverse effect status	
No	40 (36.4)
Yes	61 (55.5)
Adverse effects after vaccination	
Pain in the upper extremity	32 (31.7)
Malaise	13 (12.9)
Fever	12 (11.9)
Headache	10 (9.9)
Arthralgia	7 (6.9)
Myalgia	6 (5.9)
Flu-like symptoms	4 (4.0)
Chest pain	3 (3.0)
Increase in blood pressure	1 (1.0)
Vomiting	1 (1.0)
Diarrhea	1 (1.0)
Dyspnea	1 (1.0)

COVID-19: Coronavirus disease-2019

Discussion

This study showed that BMI, HT, cough, and dyspnea were the most important predictors associated with COVID-19 pneumonia in rheumatic patients receiving bDMARD or tsDMARD therapies. Moreover, the presence and number of comorbidities were higher in the group that developed pneumonia. Although the number of vaccines administered before COVID-19 infection was similar in the groups with and without pneumonia, the number of vaccines administered after COVID-19 pneumonia was significantly higher in the pneumonia group. These findings can be attributed to different COVID-19 variants. Coronavirus disease-2019 can affect various organs or systems, but respiratory system involvement is prominent. Symptoms due to a respiratory tract infection can range in severity from cough and sputum to ARDS and respiratory failure. It has been demonstrated that some abnormalities in pulmonary function tests persist in patients discharged after recovering from COVID-19 pneumonia (21).

Non-contrast CT has become an important imaging tool for diagnostic purposes in individuals with false-negative COVID-19 RT-PCR tests and for the prediction of disease prognosis and choice of treatment in patients diagnosed with COVID-19. Significant relationships have been determined between CT severity scores and the severity and course of COVID-19 (22). In the present study, pneumonia was determined at a 19.1% rate. In a systematic review, Shi et al. (23) drew attention to risk factors that increase mortality rates due to COVID-19 infection, such as advanced age, male gender, smoking, comorbidities, and dyspnea symptoms. Peters et al. (24)

Table 4. Comparison of demographic characteristics, clinical data, and COVID-19 data according to the presence or absence of COVID-19-related pneumonia

Pneumonia status variables	Without pneumonia (n=89)	Pneumonia (n=21)	p-value
Age (years), mean ± SD	46.44±12.85	51.50±10.50	0.114
BMI (kg/m^2), mean ± SD	28.93±4.90	33.02±6.28	0.002*
Gender, n (%)			0.478
Female	58 (65.2)	16 (76.2)	
Male	31 (34.8)	5 (23.8)	
Disease duration, years, median (min.-max.)	10 (2-30)	8 (2-40)	0.279
Diseases, n (%)			0.063
SpA	55 (61.8)	12 (57.1)	
RA	22 (24.7)	3 (14.3)	
Behcet and other vasculitis	5 (5.6)	5 (23.8)	
FMF	7 (7.9)	1 (4.8)	
Biologics			0.846
Anti-TNF	68 (76.4)	15 (71.4)	
Non-TNF	21 (23.6)	6 (28.6)	
Smoking, n (%)			0.116
No	73 (82.0)	20 (95.2)	
Yes	16 (18.0)	1 (4.8)	
HT, n (%)			0.030*
No	63 (70.8)	9 (42.9)	
Yes	26 (29.2)	12 (57.1)	
DM, n (%)			0.043*
No	70 (78.7)	12 (57.1)	
Yes	19 (21.3)	9 (42.9)	
Comorbidity status, n (%)			0.043*
No	43 (48.3)	5 (23.8)	
Yes	46 (51.7)	16 (76.2)	
Total number of comorbidities, median (min.-max.)	1 (0-4)	1 (0-3)	0.018*
Comorbid diseases, n (%)			0.021*
<2	69(77.5)	11(52.4)	
≥2	20(22.5)	10(47.6)	
Cough, n (%)			0.003*
No	46 (51.7)	3 (14.3)	
Yes	43 (48.3)	18 (85.7)	
Dyspnea, n (%)			0.014*
No	53 (59.6)	6 (28.6)	
Yes	36 (40.4)	15 (71.4)	
Vaccination before COVID-19 infection, n (%)			
No	62 (69.7)	16 (76.2)	
Yes	27 (30.3)	5 (23.8)	0.745
Total amount of COVID-19 vaccinations, median (min.-max.)	2 (0-4)	3 (2–4)	0.100
Amount of vaccinations before COVID-19 infection, median (min.-max.)	0 (0-3)	0 (0–3)	0.514
Amount of vaccinations after COVID-19 infection, median (min.-max.)	2 (0-4)	3 (0–4)	0.043*
Non-healing complaints, n (%)			0.028*
No	61 (68.5)	9 (42.9)	
Yes	28 (31.5)	12 (57.1)	
COVID-19 treatment, n (%)			0.003*
No	25 (28.1)	0 (0)	
Yes	64 (71.9)	21 (100)	

*P<0.05
SD: Standard deviation, BMI: Body mass index, min.: Minimum, max.: Maximum, TNF: Tumor necrosis factor, HT: Hypertension, DM: Diabetes mellitus

Table 5. Identification of predictor(s) associated with COVID-19 pneumonia								
Univariate analyses					**Enter model**			
	B	**95% CI**	**OR**	**value**	**B**	**95% CI**	**OR**	**value**
Age	0.032	0.992-1.075	1.032	0.117				
Male gender	-0.532	0.196-1.747	0.585	0.337				
BMI	0.127	1.041-1.237	1.135	0.004*	0.107	1.005-1.233	1.113	0.040*
HT (Yes/Ref. No)	1.173	1.215-8.587	3.231	0.019*	1.233	1.053-12.355	2.658	0.041*
DM (Yes/Ref. No)	1.016	1.014-7.526	2.763	0.047*				
Total number of comorbidities	0.524	1.050-2.716	1.689	0.031*				
Disease duration	-0.014	0.905-1.075	0.986	0.755				
Comorbid diseases (≥2/Ref. <2)	1.143	1.165-8.445	3.136	0.024*				
Number of COVID-19 vaccinations before infection	-0.158	0.532-1.370	0.854	0.512				
Cough (Yes/Ref. No)	1.859	1.765-23.341	6.419	0.005*	1.606	1.177-21.090	4.982	0.029*
Dyspnea (Yes/Ref. No)	1.303	1.305-10.383	3.681	0.014*	1.266	1.022-12.301	3.979	0.046*

*P<0.05
CI: Confidence interval, BMI: Body mass index, HT: Hypertension, Ref.: Reference, DM: Diabetes mellitus

showed that obesity significantly impacts COVID-19 mortality and that higher BMI values are associated with higher mortality rates in women than in men. Similarly, Cottini et al. (25) reported that obesity increases hospitalization and worsens the outcome of COVID-19. In another study examining the predictors of mortality in COVID-19 pneumonia, comorbidities also had a significant effect (26).

In our study, the factors associated with pneumonia, an involvement that affected the mortality of COVID-19, were as follows: comorbidities (especially HT), BMI, cough, and symptoms of dyspnea, which Shi et al. (23) correlated with mortality. Smoking rates, which have been emphasized for their importance to the prognosis of COVID-19, were low in our patient group. Looking at it in reverse, not smoking may be a factor in their survival. In one study, which is the first report on factors associated with COVID-19 pneumonia in Turkey, researchers found that in multivariate analysis, obesity, not being actively smoking, cough at first admission, and shortness of breath were determined as independent risk factors for the development of pneumonia. CRP, D-dimer, and ferritin values among 108 (26.1%) patients with a BMI >30 were high, and 60.9% of the patients had pneumonia (27). In this study, coughing, shortness of breath, and obesity were related to COVID-19 pneumonia. Laboratory parameters such as neutrophil/lymphocyte ratio and d-dimer levels can predict mortality (28). In this study, labaratory parameters during infection were not reached. No correlation was detected between smoking and COVID-19. In the present study, 15.5% of the study group smoked. Frequent hospital visits can encourage patients with rheumatic diseases to stop smoking. Similar to the general population, the relationship between severe COVID-19 and comorbidities has also been demonstrated in individuals with rheumatic disease (29). Fredi et al. (30) found that poor outcomes in rheumatic diseases were related to advanced age and accompanying comorbidities rather than the type of disease. In their case-control study, it was also noted that obesity and HT were higher in severe COVID-19 cases. Bakasis et al. (31) reported that the presence of underlying lung involvement, along with advanced age and comorbidities, is a risk factor for hospitalization due to COVID-19. In addition, a French rheumatic disease cohort (28) indicated that advanced age, obesity, male gender, and HT were associated with severe COVID-19. Consistent with the literature in the current study, comorbidities and their subgroups were higher in rheumatic patients with pneumonia than in those without pneumonia and showed significant effects in univariate regression analyses. Moreover, obesity and HT were independent risk factors associated with COVID-19-related pneumonia in the multiple regression model. Similar to the results of Fredi et al. (30), there was no difference between the groups with and without pneumonia in terms of disease subtypes. Dyspnea, a risk factor associated with hospitalization in previous studies (31), was significantly higher in the pneumonia group and was an independent risk factor for predicting pneumonia in the regression analysis. Conversely, age had no significant effect on pneumonia in our cohort.

This finding can be explained by the fact that the average age of the patients in our study was 47 years; that is, the majority were not elderly. In the present study, not age but obesity is a risk factor, similar to the literature. With the onset of the COVID-19 pandemic, it was thought that the biological treatments used in rheumatic diseases would lead to a serious COVID-19 infection due

to decreased immunity (30,31). However, in the cytokine storm associated with the pathological immune response in some individuals infected with COVID-19, biological therapies have become significant treatment options in subsequent periods (11). IL-6, IL-1, JAK, and TNF inhibitors, which are frequently prescribed for rheumatic diseases, have been used for this purpose (11,13). Santos et al. (11) reported that the use of biologics in rheumatologic diseases was typically not associated with poor outcomes in COVID-19 and that IL-6 inhibitors might even have a protective effect. Baslılar and Pehlivan (32) determined that COVID-19 patients treated with anti-TNF agents had mild clinical signs and a good disease prognosis. Contrary to these good results, several studies have emphasized the importance of the direct relationship between rituximab and severe COVID-19 (33,34). In our study, 94.6% of the patients used IL-6, IL-1, TNF, or JAK inhibitors. Only three patients underwent rituximab therapy. Although some of them had pneumonia, the high rate of treatment use associated with a good prognosis in our patients who recovered after the COVID-19 infection may be one of the factors that ensured their survival. Moreover, when we classified the patients' medications as anti-TNF and non-TNF treatments, we could not detect a significant difference between the groups with and without pneumonia. In a study from Turkey, it was reported that high-dose anakinra can be effective in COVID-19 (35). Biological and synthetic DMARDs can prevent a cyotokine storm and lead to a better prognosis. In addition, these results may be due to the young age of our cohort. 25 patients with systemic rheumatic diseases who received the COVID-19 vaccine have been shown to have better COVID-19 infection outcomes than those who did not (36). In our cohort, 91.8% of patients had at least one vaccination at the time of data collection, whereas this rate was only 29.1% during COVID-19 RT-PCR positivity. The number of vaccines administered after the COVID-19 infection was significantly higher in the group with pneumonia than in the group without pneumonia. This difference can be explained by the fact that, as Karlsson et al. (37) noted, people who believe that COVID-19 is a serious disease are more likely to get vaccinated. A study showed that the unvaccinated patients developed more severe forms compared with the vaccinated ones, and a higher proportion of them needed hospitalization (38).

As the vaccination rates increased, we detected a decrease in pneomonia. A recent meta-analysis suggests After COVID-19 mRNA vaccination, patients with autoimmune diseases had lower total antibody titers, IgG seroconversion, and local and systemic adverse events compared with healthy controls (39). In the present study, the most frequent side effect was pain in the upper extremity. Furthermore, healthy controls were not included in this study. In addition, total antibody titers and IgG seroconversion were not studied. The strength of this study is that, to the best of our knowledge, it is the first to consider only patients using biological therapy and to evaluate rheumatic patients who survived after a COVID-19 infection. Nevertheless, this study has some limitations. First, we excluded healthy controls or patients who died of COVID-19 while using biological therapy to compare our results. Second, the negative impact of rituximab could not be compared with treatments thought to positively impact COVID-19 prognosis in terms of pneumonia development. The main factor was that only three patients were using rituximab. In addition, the study was conducted in a heterogeneous group.

Conclusion

Our study demonstrated that comorbidities, especially BMI and HT, were the most important predictors associated with COVID-19 pneumonia in rheumatic patients receiving bDMARD or tsDMARD therapies. It was also found that new-onset cough and dyspnea in rheumatic patients using these therapies may serve as warning symptoms of COVID-19-related pneumonia for rheumatologists. However, we failed to find a relationship between the number of pre-infectional COVID-19 vaccines and pneumonia. A healthy diet, regular exercise program, cessation of smoking, and vaccination can be beneficial in preventing COVID-19.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Erciyes University Faculty of Medicine Clinical Research Ethics Committee (date: March 9, 2022, approval no: 2022/205).

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

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

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

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Original Article

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Comparison of Fatigue Levels, Muscle Strength, Balance, and Exercise Performance of Young Adults with a History of Mild COVID-19 and Healthy Adults

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Abstract

Aim: The coronavirus disease-2019 (COVID-19) infection directly impacts fatigue and exercise performance. More studies have focused on these problems and were conducted with hospitalized patients and/or adult and geriatric populations. The aim of this study was to explore the effects of mild COVID-19 on fatigue, muscle strength, balance, and exercise performance, specifically in young adults.

Methods: This research was designed as a case-control study, and tests were conducted between January 2022 and June 2022. The study included 60 participants aged 18-28, consisting of individuals who had a mild COVID-19 diagnosis within the past year (study group, n=30) and tested negative during the study, as well as a control group of individuals who had no COVID-19 diagnosis or symptoms within the past year (control group, n=30). The participants' fatigue levels (Chalder Fatigue Scale), lower (Biodex Isokinetic-Dynamometer) and upper (Jamar-Handgrip Dynamometer) extremity muscle strength, balance (Y-Balance Test), and exercise performance (Queen's College Step Test) were evaluated using various standardized tests.

Results: Measurements showed that individuals with COVID-19 had an increase in fatigue scores (p=0.02). It was determined that fatigue was particularly prominent in women. Due to this difference that arose according to gender, it was observed that fatigue scores in those who had experienced COVID-19 were negatively correlated with muscle strength measurements.

Conclusion: This study showed that symptoms of fatigue persisted in younger individuals, especially women, even after the COVID-19 infection. We think the next research should focus on COVID-19 symptoms, surveillance, and therapy in different age groups.

Keywords: COVID-19, fatigue, dyspnea, muscle weakness

Introduction

Coronavirus disease-2019 (COVID-19) has caused a pandemic because of its rapid transmission (1). The virus severely affects various human tissues, including the lungs and heart, leading to serious and even fatal health issues (2). It has been reported that there is a rapid onset of fatigue, loss of strength and endurance, and a decrease in aerobic and lung capacity due to multisystemic effects following the COVID-19 illness (3). Immobility resulting from hospitalizations and long periods of staying at home due to pandemic conditions also contributes to these effects (4).

In a study on the severe acute respiratory syndrome (SARS) outbreak, patients were followed for fatigue at 3, 6, and 12 months after hospital discharge. Findings showed persistent fatigue during recovery: 64% at three months, 54% at six months, and 60% at 12 months (5). Another study related to COVID-19 reported that persistent fatigue affected a significant group of patients (13-33%) after 16-20 weeks of symptom onset (6). During early recovery, patients with severe COVID-19 showed reduced functional capacity, as evidenced by shorter 6-min walking distances compared with those with milder disease. This suggests weaker exercise capacity in severely affected patients (7). In addition, a systematic review highlighted that 41% of patients experienced a decline in aerobic capacity during the 3-month period following the disease (8). It has not been proven that COVID-19 directly affects muscle weakness and atrophy. However, it has been noted that both symptoms are commonly observed (9).

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Studies related to COVID-19 have evaluated exercise capacity, functional capacity, muscle strength, and fatigue (10-12). They focused mainly on individuals who had to be hospitalized or required intensive care and oxygen therapy. Research on the effects of COVID-19 on young populations who experienced the disease while standing and without known respiratory distress is limited. However, given the potential long-term effects of the disease on physical performance, muscle strength, balance, and fatigue, it is important to compare these outcomes between individuals who have and those who have not experienced COVID-19 (13,14). This will help to better understand the impact of the disease on young populations and inform strategies for prevention and treatment. In this context, the aim of the study was to compare fatigue, muscle strength, balance, and physical performance between young individuals who have and have not experienced COVID-19.

Methods

Compliance with Ethical Standards

Participants were informed about the study, and written consent was obtained. The study was conducted in accordance with the Declaration of Helsinki. Ethical permission for this study was obtained from the Ethics Committee of Marmara University, Faculty of Health Sciences for Non-Interventional Clinical Studies (date: 27.01.2022, approval no: 16).

Study Design and Participants

The study population consisted of young individuals aged 18-28 who had mild COVID-19 in the past year without any history of immobilization or hospitalization and known respiratory distress, as well as young individuals who had never been diagnosed with COVID-19. Individuals with neuromusculoskeletal problems, regular physical activity, and a history of orthopedic, rheumatologic, systemic diseases, and psychological problems in the past six months were excluded from the study. Volunteers were divided into two groups: the study group (n=30), consisting of individuals who had been diagnosed with COVID-19 in the past year, and the control group (n=30), consisting of individuals who had never been diagnosed with COVID-19 (Figure 1).

Applied Tests and Assessments

The Chalder Fatigue Scale (CFS), Y Balance Test (YBT), Queen's College Step Test (QCST), Jamar Handgrip Dynamometer (JHD), and Biodex System 3 Pro isokinetic dynamometer were used for the evaluations. The content of the tests applied in the study was explained to the volunteers at the beginning of the tests. After the necessary directions were given, the relevant tests were applied. After each completed test application, 15-minute rest periods were allowed. The order of the tests was conducted in the same way for each participant.

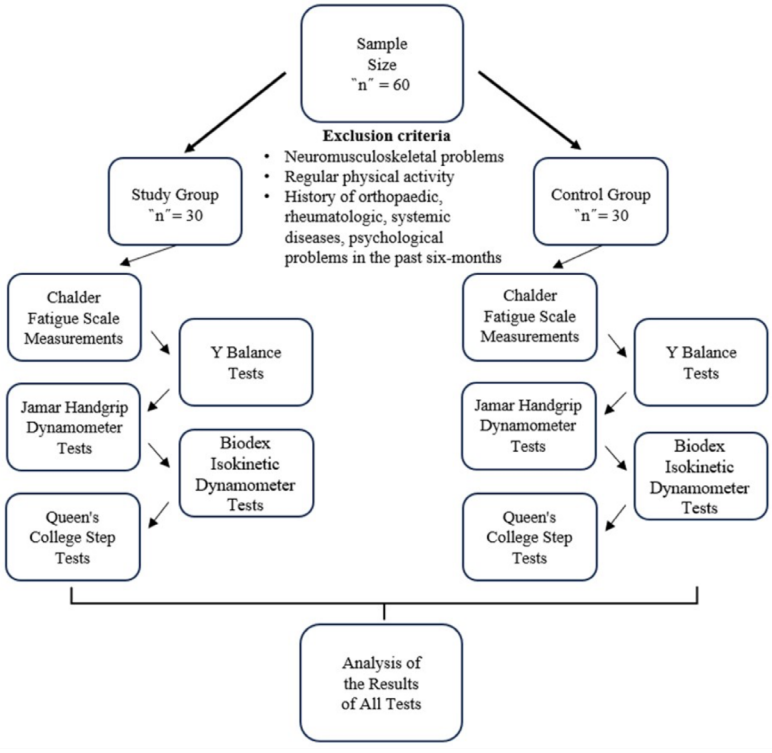

Figure 1. Flow diagram of the study

Chalder Fatigue Scale

The CFS measures fatigue levels over the past month using 11 questions. Seven questions focused on physical fatigue and four on mental fatigue. Scores for each question range from 0 to 3, and a higher total score indicates greater fatigue (15).

"Y" Balance Test

The YBT, validated by Plisky et al. (16), was used to measure dynamic balance. Participants tested barefoot and reached in three directions: anterior (A), posteromedial (PM), and posterolateral (PL). Reach distances on surface tapes were measured from specific points on the foot. Participants kept their hands on their iliac crests and their heels on the surface while reaching. Before the official test, they practiced six times in each direction for both legs. Tests were repeated if balance was lost or if other specific criteria were not met (16).

Jamar Handgrip Dynamometer

The JHD was used to measure grip strength as an objective assessment of overall body strength and upper extremity performance. Participants were seated with their elbows flexed at 90 degrees and their wrists in a neutral position. Grip strength was measured for both hands through three repetitions, and the dominant hand was noted. The average of the three repetitions was recorded as the final measurement (17).

Biodex Isokinetic Dynamometer

The Biodex System 4 ProTM device was used to assess the maximum isokinetic torque production of the quadriceps femoris and hamstring muscle groups. Tests were conducted at speeds of 180 s1, 120 s1, 90 s1, and 60 s1 in the isokinetic concentric mode, which is known for its statistically significant test-retest reliability. Maximum voluntary contractions lasting up to 3 s were performed, with 1-min rest periods between assessments. The maximum torque force parameters were used for the evaluation (18).

Queen's College Step Test

Queen's College Step Test is a method used to determine cardiorespiratory fitness in terms of VO_{2max} (19). The test was conducted according to the manual and was performed using a 41.3 cm (16.25 inches) high step. Participants were asked to step onto the platform for three minutes, maintaining a rhythmic pace of 22 steps per minute for females and 24 steps per minute for males. At the end of the 3 min, their heart rate was measured by taking their pulse at the carotid artery during the 15-s recovery period between the 5th and 20th s. The heart rate was then used to estimate VO_{2max}.

Estimated VO_{2max} calculation using QCST (20):

For men: VO_{2max}=111.33 - [0.42 × pulse/min]

For women: VO_{2max}=65.81- [0.1847 × pulse/min]

Flow chart of the study (CFS: Chalder Fatigue Scale, YBT: Y Balance Test, JHD: Jamar Handgrip Dynamometer, QCST: Queen's Collage Step Test) (Figure 2).

Sample Size

When the statistical significance level was determined as p≤0.05 and the test power was determined as 90%, a minimum of 40 participants were required for the study when t-tests and Wilcoxon-Mann-Whitney U tests were applied to the two-group means. This analysis was performed using G Power 3.1.9.7. To account for the risk of participants discontinuing the study because of secondary issues or dropping out, 60 volunteers were included in the study.

Statistical Analysis

Statistical Package for Social Sciences (SPSS) Windows v22.0 (SPSS Inc., IBM Corp., Armonk, New York) was used for all statistical analyses. The mean and standard deviation were used for quantitative results, and percentage (%) values were used for qualitative results. The normal distribution of data was assessed by the one-sample Kolmogorov-Smirnov test and by examining histograms. Independent samples t-tests were used to determine the differences between group parameters, and Pearson correlation analysis was used to evaluate the relationship between parameters. The level of statistical significance was set at p≤0.05.

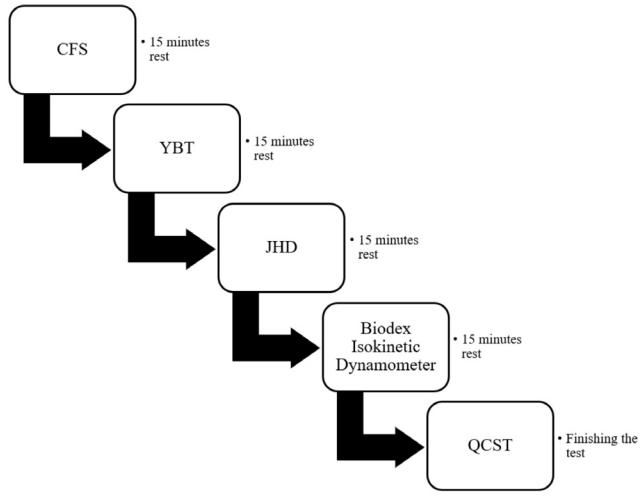

Figure 2. Flow chart of the study
CFS: Chalder Fatigue Scale, YBT: Y Balance Test, JHD: Jamar Handgrip Dynamometer, QCST: Queen's Collage Step Test

Results

Our study included 60 volunteers, including a study group with a history of COVID-19 (n=30) and a control group without (n=30). The demographic characteristics of both groups were statistically similar in the comparisons (Table 1).

In assessing fatigue via the CFS, the study group exhibited a significantly higher mean CFS score of 16±4 compared with 13.7±3.4 in the control group. This difference was statistically significant with a p value of 0.02 (Figure 3), indicating that post-COVID-19 individuals exhibited increased levels of fatigue.

Physical performance metrics such as balance (YBT), grip strength (JHD), and knee muscle strength showed no significant differences between the two groups (all p>0.05, Table 2).

The physical performance measurements, balance (YBT), grip strength (JHD), and knee muscle strength showed no significant difference between the two groups (all p>0.05, Table 2).

Cardiovascular measures were assessed using the QCST. Heart rate and estimated VO_{2max} were found to be similar between the groups (p=0.6 for heart rate and p=0.58 for VO_{2max}, Table 2).

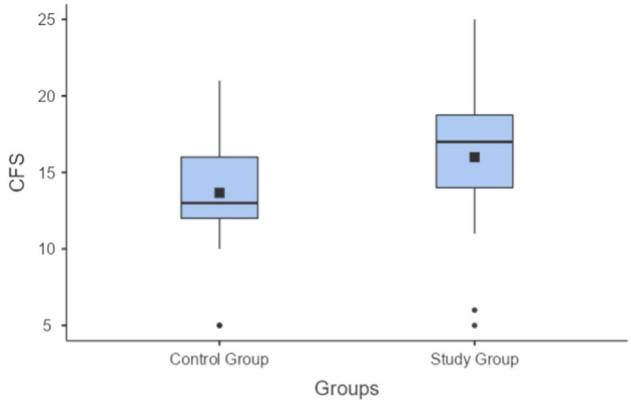

Figure 3. Graph of chalder fatigue scale means (p=0.02)
CFS: Chalder Fatigue Scale

After the gender-specific analysis, while male participants' results were similar, the CFS scores of females with COVID-19 histories were higher (p<0.05).

Correlation Analysis

In the study group, moderate correlations were found between gender and balance tests (p<0.05), as well as between gender and fatigue scores (r=-0.503, p=0.005). Negative correlations were observed between CFS scores and knee muscle strength measurements, specifically at 60° knee extension (r=-0.487, p<0.05), 90° knee extension (r=-0.478, p<0.05), and others. Additionally, a moderate negative correlation was found between CFS scores and JHD measurements for both the right hand (r=-0.424, p=0.019) and the left hand (r=-0.438, p=0.016).

Heart rate metrics from the QCST were negatively correlated with knee angular torque measurements at various angles in the study group, with coefficients ranging from r=-0.472 to r=-0.571 (all p<0.05). Moreover, strong positive correlations were identified between estimated VO_{2max} and knee flexion-extension angular torque measurements, with r-values up to 0.783 (all p<0.05, Study group correlation analyzes in Table 3, Control group correlation analyzes in Table 4).

Discussion

In this study, we aimed to compare exercise performance, muscle strength, balance, and fatigue levels between young individuals with mild COVID-19 in the past year and those without COVID-19. Our results showed that individuals who had COVID-19 in the past year had increased fatigue compared with those who did not, but there were no significant changes in muscle strength, balance, or exercise performance.

Studies on the effects of COVID-19 on muscle strength and exercise performance have often focused on cases that require hospitalization or intensive care unit stays (21,22). The systemic effects of the disease, the intense and severe cytokine storm, and the adverse effects of steroid treatments administered in response, as well as complications in the musculoskeletal system, are

Table 1. Socio-demographic characteristics of individuals

Demographic headlines	Control group Mean ± SD	Study group Mean ± SD	p-value
Average age (years)	22.46±1.5	23±1.1	0.12[a]
Height (cm)	167.93±9.57	169±9.22	0.47[a]
Body weight (kg)	62.6 ±10.49	64.36±13.78	0.58[a]
Female/Male (n)	18/12	17/13	0.79[a]
Cigarette (use/not use)	19/11	18/12	0.79[a]
Dominant side (right/left)	27/3	29/1	0.31[a]

[a] Independent samples t-tests were applied, SD: Standard deviation

Table 2. Balance, grip strength, knee muscle strength and exercise performance test results of the groups			
Test Methods and Parameters	**Study Group**	**Control Group**	**p-value**
	Mean ± SD	**Mean ± SD**	
Y Balance Test Reach Direction			
Right Anterior (cm)	70.17±7.15	70.73±10.58	0.81[a]
Right Posterolateral (cm)	96.41±12.85	96.1±12.81	0.93[a]
Right Posteromedial (cm)	87.98±14.06	90.3±11.06	0.49[a]
Left Anterior (cm)	69.78±7.25	72.3±9.87	0.26[a]
Left Posterolateral (cm)	94.1±13.99	98.65±13.05	0.2[a]
Left Posteromedial (cm)	89.6±13.45	91.3±12.08	0.6[a]
Jamar Hand-Grip Dynamometer Related Limb			
Right Hand (kg)	30.38±11.39	30.09±9.54	0.92[a]
Left Hand (kg)	27.3±10.21	28.29±9.13	0.69[a]
Biodex Isokinetic System Measurement Angles			
Extension 60° (Nm)	74.84±35.51	77.51±35.49	0.77[a]
Flexion 60° (Nm)	107.54±40.48	105.72±47.93	0.87[a]
Extension 90° (Nm)	70.02±31.44	71.86±28.28	0.81[a]
Flexion 90° (Nm)	94.8±34.8	92.59±37.86	0.82[a]
Extension 120° (Nm)	64.2±27.89	66.46±24.53	0.74[a]
Flexion 120° (Nm)	84.29±30.68	80.08±30.70	0.6[a]
Extension 180° (Nm)	57.25±25.36	60.26±20.16	0.61[a]
Flexion 180° (Nm)	69.93±29.65	68.17±24.97	0.81[a]
Queen's Collage Step Test Parameters			
Heart Rate Per Minute (Beats/Minute)	163.47±12.32	165.3±14.73	0.6[a]
Estimated VO_{2max}	38.71±5.77	37.86±6.25	0.58[a]

[a] Independent samples t-tests were applied, SD: Standard deviation, cm: Centimetre, kg: Kilogram, Nm: Newton Meter, Tests Applied: Y Balance Test - Jamar Hand-Grip Dynamometer - Biodex Isokinetic Dynamometer System - Queen's Collage Step Test

Table 3. Study group correlation analyzes of gender, fatigue, exercise performance, and balance measurements with knee flexion-extension angular torque measurements											
Study Group (Isokinetic Dynamometer Measurement Angles)	**Gender**		**Chalder**	**QCST**		**YBT**					
				HR	**VO_{2Max}**	**Right Leg Anterior**	**Right Leg PL**	**Right Leg PM**	**Left Leg Anterior**	**Left Leg PL**	**Left Leg PM**
60° Knee Extension	r	0.721**	-0.487**	-0.539**	0.783**	NS	0.500**	0.521**	NS	0.579**	0.519**
	p	0.000	0.006	0.002	0.000		0.005	0.003		0.001	0.003
60° Knee Flexion	r	0.541**	-0.411*	-0.571**	0.689**	0.407*	0.558**	0.475**	NS	0.546**	0.508**
	p	0.002	0.024	0.001	0.000	0.025	0.001	0.008		0.002	0.004
90° Knee Extension	r	0.779**	-0.478**	-0.486**	0.787**	0.361*	0.501**	0.522**	NS	0.561**	0.545**
	p	0.000	0.008	0.007	0.000	0.050	0.005	0.003		0.001	0.002
90° Knee Flexion	r	0.622**	NS	-0.519**	0.702**	0.484**	0.553**	0.493**	NS	0.536**	0.536**
	p	0.000		0.003	0.000	0.007	0.002	0.006		0.002	0.002
120° Knee Extension	r	0.743**	-0.478**	-0.504**	0.779**	NS	0.542**	0.528**	NS	0.597**	0.569**
	p	0.000	0.008	0.005	0.000		0.002	0.003		0.001	0.001
120° Knee Flexion	r	0.627**	-0.369*	-0.566**	0.741**	0.426*	0.563**	0.491**	NS	0.568**	0.545**
	p	0.000	0.045	0.001	0.000	0.019	0.001	0.006		0.001	0.002
180° Knee Extension	r	0.726**	-0.482**	-0.472**	0.740**	NS	0.561**	0.545**	NS	0.605**	0.574**
	p	0.000	0.007	0.008	0.000		0.001	0.002		0.000	0.001
180° Knee Flexion	r	0.639**	-0.387*	-0.466**	0.680**	0.456*	0.632**	0.530**	NS	0.593**	0.598**
	p	0.000	0.035	0.009	0.000	0.011	0.000	0.003		0.001	0.000

Pearson Correlation Analysis Applied, *: p≤0.05, **: p≤0.01, Isokinetic Dynamometer Measurement Angles: Biodex Isokinetic System Measurement Angles, QCST: Queen's Collage Step Test, YBT: Y Balance Test, HR: Heart rate, PL: Posterolateral, PM: Posteromedial, NS: Not significant

Table 4. Control group correlation analyzes of gender, exercise performance, and balance measurements with knee flexion-extension angular torque measurements

Control Group (Isokinetic Dynamometer Measurement Angles)	Gender		Chalder	QCST		YBT					
				HR	VO_{2Max}	Right Leg Anterior	Right Leg PL	Right Leg PM	Left Leg Anterior	Left Leg PL	Left Leg PM
60° Knee Extension	r	0.681**	NS	-0.379*	0.631**	NS	NS	NS	NS	NS	NS
	p	0.000		0.039	0.000						
60° Knee Flexion	r	0.641**	NS	NS	0.418*	NS	NS	NS	NS	NS	NS
	p	0.000			0.022						
90° Knee Extension	r	0.683**	NS	-0.415*	0.685**	0.412*	NS	NS	NS	NS	NS
	p	0.000		0.023	0.000	0.023					
90° Knee Flexion	r	0.686**	NS	NS	0.457*	NS	NS	NS	NS	NS	NS
	p	0.000			0.011						
120° Knee Extension	r	0.732**	NS	-0.381*	0.683**	0.439*	NS	NS	NS	0.378*	NS
	p	0.000		0.038	0.000	0.015				0.039	
120° Knee Flexion	r	0.678**	NS	NS	0.494**	NS	NS	NS	NS	NS	NS
	p	0.000			0.006						
180° Knee Extension	r	0.747**	NS	NS	0.613**	0.365*	NS	NS	NS	0.389*	NS
	p	0.000			0.000	0.047				0.033	
180° Knee Flexion	r	0.667**	NS	NS	0.416*	NS	NS	NS	NS	NS	NS
	p	0.000			0.022						

Pearson Correlation Analysis Applied, *: p≤0.05, **: p≤0.01, Isokinetic Dynamometer Measurement Angles: Biodex Isokinetic System Measurement Angles, QCST: Queen's Collage Step Test, YBT: Y Balance Test, HR: Heart rate, PL: Posterolateral, PM: Posteromedial, NS: Not significant

considered the main causes of losses in muscle strength and exercise performance in this group (23). Additionally, statistically significant decreases in muscle strength and exercise performance after COVID-19 have been reported in cases followed up on the ward (21).

Our study was conducted with the participation of young individuals (aged 18-28) who had mild COVID-19 and did not require hospitalization. Our measurements showed no significant differences between the two groups, except for fatigue scores. This finding is consistent with the literature results for young individuals in the mild COVID-19 category and may explain why no significant changes were observed in our study.

Fatigue is influenced by many factors, such as age, gender, disease status, and mental conditions. It also impairs the quality of life and reduces functionality (12). Due to these effects, fatigue is an important factor that affects life throughout the lifespan. Fatigue, which is also one of the most common symptoms of COVID-19 infection, is seen as the most persistent and performance-reducing symptom among COVID-19 symptoms. In a systematic review and meta-analysis study, it was reported that fatigue developed in 99.1% of cases, especially in patients with post-COVID-19 syndrome lasting 12 weeks or longer (24). The exact cause of the fatigue observed because of the COVID-19 infection is not yet fully understood. However, it is thought to be caused by factors such as inflammation, mitochondrial dysfunction, autonomic nervous system anomalies, poor nutritional conditions, respiratory complications, obesity, and physical inactivity, according to some estimates (25,26).

In our study, it was found that there was a difference in fatigue between individuals who had COVID-19 and those who did not, based on the results of CFS (p=0.02). This result is consistent with those of previous studies (24). However, statistical analysis between the study and control groups showed no difference in fatigue scores between men who had COVID-19 and those who did not (p=0.748), whereas a difference was observed in women (p=0.001). This result is consistent with the research conducted by Rudroff et al. (27). Rudroff et al. (27) stated that the exact reason for higher fatigue scores in women is unknown. However, they concluded that anxiety, depression, and sex hormones may be causative factors. None of our participants had any known psychological problems. The effect of the menstrual cycle and hormonal factors on fatigue is emphasized in the literature (28). Because we did not inquire about participants' ovarian hormone concentrations and menstrual phase parameters, as well as their depression and anxiety scores, and we could not perform a correlation analysis on this topic, we cannot make a clear interpretation. However, the use of CFS in our evaluation, which is mainly used to assess physical fatigue and whose exclusion criteria include psychogenic

problems, strengthens the claim that our fatigue measurements are not related to psychological conditions and that our results are reliable.

Previous studies have emphasized muscle strength loss and balance loss due to physical inactivity and inflammation encountered during the COVID-19 process (29,30). However, some studies have reported that rapid recovery of muscle strength occurs in young individuals (31). The similarity of the strength and balance measurements between the groups in our study may be related to the rapid recovery process of the young population. While the literature shows cases where this difference occurs due to prolonged post-COVID-19 syndrome, the mild COVID-19 status of our cases, the age factor, and the normal course of the recovery process can be associated with obtaining results independent of prolonged COVID-19 (32).

Soares et al. (23) showed that skeletal muscle atrophy can develop because of COVID-19 infection. In the study conducted by de Andrade-Junior et al. (22) on 32 patients, it was observed that individuals who had severe COVID-19 with an average age of 64.1 years had 30% atrophy in their rectus femoris cross-sectional areas. In this regard, when our study was reviewed again, it was determined that the individuals included in the study had a mild COVID-19 infection, so there was no exposure to the adverse effects of medication or long-term inactivity. Therefore, we anticipate that any potential muscle atrophy did not develop, or if it did, it was not at a level that would affect muscle strength. In addition, due to the age range of the participants in the sample being composed of young individuals, we anticipate that any potential atrophy would regenerate rapidly and not be reflected in the tests conducted. This view is supported by the study by Muehlbauer et al. (30), which showed that muscle atrophy is rapidly eliminated in young individuals. In our study, a moderate negative correlation was observed between fatigue score, JHD measurements, and Biodex angular torque measurements in the correlation analysis conducted among the study group. This is thought to be due to the significant difference between the fatigue scores of women (mean: 17.52±2.83) and men (mean: 13.36±4.61) in the study group (p=0.005). This difference may be related to gender.

Coronavirus disease-2019 has also been shown to have neurological effects. These effects include hyposmia, anosmia, myalgia, headache, confusion, delirium, dizziness, encephalopathy, stroke, epilepsy, Guillain-Barré syndrome, Miller-Fischer syndrome, and acute myelitis. Many of these diseases adversely affect the balance. Adverse effects on balance are important factors for mobility, functionality, and quality of life. Studies have reported that balance is negatively affected in COVID-19 patients compared with healthy individuals (33). In a study by de Sousa et al. (34), conducted on post-acute COVID-19 patients who were not hospitalized and had an average age of 35, it was stated that the balance of COVID-19 patients was negatively affected compared with the control group, and their quality of life was also adversely affected. In addition, they found that changes in balance values were correlated with physical capacity, hand grip strength, and mental health evaluation parameters (34). In a functional balance assessment study conducted by Guzik et al. (35) on young individuals with an average age of 22 years who had a moderate level of COVID-19, balance was negatively affected. However, in contrast to this information, Ychowska et al. (36) reported no significant difference in stabilometric measurements between individuals who had mild COVID-19 within two-four weeks and those who did not (average age 40 and 38.9, respectively). In addition, they noted that balance impairment increased in COVID-19 patients who had respiratory complaints compared with those without respiratory involvement (36).

In the correlation analysis performed within our study groups, it was determined that the balance scores of individuals with COVID-19 were associated with gender. No relationship was found among individuals without COVID-19. Plisky et al. (16) reported a difference in YBT scores based on gender in their study on healthy individuals, with higher scores in males. In our study, the high YBT scores in both groups of males were associated with anatomical differences compared with females. Shamsi et al. (37) predicted that gender is an important variable for YBT (38), and their study results support our view. Regarding COVID-19, our study found no loss of balance performance, which is similar to Ychowska et al.'s (36) studies.

Lewis et al. (38) highlighted the effect of heart rate variability during exercise on physical work capacity, stating that decreases in heart rate were inversely proportional to increases in muscle strength. The negative correlation between heart rate measurements during QCST, angular torque measurements, and JHD measurements obtained from the Biodex device in the study group is consistent with the findings of Lewis et al. (38). Additionally, the young age of the participants is consistent with the level of results obtained. In the control group, there were differences in angular torque and grip strength measurements by gender. The difference between our groups can be attributed to the COVID-19 infection, which can cause a loss in heart performance that may not cause complaints in daily life but may become apparent during submaximal exercise testing. This idea is supported by Wu et al.'s (39) study, where they found similar heart rate values after a 6-minute walk test in COVID-19 patients

with and without cardiac damage. They interpreted this result as cardiac fibrosis developing in COVID-19 patients who developed cardiac damage; however, because the fibrosis was in the early stages, there was no difference between the two groups.

The correlation between the estimated VO_{2max} measurements obtained from QCST and the isokinetic angular torque measurements obtained from Biodex agrees with the expected results. Lovell et al. (40) demonstrated that as lower extremity muscle strength increased, VO_{2max} measurements also increased. The negative correlation between estimated VO_{2max} measurements and fatigue scores in the study group was attributed to the lower fatigue scores of male participants in the study group. This is because male participants had higher muscle strength than females, and a negative correlation between fatigue scores and VO_{2max} measurements was expected because of the higher fatigue scores in female participants.

Study Limitations

This study has some limitations that should be considered. The difficulty of implementing the QCST and the requirement for continuous step cadence with a metronome may have negatively affected the participants' adaptation to the test. However, this test was chosen because of its ease of use, practical estimation of VO_{2max}, and minimal equipment requirements. For balance assessment, the decision not to use a computerized system may be attributed to the ease of using YBT in different clinical conditions and its frequent preference. In addition, limited access and the high cost of computerized systems played an effective role in our choice to use the YBT. Despite these limitations, our research has strengths. The researchers who administered the tests and evaluated the results during the study were different. In addition, the tests used in the assessments were selected in accordance with the target parameters. These tests are basic, non-invasive, cheaper, easy to understand, and suitable for every clinical situation. The sample of the study was selected from young adults, and our results contributed to the literature from this perspective.

Conclusion

The study focuses on the impact of COVID-19 on young adults, especially women, emphasizing that fatigue is a significant issue even in mild cases that do not require hospitalization. While muscle strength, exercise performance, and balance were generally unaffected in this group, fatigue symptoms were notably higher in the first year post-diagnosis than in those without COVID-19. The study also found some correlation between fatigue and other physical parameters, suggesting that the issue is complex. The data on the fatigue of COVID-19-related events are limited; therefore, these outcomes may be valuable for future research. The researchers believe that the mild disease history and young age of the participants could be factors in these outcomes. We think the next research should focus on COVID symptoms, surveillance, and therapy in different age groups.

Ethics

Ethics Committee Approval: Ethical permission for this study was obtained from the Ethics Committee of Marmara University Faculty of Health Sciences for Non-Interventional Clinical Studies (date: 27.01.2022, approval no: 16).

Informed Consent: Participants were informed about the study, and written consent was obtained.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

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

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Original Article

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Predictors of Sexual Dysfunction in Women Seeking Treatment for Opioid Use Disorder: A Comparative Cross-Sectional Study from a Tertiary Center

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Abstract

Aim: There is a critical need for scientific evidence on the sexual and reproductive health of women with opioid use disorder (OUD). The main objective of this study was to evaluate sexual dysfunction (SD) and depression in women with OUD and compare them with healthy controls, in addition to exploring possible predictors of SD.

Methods: This cross-sectional study was conducted between January and July 2023. Thirty-four women with OUD, according to the DSM-5, and 30 healthy controls were included. The Female Sexual Function Index (FSFI), Patient Health Questionnaire-9 (PHQ-9), and sociodemographic questionnaire were used to evaluate SD, depression, and characteristics related to substance use and sexual/reproductive history. Logistic regression analysis was performed to determine the predictors of SD in women with OUD.

Results: Twenty-nine percent (n=10) of the participants with OUD had SD. The scores of the FSFI desire, arousal, lubrication, orgasm (p=0.001 for all), satisfaction (p=0.001) subscales, and the total score (p<0.001) were lower in women with OUD than in the controls. Daily dosage of buprenorphine/naloxone [Odds ratio (OR)=1,956, p=0.027, 95% confidence interval (CI)=1,079-3,545] and PHQ-9 score (OR=1,403, p=0.012, 95% CI=1,076-1,829) were significantly associated with SD in women with OUD.

Conclusion: The high prevalence of SDs highlights the unmet sexual health needs of women with OUD. Screening and addressing depressive symptoms should be one of the first steps when caring for SDs in women with OUD.

Keywords: Opioid use disorder, sexual dysfunction, depression, female, buprenorphine/naloxone drug combination

Introduction

Opioid use disorder (OUD) is a chronic, relapsing condition that necessitates long-term treatment, particularly pharmacological management [opioid maintenance treatment (OMT)] combined with psychosocial interventions. OMTs include methadone (mu-opioid receptor agonist) and buprenorphine (bup) (a partial mu (μ) receptor agonist). Bup is the only OMT legally available in Turkey and can be prescribed as a bup/naloxone (nal) combination for the maintenance treatment of OUD. Maintenance of abstinence is a major issue in OUD, and the adverse effects of OMTs can disrupt treatment compliance.

Opioids, both endogenous and exogenous, both as a substance for abuse or for therapeutic purposes (such as in bup/nal), may influence the endocrine system (1) and have a role in sexual functioning (2). They have been demonstrated to cause hypogonadism by disrupting the hypothalamic-pituitary-adrenal axis, leading to a decrease in libido and erectile dysfunction in men (1,3). Additionally, they might also have an impact on the entire sexual cycle. The majority of research on alterations in

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sexual functioning was collected from male participants with OUD and/or OMT (4-6). A meta-analytic study of men with OUD revealed that the prevalence of sexual dysfunction in those taking methadone was 52%, almost twice that of those taking buprenorphine (24%), which is still highly prevalent (7). Despite the more severe medical, psychiatric, and functional consequences associated with substance use disorders (SUDs) in women, there is still very little research on sexual dysfunctions in women with OUD (8).

In addition to sexual health concerns, poor reproductive outcomes, such as an increased risk of contracting and transmitting sexually transmitted infections, a higher prevalence of unintended pregnancies, and a lower amount of contraceptive use, are frequently presented among women with SUDs (9-12). Reproductive and sexual health are essential parts of human well-being and interrelatedly affect each other. Additionally, psychiatric and social conditions may further complicate the reproductive and sexual outcomes of women with OUD (11). Therefore, collaborative management and implications of reproductive and sexual health interventions with OMTs may be beneficial (13).

Depression is the most common psychiatric comorbidity associated with OUD and has a bidirectional relationship with sexual dysfunction (14,15). Research has indicated that a large number of women with depression, ranging from 70% to 80%, may suffer from sexual dysfunction (16). On the other hand, the lifetime prevalence of depression in people with OUD could be up to 75% (14). The link between SD and depression in OUD could be due to comorbidities (psychiatric disorders, other treatments, etc.) and conditions (low socioeconomic status, traumatic experiences, etc.) associated with OUD (17). Furthermore, long-term OMT may lead to opioid-induced hypogonadotropic hypogonadism, which can impair androgen production and thus affect sexual function in women with OUD (17). However, there is still a lack of clarity.

There is a critical need for scientific evidence to identify practice gaps and guide planning and action to meet the sexual and reproductive health needs of women with OUD. The objective of this study was to examine and evaluate sexual dysfunction and depressive symptomatology in women seeking treatment for OUD and to compare it with a healthy control group in a Turkish sample. Our second aim was to explore the predictors and clinical correlates of sexual dysfunction in women with OUD. In addition, we investigated the characteristics related to the reproductive health of treatment-seeking women with OUD.

Methods

Compliance with Ethical Standards

The study was approved by the Clinical Research Ethics Committee of University of Health Sciences Turkey, Erenkoy Training and Research Hospital for Psychiatry and Neurological Diseases (date: 07.04.2023, approval no: 26) and executed in compliance with the regulations set forth in the Declaration of Helsinki and International Conference on Harmonization/Good Clinical Practice guidelines. Written informed consent was obtained from all participants before they enrolled in the study.

Study Design

This single-center, cross-sectional study included 34 treatment-seeking individuals with a diagnosis of OUD according to the Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5), who had applied for inpatient, outpatient, and rehabilitation clinics in the Alcohol and Substance Use Research, Treatment, and Education Center of Erenkoy Training and Research Hospital for Psychiatry and Neurological Diseases. This specialized unit is a referral center for primary and secondary healthcare services and admits patients from a broad geographical region, including urban and rural areas. The diagnosis of participants was confirmed by mental health professionals (M.E. and M.K.K.) who have expertise in addiction medicine. The participants were enrolled in the study consecutively between January and July 2023. Participants were included if they were 1) a woman aged 18-65 years, 2) diagnosed with OUD according to, and 3) sexually active during the last four weeks. Because no women with OUD within the inclusion criteria were hospitalized on the specified dates of our study, only outpatient participants were included. The exclusion criteria were as follows: 1) illiteracy; 2) being under the influence of any substance or alcohol or exhibiting withdrawal symptoms; 3) previous or current psychosis, intellectual disability, bipolar disorder, organic mental disorder, or dementia; 4) severe vital organ dysfunction; 5) being pregnant, in the postpartum period, on lactation, or on menopause; 6) the presence of a previously diagnosed neurological, metabolic, or endocrinological disorder. Before starting the study, six patients were excluded due to not being sexually active during the last four weeks, one for menopause, and two for not fulfilling the self-report scales (Figure 1). The control group comprised individuals who had attended the routine medical board report to apply for a job, as well as medical staff, their family members, and students. A sociodemographic and clinical data form, the Patient Health Questionnaire-9 (PHQ-9), and the Female Sexual Function Index (FSFI) were used for the analysis.

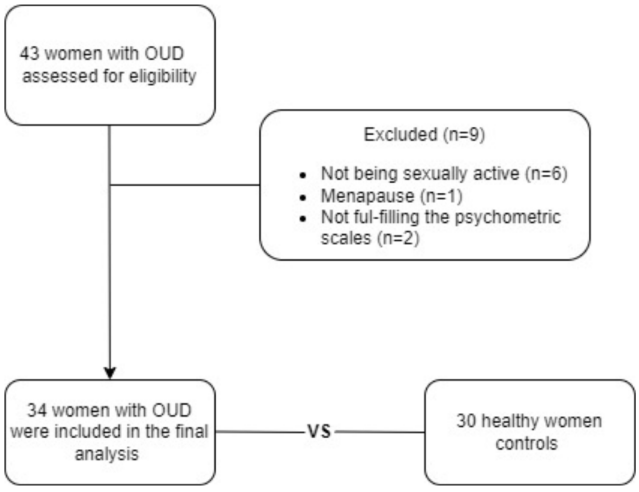

Figure 1. Study flow chart
OUD: Opioid use disorder

Sociodemographic and Clinical Data Form

The sociodemographic data form designed by the researchers contained information about the participants' demographic data, characteristics related to substance use, and brief sexual and reproductive histories. Height (cm) and weight (kg) with light clothing were measured. Body mass index [weight (kg)/height^2 (m^2)] was calculated to assess relative body fatness. Those with a menstrual cycle of 21-45 days were considered regular, while others were presumed to have an irregular menstrual cycle, and those without a menstrual period for 3 consecutive months were considered amenorrheic (18). Birth control planning methods were considered effective if the contraception method was one of the following: oral contraceptive pills, estrogen-progestin patches, condoms, diaphragms, or intrauterine devices.

Patient Health Questionnaire-9

The PHQ-9 depression module was employed to measure depressive symptoms. The PHQ-9 is a reliable and valid self-report tool for clinical and research use that evaluates the DSM criteria of depression from 0 (not at all) to 3 (nearly every day), producing a severity score ranging from 0 to 27 (19). A score of 5, 10, 15, or 20 corresponds to mild, moderate, moderately severe, and severe depression, respectively. PHQ-9 was found to be a valid and reliable screening tool for people with SUD (20).

Female Sexual Function Index

The FSFI was used to assess sexual functions over the last four weeks. This self-report scale consists of 19 items and 6 domains: desire, arousal, lubrication, orgasm, saturation, and pain (21). The first two items are rated on a five-point Likert scale (1 to 5), and the other items are rated on a six-point scale (0-6). The total score of the scale ranges between 2 and 36, and higher scores indicate better sexual functioning. A study on the reliability and validity of the Turkish version was conducted by Aygin (22) and demonstrated an internal consistency coefficient ranging between 0.70 and 0.96. The established cut-off for a diagnosis of sexual dysfunction in women across ages (18-74 years) and lifestyles is ≤26.55 for the total score (23).

Statistical Analysis

All statistical analyses were conducted using SPSS (Statistical Package for Social Science) version 21.0 software (IBM SPSS Statistics, New York, United States). The Kolmogorov-Smirnov test was performed to test normality. Non-normally distributed data are presented as medians and interquartile ranges (25th percentile and 75th percentile). Since the continuous variables did not follow a normal distribution, the Mann-Whitney U test was used to compare the characteristics of the OUD and control groups. Numbers and percentages are provided for the categorical data. The chi-square test was used to compare categorical variables. A binary logistic regression analysis was performed on the possible factors identified using univariate analyses to determine the predictors of sexual dysfunction in women with OUD. The presence of sexual dysfunction was defined according to the FSFI cutoff score. The Hosmer-Lemeshow test indicated that the model fits the data well [χ^2 (8)=8,204, p=0.414). The likelihood ratio test [χ^2 (2)=18,716, p<0.001) demonstrated that the logistic model was more effective than the intercept-only model. The level of significance was set at p<0.05 for all analyses.

Results

The socio-demographic, reproductive, and sexual history characteristics of OUD and control participants are presented in Table 1. Thirty-four women with OUD and thirty controls were recruited for the study. There was no statistical difference between the control and OUD groups in terms of age (p=0.083). Years of education, being employed or a student, and being married were statistically significantly higher in the control group (p=0.001, p<0.001, p<0.001,respectively). The control group employed effective contraception more frequently (p=0.007), whereas women with OUD had more abortion histories (p=0.042) and a greater number of sexual partners in the last year (p=0.011).

FSFI scores among the OUD and control groups revealed significant differences in desire, arousal, lubrication, orgasm, satisfaction, and total score, indicating worse sexual functionality in women with OUD (Table 2). The pain subscale of FSFI did not differ between the two groups (p=0.196). Patients with OUD had significantly

Table 1. Socio-demographic, reproductive, and sexual history characteristics of participants			
	OUD (n=34)	**Controls (n=30)**	**Statistics**
Age	25.5 (24-37)	29 (27-36)	p=0.083
Education (in years)	12 (8-13)	15 (13-15)	**p=0.001**
Occupational status -Employed/student -Unemployed	 13 (38.2%) 21 (61.8%)	 29 (96.7%) 1 (3.3%)	**p<0.001**
Marital status -Single -Married	 23 (67.6%) 11 (32.4%)	 6 (20%) 24 (80%)	**p<0.001**
Having children (yes)	12 (37.5)	13 (43.3%)	p=0.640
BMI (kg/m^2)	21.16 (19.81-25)	23.09 (20.6-25.8)	p=0.102
Menstrual cycle -Regular -Irregular -Amenorrhea	 27 (79.4%) 2 (5.9 %) 5 (14.7%)	 28 (93.3%) 2 (6.7%) 0	p=0.091
Sexual orientation -Heterosexual -Homosexual -Other	32 (100%)	30 (100%)	-
Birth control method -Effective (yes) -Condom -Oral contraceptive -Penile withdrawal before ejaculation -Intrauterine device -None	 8 (23.5%) 4 (11.8%) 3 (8.8%) 4 (11.8%) 1 (2.9%) 22 (64.7%)	 17 (56.7%) 10 (33.3%) 3 (10%) 3 (10%) 4 (13.3%) 10 (33.3%)	**p=0.007***
No. of pregnancies	1 (0-1)	0 (0-1)	p=0.835
No. of deliveries	0 (0-1)	0 (0-1)	p=0.778
No. of abortions	0 (0-1)	0 (0-0)	p=0.042
No. of sexual partners in last year	1 (1-2)	1 (1-1)	p=0.011
Sexual activity while intoxicated -Last year (Yes) -Life-long (Yes)	 8 (23.5%) 24 (70.6%)	 0 0	 **p=0.005** **p<0.001**
Exchanged sex for money/substance -Last year (yes) -Life-long (yes)	 2 (5.9%) 3 (8.8%)	 0 0	 p=0.177 p=0.096
*Effective vs. ineffective/none, OUD: Opioid use disorder Mann-Whitney U and chi-squared tests were performed			

Table 2. Psychometric scale scores among comparison groups			
	OUD	**Controls**	**Statistics**
Desire	3 (1.8-4.2)	4.2 (3.6-4.8)	**p<0.001**
Arousal	3 (1.8-3.9)	4.8 (3.9-5.1)	**p<0.001**
Lubrication	3.75 (2.7-4.5)	5.25 (4.5-6)	**p<0.001**
Orgasm	3.6 (2.4-4.8)	5 (4.8-5.6)	**p<0.001**
Satisfaction	4.4 (2.4-5.2)	5.2 (4.8- 5.6)	**p=0.001**
Pain	4.6 (3.6- 5.6)	5.2 (4.4-5.8)	p=0.196
Total-FSFI	22.35 (16.5-26.7)	29.75 (27.8-31.3)	**p<0.001**
PHQ-9	12.5 (10-19)	5 (4-9)	**p<0.001**
OUD: Opioid use disorder, FSFI: Female sexual function index, PHQ-9: Patient health questionnaire-9. Mann-Whitney U test was performed			

higher scores on the PHQ-9 than controls (p<0.001). Of the OUD group, 76.5% (n=26) had moderate to severe depression, whereas this rate was 20% in the controls.

29.4% (n=10) of the participants with OUD had sexual dysfunction, according to the FSFI. There was no statistically significant difference in the age at onset of substance use (p=0.956), age at onset of opioid use (p=0.752), duration of opioid use (p=0.752), history of inpatient treatment for OUD (p=0.452), or presence of intravenous administration of opioids (p=0.961) between women with and without sexual dysfunction in the OUD group. The daily dosage of bup/nal treatment (p=0.042) and the total score of PHQ-9 (p=0.003) were significantly higher in the group with sexual dysfunction. Characteristics related to substance use and depression in the OUD group according to the presence of sexual dysfunction are summarized in Table 3.

Logistic regression analysis revealed that the daily dosage of bup/nal treatment (OR=1,956, p=0.027, 95% CI=1,079-3,545) and total PHQ-9 score (OR=1,403, p=0.012, 95% CI=1,076-1,829) were significantly associated with the presence of sexual dysfunction in women with OUD. Table 4 demonstrates the results of the logistic regression.

Discussion

The aim of the present study was to explore sexual dysfunctions, depressive symptomatology, and characteristics related to reproductive health in women with OUD and to compare them with a healthy control group, in addition to investigating predictors and clinical correlates of sexual dysfunction in women with OUD. Our results revealed that almost a third of the women with OUD had been experiencing sexual dysfunction, differing significantly from the healthy controls in all domains of sexual functioning except for pain. Depression, along with the daily dosage of bup/nal treatment, predicted sexual dysfunction in women with OUD. It was established that women with OUD had inadequate resources regarding reproductive health (utilizing ineffective birth control methods and higher abortion rates) and exhibited risky sexual behaviors (engaging in sexual activity while intoxicated).

Despite the greater prevalence of UOD in men, the gender gap has been narrowing, indicating a critical need for study in women with OUD. A 2022 study conducted in Turkey revealed that 7.6% of those who declared that they had used heroin at any point in their lives were women (24). Women with SUDs tend to demonstrate a higher degree of impairment in terms of employment, social/family functioning, and medical functioning compared with men, as well as worse psychiatric outcomes (8). Due to the high level of burden associated with OUD in women, every effort to improve quality of life and treatment compliance, including assessment and intervention for sexual dysfunctions, is critical.

Studies on men with bup/nal treatment due to OUD demonstrated significant sexual dysfunctions such as erectile dysfunction (25,26), loss or reduction in sexual desire, and ejaculatory problems. A 4-month follow-up study in men with OUD revealed that bup/nal treatment resulted in an increase in sexual problems (6). Our research revealed a significant decrease in almost all domains of sexual functioning in women with OUD compared with controls. In line with our findings, a limited number of other studies have shown worse sexual functioning in women with OUD (17,27). It is likely that the widespread sexual dysfunction experienced by women with OUD is the result of a variety of biological, medical, psychological, sociocultural, political, economic, and interpersonal factors, thus demonstrating the complexity of the relationship between sexuality and OUD. Despite the high rates of sexual dysfunction in OUD, help-seeking behavior was observed to be very low in previous research, underpinning the need for proactive inquiry about the sexual health of patients (28).

Opioids, serotonin, and endocannabinoids are key neuromodulators of inhibitory pathways in the female sexual response cycle; thus, OUD and OMT may have a

Table 3. Characteristics related to substance use and depression in OUD group according to presence of sexual dysfunction

	SD+ (n=10)	SD- (n=24)	Total (n=34)	Statistics
Age at onset of substance use	17.5 (15.5-22)	19 (16-21)	18 (16-22)	p=0.956
Age at first opioid use	18 (17-22.5)	20 (18-21)	18.5 (17-22)	p=0.752
Duration of opioid use (months)	60 (36-90)	66 (36-108)	60 (36-96)	p=0.752
IV usage (yes)	7 (27.3%)	3 (30%)	10 (29.4%)	p=0.961
Daily dosage of Bup/Nal treatment	10 (8-14)	9 (4-10)	10 (8-12)	**p=0.042**
History of inpatient treatment for OUD (yes)	13 (54.2%)	4 (40%)	17 (50%)	p=0.452
PHQ-9	15.5 (12-19)	9 (5-11)	12.5 (10-19)	**p=0.003**
BMI	20.63 (19.87-25.2)	23.25 (18.37-23.83)	21.16 (19.81-25)	p=0.809

Mann-Whitney U and chi-squared tests were performed.
OUD: Opioid use disorder, SD: Sexual dysfunction, Bup/Nal: Buprenorphine/Naloxone, PHQ-9: Patient health questionnaire-9, BMI: Body mass index

Table 4. Logistic regression analysis of predictors of sexual dysfunction in women with OUD

	SE	Wald χ^2	P-value	OR	95% CI
Bup/Nal dosage	0.303	4.888	0.027	1.956	[1.079-3.545]
PHQ-9	0.135	6.245	0.012	1.403	[1.076-1.829]

A binary logistic regression analysis was performed
OUD: Opioid use disorder, Bup/Nal: Buprenorphine/Naloxone, PHQ-9: Patient health questionnaire-9, SE: Standard error, P: Statistical significance, OR: Odds ratio, CI: Confidence interval

considerable negative effect on sexual functions (29). Substance use rapidly reduces the response to biological rewards, including sex, and impairs the behaviors that are normally rewarding (30). Additionally, opioid agonists may inhibit the pulsatile secretion of the gonadotropin-releasing hormone in the hypothalamus, leading to hypogonadotropic hypogonadism, which may be one of the other underlying factors between OUD and sexual dysfunctions (31,32). Survivors of cancer who have chronically consumed opioids were shown to have higher levels of sexual dysfunction, which is probably due to similar etiopathogenetic mechanisms (33). However, there are other studies demonstrating better sexual functioning on maintenance compared with treatment-naïve men with OUD (34).

Our results revealed that the dosage of bup/nal treatment is a predictor of sexual dysfunction in women with OUD. Studies on opioid doses (either methadone, buprenorphine/naloxone, or opioids prescribed for pain) have demonstrated contradictory findings regarding their relationship with sexual functions in men (35,36). Zamboni et al. (17) reported a positive correlation between methadone dose and sexual dysfunction in women with OUD; however, this was not present in the but group. Clearly, further evidence accompanied by biological indicators such as gonadotropin and sex hormone levels is needed to determine if a dose-effect relationship exists between SD and opioids.

There are other important factors that can affect the sexual functions of women with OUD. It is noteworthy that traumatic experiences, which affect sexuality, are more common in women with SUDs (27). A higher prevalence of psychiatric comorbidities, such as depression and anxiety, in women with OUD could also contribute to negative sexual functioning (37). In parallel, our results showed that depressive symptoms predict sexual dysfunction in women with OUD, underpinning the need for screening and effective management strategies for psychiatric comorbidities in OUD.

Women with OUD face a plethora of obstacles, such as organizational, financial, social, and psychological issues, which in turn can lead to risks concerning their reproductive health. In our study, we observed that women with OUD used less efficient birth control methods and had higher rates of abortion than the controls. In addition, risky behaviors such as engaging in sexual activity while intoxicated carry the risk of non-consensual sex and sexually transmitted diseases, which are common among women with OUD (38-40). Coupled with OUD, these situations could create greater vulnerability for sexual dysfunction and create barriers to a healthy sexual life.

Study Limitations

The inability to evaluate the baseline sexual functions of patients before OUD diagnosis and the cross-sectional design of the study limit the ability to establish cause-and-effect relationships. Evaluation of sexual functions by self-reporting may have led to recall bias. However, it may have facilitated self-disclosure about sexuality for participants. Although we had a relatively small sample size, it demonstrated substantial differences between the control and OUD groups. Moreover, the limited number of participants may have been a result of the dominance of males with OUD, coupled with women's difficulty in accessing treatment for OUD. Despite its limitations, our article made a valuable contribution to the literature by providing data on sexual dysfunction in women with OUD, which is rarely reported, and comparing it with healthy controls.

Conclusion

These data highlight the unmet sexual and reproductive health needs of women with OUD. Sexual dysfunction is common in women with OUD, which can create a major impediment to adherence to long-term OMT. The presence of depressive symptoms may have a substantial impact on sexual functions; therefore, better screening and intervention strategies should be implemented in routine care for women with OUD. Owing to the common adversities concerning reproductive health, women with OUD could benefit from integrated services in addiction care and sexual and reproductive health.

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Ethics

Ethics Committee Approval: The study was approved by the Clinical Research Ethics Committee of University of Health Sciences Turkey, Erenkoy Training and Research Hospital for Psychiatry and Neurological Diseases (date: 07.04.2023, approval no: 26) and executed in compliance with the regulations set forth in the Declaration of Helsinki and International Conference on Harmonization/Good Clinical Practice guidelines.

Informed Consent: Written informed consent was obtained from all participants before they enrolled in the study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: E.E.B., R.B., Design: N.G.U.S., M.E., M.K.K., Data Collection or Processing: N.G.U.S., M.E., M.K.K.,

Analysis or Interpretation: N.G.U.S., M.E., Literature Search: N.G.U.S., M.E., Writing: N.G.U.S., M.E., M.K.K., E.E.B., R.B.

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

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Association of Stress and Laryngopharyngeal Reflux with Vocal Fold Polyps

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Abstract

Aim: Stress and laryngopharyngeal reflux can cause many laryngeal pathologies. In this study, we aimed to investigate the role of stress and laryngopharyngeal reflux (LPR) in the development of vocal fold polyps.

Methods: Forty-five patients who were scheduled for surgery because of vocal fold polyps between October 2021 and May 2022 were included in the study. A control group was formed from 45 patients who applied to the otolaryngology outpatient clinic with the complaint of hoarseness lasting more than 3 weeks and had no vocal cord lesion in their 70-degree rigid endoscopic examination. Participants were asked to complete the reflux symptom index and depression anxiety stress scale (DASS) questionnaires. Reflux finding score (RFS) and grade, roughness, pallor, asthenia, strain, instability (GRBASI) voice analyses were conducted by two otolaryngologists familiar with both scales.

Results: There was no significant difference between the speech characteristics of the patient groups. Reflux symptom index, RFS, and GRBASI scores were significantly higher in the group with vocal fold polyps (p=0.000, p=0.000, and p=0.009, respectively). Stress scores for DASS were significantly higher in the control group (p=0.025). There was no significant difference between the two groups in terms of depression and anxiety scores.

Conclusion: Laryngopharyngeal reflux is more prevalent in patients with vocal fold polyps. This may be related to mucosal or submucosal damage from LPR. We also observed that increased stress can cause hoarseness without vocal fold lesions.

Keywords: Voice, vocal cords, laryngopharyngeal reflux, anxiety

Introduction

Hoarseness is defined as an altered voice quality that impairs communication and has a prevalence of approximately 1% among patients (1). The etiology mainly includes laryngitis, functional dysphonia, benign or malignant vocal fold lesions, vocal cord paralysis, aging, and psychogenic factors (2). The duration of the complaint should be carefully questioned in the assessment of hoarseness. For example, hoarseness lasts less than 3 weeks in respiratory tract infections, and psychogenic factors should be considered in cases of sudden loss of voice (3).

Providing high-resolution image quality, rigid transoral laryngoscopy is a favorable way to screen and examine vocal fold mucosal lesions (4). If dysphonia does not resolve within 3 weeks or if a serious underlying cause is suspected, clinicians should perform diagnostic laryngoscopy at any time and advocate voice therapy for appropriate indications (5). Surgery is preferred in patients with suspected malignancy, benign vocal fold lesions (BVFL) that do not respond to conservative management, or glottic insufficiency. In addition, botulinum toxin injection may be a therapeutic option for patients with spasmodic dysphonia and laryngeal dystonia (6).

Vocal fold polyp (VFP) is a proliferative disease that occurs in the superficial layer of the vocal fold's lamina propria and is a benign lesion. Microsurgery in treatment is a method that improves voice quality and has a low recurrence rate (7). However, the risks associated with surgery and anesthesia lead some patients to opt for voice therapy. Although voice therapy has certain therapeutic effects on VFPs, the success of treatment can be affected by many factors, such as the length of therapy and patient education (8).

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In recent years, studies investigating the relationship between benign vocal cord lesions such as polyps, nodules, Reinke's edema, and laryngopharyngeal reflux (LPR) have become popular. Although there are many studies supporting this association, the epidemiological evidence still remains unclear (9,10). Furthermore, some studies have reported that emotionally maladjusted conditions, including depression and anxiety combined with LPR, could exacerbate the symptoms of BVFL in adults (11,12). In line with this information, we investigated the role of stress and LPR in the development of VFPs.

Methods

Compliance with Ethical Standards

The study was approved by the Institutional Review Board of University of Health Sciences Turkey, Istanbul Training and Research Hospital, (approval no: 2766, date: 05.03.2021). All procedures were performed in accordance with the ethical standards set forth in the World Medical Association Declaration of Helsinki (Scotland 2000). Informed consent forms were obtained from all patients.

Patients and the Study Design

Forty-five patients who were scheduled for surgery because of VFPs between October 2021 and May 2022 were included in the study. A control group was formed from 45 patients who applied to the otolaryngology outpatient clinic with the complaint of hoarseness lasting more than 3 weeks and had no vocal cord lesion in their 70-degree rigid endoscopic examination. The diagnosis was confirmed by videolaryngostroboscopy (VLS) in all patients, and the examinations were recorded. The age distribution between the two groups was matched. Attention was also paid to gender matching between both groups, as women with voice disorders were more likely to report stress, anxiety, and depression.

The following groups were excluded from the study: a) causes of benign vocal cord lesions other than VFPs; b) lesions suggestive of malignant vocal fold tumors such as leukoplakia; b) dysphonic patients with a history of psychiatric medication or suspected psychological-based voice pathology; c) patients diagnosed with dysphonia due to systemic diseases; d) patients with neurological pathologies such as vocal cord paralysis or paresis; and e) patients diagnosed or treated for gastroesophageal reflux (Figure 1).

All patients included in the study were asked to complete the reflux symptom index (RSI) and depression anxiety stress scale (DASS) questionnaires. RFS and grade, roughness, pallor, asthenia, strain, instability (GRBASI) voice analyses were conducted by two otolaryngologists familiar with both scales. The two groups were compared with their questionnaire scores and examination findings (Figure 2). The treatment of patients in the group with VFPs was surgically planned. RSI and RFS were used to evaluate LPR, and reflux treatment was added to patients with high RFS and RSI scores.

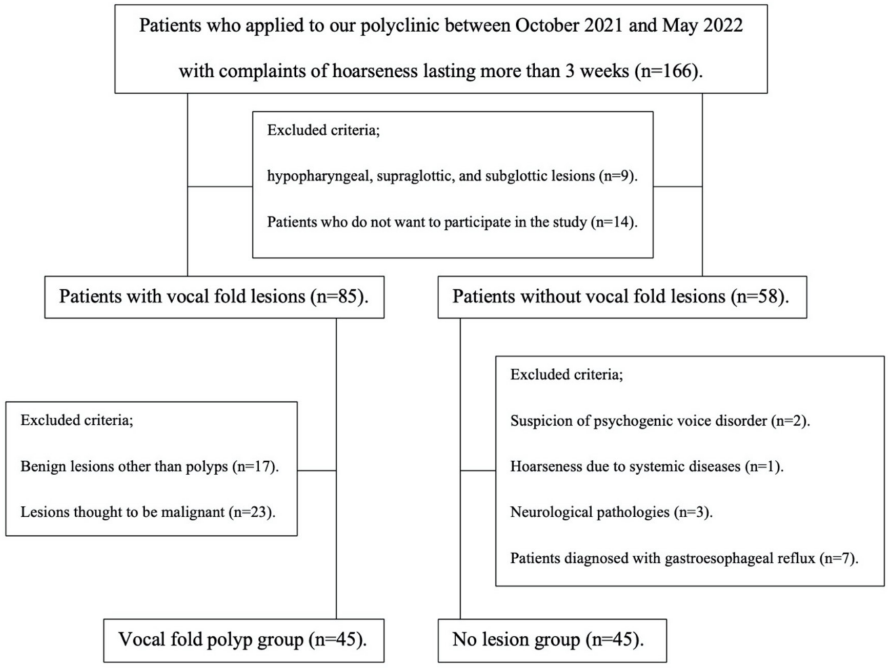

Figure 1. Flowchart of the study

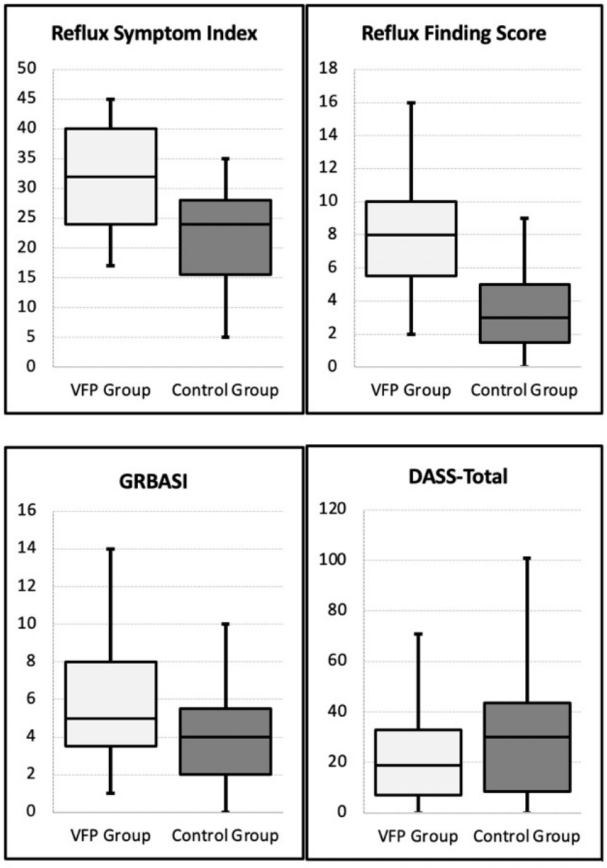

Figure 2. Comparison of the scores of both groups
VFP: Vocal fold polyp, GRBASI: Grade, roughness, pallor, asthenia, strain, instability, DASS: Depression anxiety stress scale

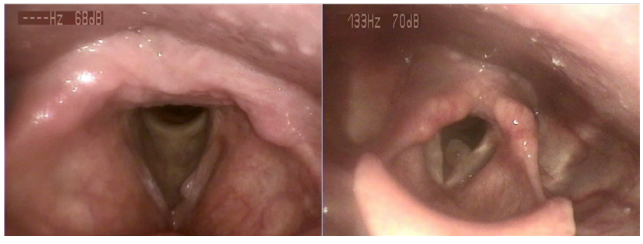

Figure 3. Videolaryngostroboscopic examination of patients with vocal fold polyp

Videolaryngostroboscopy

Videolaryngostroboscopic was examined by two otolaryngologists via a rigid endoscope using the Xion stroboscopy system (Xion EndoSTROB, Berlin, Germany) (Figure 3). The records were based on the visualization of the participants' comfortable loudness and modal phonation of the/ee/vowel sound on VLS. The standard evaluation forms of the reflux finding score (RFS) and voice quality scale GRBASI were scored and filled out during enrollment.

Reflux Finding Score

This scale provides an assessment of the physical manifestations of reflux in videolaryngostroboscopy. Scores were assessed and rated by a single otolaryngologist. Subglottic edema, ventricular obliteration, erythema/hyperemia, vocal fold edema, diffuse laryngeal edema, posterior commissure hypertrophy, granuloma/granulation tissue, and thick endolaryngeal mucus were scored using the standard RFS evaluation form. Based on previous confirmed studies, an RFS of 7 was considered positive (13).

Grade, Roughness, Pallor, Asthenia, Strain, Instability

The GRBASI scale, which evaluates the grade of dysphonia, roughness, shortness of breath, asthenia, strain, and instability, is used by clinicians as a vocal assessment tool (14). In this study, auditory-perceptual voice analyses were conducted by an otolaryngologist blind to diagnoses and a speech therapist familiar with both scales using the sustained vowel and reading tasks of the sentences. Each evaluation on the scale was evaluated over 18 points out of 3 as normal (0 points), mild (1 point), moderate (2 points), and severe (3 points).

Reflux Symptom Index

We used the Turkish version of the RSI developed and validated by Akbulut et al. (15). Reflux symptom index is a nine-item questionnaire created to scale the severity of reflux symptoms. Each item was scaled from 0 to 5, with 0 representing no problem and 5 representing a severe problem. Based on the validated Turkish version, an RSI of 12.5 was considered positive for reflux.

Depression Anxiety Stress Scale-42

We used the DASS-42 item validated by Hekimoglu et al. (16), which measures depression, anxiety, and stress moods in the last week. For each of the 3 subscales, 14 responses were evaluated between 0 (did not apply) and 3 (applied most of the time) points. Responses were evaluated to form each subscale and the total DASS-42 score.

Statistical Analysis

The IBM SPSS 28.0 package program (SPSS Inc.; Chicago, IL,USA) was used for the analysis. In the descriptive statistics of the data, the mean, standard deviation, and median values were used. The distribution of variables was measured using the Kolmogorov-Smirnov test and the Mann-Whitney U test in the analysis of quantitative independent data. The chi-square test was used in the analysis of qualitative independent data, and the Fischer test was used when the chi-square test conditions were not met. Spearman correlation analysis was used in the correlation analysis. Statistical significance was granted at a p level ≤ 0.05.

Results

The mean age of the patients included in our study was 41.5 years (range from 17 to 73). The mean age of the VFP group was 43.0±11.9 years, and that of the control group was 39.1±14.3. Given the likely influence of gender on the findings, there were equivalent numbers of women in both groups that permit a fair and valid comparison. Of the 90 patients, 45 were smokers. The demographic status and speech characteristics of the patients are given in Table 1. As stated in this table, no significant difference was found between the VFP and control groups in terms of age, gender, smoking, talkativeness, and speaking loudly.

The reflux symptom index, RFS, and GRBASI score were found to be significantly higher in the group with VFPs (p=0.000, p=0.000, and p=0.009, respectively) (Table 2). When the VFPs and control groups were evaluated in terms of DASS scores, the stress scores were significantly higher in the control group (p=0.025). There was no significant difference between the groups in terms of depression, anxiety, and total DASS scores (Table 2). A significant (p<0.05) correlation was observed between the reflux symptom index, RFS, GRBASI score, and DASS scores (Table 3).

Table 1. The demographic status and speech characteristics of the patients

		VFP group (n=45)		No lesion group (n=45)		p-value
		Mean ± SD / n%	Median	Mean ± SD / n%	Median	
Age		43.0±11.9	44.0	39.1±14.3	37.0	0.111[m]
Gender	Female	21±46.7%		32±71.1%		**0.018**[X²]
	Male	24±53.3%		13±28.9%		
Smoking	No	25±55.6%		20±44.4%		0.292[X²]
	Yes	20±44.4%		25±55.6%		
Talkativeness	Average talker	1±2.2%		3±6.7%		0.421[X²]
	Talkative	30±66.7%		32±71.1%		
	Extremely talkative	14±31.1%		10±22.2%		
Speaking loudly	Rarely	20±44.4%		21±46.7%		0.495[X²]
	Sometimes	20±44.4%		22±48.9%		
	Often	5±11.1%		2±4.4%		

[m]: Mann-Whitney U test, [X²]: Chi-square test (Fisher's exact test), VFP: Vocal fold polyps, SD: Standard deviation

Table 2. Comparison of the scores of both groups

		VFP group (n=45)		No lesion group (n=45)		p-value
		Mean ± SD / n%	Median	Mean ± SD / n%	Median	
Reflux symptom index		31.9±8.7	32.0	22.0±9.0	24.0	**0.000**[m]
Reflux finding score		7.7±3.1	8.0	3.2±2.6	3.0	**0.000**[m]
GRBASI		5.7±3.1	5.0	4.0±2.6	4.0	**0.009**[m]
DAS scales						
Depression		4.0±5.7	2.0	4.4±7.0	1.0	0.511[m]
Depression	Normal	42±93.3%		38±84.4%		0.180[X²]
	Mild	1±2.2%		2±4.4%		
	Moderate	0±0.0%		3±6.7%		
	Severe	1±2.2%		1±2.2%		
	Extremely severe	1±2.2%		1±2.2%		
Anxiety		8.7±6.3	9.0	9.3±7.6	8.0	0.945[m]
Anxiety	Normal	20±44.4%		21±46.7%		0.832[X²]
	Mild	5±11.1%		5±11.1%		
	Moderate	14±31.1%		9±20.0%		
	Severe	2±4.4%		5±11.1%		
	Extremely severe	4±8.9%		5±11.1%		

Table 2. Continued						
		VFP group (n=45)		No lesion group (n=45)		p
		Mean ± SD / n%	Median	Mean ± SD / n%	Median	
Stress		8.9±7.6	8.0	15.1±11.8	16.0	**0.025**[m]
Stress	Normal	34±75.6%		20±44.4%		**0.003**[X2]
	Mild	4±8.9%		8±17.8%		
	Moderate	6±13.3%		7±15.6%		
	Severe	1±2.2%		7±15.6%		
	Extremely severe	0±0.0%		3±6.7%		
DASS-total		21.4±16.3	19.0	28.8±23.0	30.0	0.159[m]

[m]: Mann-Whitney U test, [X2]: Chi-square test (Fisher's exact test), VFP: Vocal fold polyps, SD: Standard deviation

Table 3. Correlation of RSI, RFS, GRBASI with DASS						
	Reflux symptom index		Reflux finding score		GRBASI	
	r	p	r	p	r	p
DAS scales						
Depression	0.318	**0.002**	0.236	**0.025**	0.299	**0.004**
Anxiety	0.493	**0.000**	0.284	**0.007**	0.379	**0.000**
Stress	0.296	**0.005**	0.190	0.073	0.273	**0.009**
DASS-total	0.413	**0.000**	0.247	**0.019**	0.374	**0.000**

Spearman Correlation Coefficient, DASS: Depression, anxiety, stress scales, RSI: Reflux symptom index, RFI: Reflux finding score, GRBASI: Grade, roughness, pallor, asthenia, strain, instability

Discussion

Hoarseness can be caused by many diseases, from simple upper respiratory tract infections to malignancies. Hoarseness that lasts longer than 3 weeks should be evaluated by an otolaryngologist because it may be a sign of cancer. The most common benign lesions were polyps, nodules, and Reinke's edema. In an incidence study by Jung et al. (17), it was revealed that the incidence and prevalence increased over the years and that BVFL was more common in women. We did not observe any difference in terms of age or gender between the groups included in our study.

Our intensive observation of LPR findings in patients who presented with hoarseness and in whom we could not detect any pathology during endoscopic laryngeal examination led us to this study. LPR can cause many symptoms due to caustic mucosal damage to gastric contents in the larynx and pharynx (13). Some of these symptoms are hoarseness, throat clearing, post-nasal drip, difficulty breathing, troublesome cough, heartburn, chest pain, or stomach acid coming up (18). 24-hour ambulatory pH monitoring is accepted as the gold standard for diagnosis. In their 2023 meta-analysis study, Ren et al. (19) concluded that LPR diagnosed by pharyngeal pH monitoring is associated with the formation of BVFLs. However, many clinical studies have shown that the diagnosis of LPR can be confirmed by RSI and RFS assessments (13,18,20,21). We also used RSI and RFS for LPR. The most common LPR findings in patients with vocal cord polyps were posterior commissure hypertrophy and hyperemia/edema in the arytenoid mucosa.

In the literature review of Lechien et al. (22), it was reported that the frequency of LPR was high in the patient group with BVFL and that caustic mucosal vocal fold injury caused by LPR may cause nodule, polyp, or Reinke's edema formation. Similarly, Chung et al. (23) showed that LPR may play a role in the etiology of Reinke's edema and vocal cord polyps. In addition, vocal abuse, smoking, alcohol intake, or LPR may be other etiological factors in the development of BVFL. Apart from these studies revealing the relationship between LPR and BVFL, there are also studies emphasizing that the diagnosis of reflux may be overdiagnosed and other causes of hoarseness should be considered when empirical proton pump inhibitor therapy is unsuccessful (24-26). We believe that LPR is a disease that can lead to overdiagnosis. It should not be forgotten that starting treatment by diagnosing only anamnesis, especially without endoscopic evaluation, may lead to delays in the diagnosis of laryngeal diseases. Carroll (26) stated that VLS should be applied to all patients with dysphonic complaints and that manometry or pH testing should be recommended if no pathological

condition beyond the classical LPR findings is observed. We also evaluated all our hoarseness patients with VLS. In this study, we found high RSI and RFS scores in patients with vocal cord polyps and recommended proton pump inhibitor therapy to patients without polyps but with high RSI and RFS scores.

Grade, roughness, pallor, asthenia, strain, instability is one of the most traditional approaches for describing vocal quality and is used for the auditory-perceptual evaluation of voice (27). In our study, auditory-perceptual voice analyses were conducted by two experienced otolaryngologists. Regardless of the etiology, GRBASI is widely used in all voice disorders. Nemr et al. (14) evaluated the GRBASI scale as an objective test focusing on the glottic level compared with other voice analysis scales. We compared patients with VFPs and patients without lesions using the GRBASI scale and found that patients with VFP had lower voice quality.

VHI-30 is a tool for measuring patients' perceptions of voice disorders. It is self-administered and can be scored quickly during the assessment. Evaluation is made using three subscales: Functional, physical, and emotional. Each index is evaluated over 30 questions, between 0 and 4 points, and a maximum of 120 points. Since the early 2000s, VHI has provided a concise tool for the initial and follow-up assessment of patients with any voice disorder (28). Townes et al. (29) demonstrated that VHI was significantly associated with the presence of BVFL in pediatric patients and could be useful in predicting the etiology of dysphonia. In our opinion, unlike this study, VHI cannot be expected to be specific to any voice disorder.

The relationship between depression, anxiety, stress, and voice disorders has been evaluated in many studies in the literature, and a significant relationship has been found in patients with and without BVFL (30,31). In a study by Dietrich et al. (30), it was observed that patients with hoarseness had similar profiles in depression, anxiety, and stress assessments with or without vocal cord lesions. Considering the high LPR scores in our lesion-free control group and the publications indicating that depression, anxiety, and stress are associated with LPR, we added the DASS questionnaire to our study (32,33). Stress scores were significantly higher in the group without lesions. However, there was no significant difference between the groups in the depression and anxiety scores. Considering this information, psychiatric evaluation may be considered in addition to reflux treatments in selected hoarseness patient groups.

Study Limitations

The present study has several limitations. First, further studies with larger case numbers are required. Second, as previously discussed, 24-hour pH monitoring is the gold standard for diagnosing reflux. However, RSI and RFS were used in our study. Third, the evaluation of patients with acoustic analysis and long-term results may increase the importance of the study. Despite these limitations, our study is the first to combine RSI and DASS questionnaires with RFS and GRBASI analyses to investigate the relationship between LPR and VFPs.

Conclusion

Laryngopharyngeal reflux is more prevalent in patients with VFPs. This may be related to mucosal or submucosal damage from LPR. Although we prioritize surgery in our clinical approach to VFPs, the combined treatment of antireflux and voice therapy may be an alternative for small VFPs. We also observed that increased stress can cause hoarseness without vocal fold lesions. Psychotherapy can be added to patient education as a treatment for these patients.

Ethics

Ethics Committee Approval: The study was approved by the Institutional Review Board of University of Health Sciences Turkey, Istanbul Training and Research Hospital, (approval no: 2766, date: 05.03.2021).

Informed Consent: Informed consent forms were obtained from all patients.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

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

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Original Article

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Factors Associated with Non-Hemorrhagic Extra-Axial Fluid Collection after Cranioplasty

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Abstract

Aim: Even though, cranioplasty (CP) is an easy surgery to perform, reoperation rate is high because of complications like infection, new-onset seizure, bone flap resorption, hydrocephalus, intracranial hemorrhage, and extra-axial fluid collection (EAFC). Epidural fluid collection is not well described in the literature. In this context, we aimed to evaluate non-hemorrhagic EAFC collections seen after CP procedure.

Methods: From May 2016 to December 2021, Patients with or without EAFC who have undergone CP were retrospectively evaluated with the parameters of age, gender, first surgical diagnosis, the material used in CP, sinking skin flap presence, midline shift (MS), comorbidity factors, pre-operative duration, length of hospital stay in the first surgery, pre-and post-operative Glasgow outcome scores, bleeding in the surgical site, EAFC, infection, hydrocephalus, CP area, new-onset seizure after CP, reoperation risk and reoperation time.

Results: A total of 106 patients, 70 male, and 36 female, with a mean age of 39.13±17.86 were included in the study. The number of patients with EAFC is 49 and the number of patients without EAFC is 57. The mean hospital stay day of EAFC (+) group (38.28±36.54) is longer and statistically significant compared to the EAFC (-) group (22.19±24.87) (p=0.009). Time interval between surgeries for EAFC (+) group was 215.51±284.28 days and EAFC (-) group was 226.26±509.36 days. Re-operations were performed in 16 of 49 patients who developed EAFC (32.6%) (p=0.022). Infections 68% (n=11), intracerebral hemorrhage 6.2% (n=1), seizure (6.2%), MS (6.2%), subgaleal effusion (6.2%), hydrocephalus (6.2%). Re-operation time EAFC (+) is 5.2±5.41 months and EAFC (-) 20.55±21.3 months (p=0.041).

Conclusion: Particularly in frail patients with a longer hospital stay, after CP, EAFC cases should be closely follow up due to the risk of re-surgery as a result of infection.

Keywords: Cranioplasty, epidural fluid collection, complication

Introduction

Cranioplasty (CP) is a surgical procedure performed to cosmetically close cranial bone defects to both create a physical barrier and normalize the cerebrospinal fluid (CSF) and brain-blood circulation in patients who have undergone decompressive craniotomy or craniectomy (DC) to reduce the increased intracranial pressure following a traumatic brain injury, cerebral infarct, subarachnoid bleeding, intracranial hematoma, encephalitis, sinus vein thrombosis, tumor or aneurysm surgery (1-5).

Although CP is technically an easy surgery to perform, it has up to 45.3% complication rates including infection, new-onset seizure, bone flap resorption, hydrocephalus, intracranial hemorrhage (ICH), and extra-axial fluid collection (EAFC) (2-11).

Shepetovsky et al. (7) found in their review conducted with 636 patients that the EAFC complication, among others, ranged between 1.1% and 37.3% with an average of 6.0%. Jeong et al. (12) evaluated the surgical intervention rate as 20% for patients who developed EAFC. In addition, Kim et al. (13) associated EAFC with surgical site infection after CP. The fact that EAFC requires surgical re-intervention and its possible relationship with infection suggested that further investigation is required.

In this study, we aimed to retrospectively evaluate the relationship between non-hemorrhagic EAFC and the patient's age, gender, first surgical diagnosis, the material

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used in CP, presence of sinking skin flap (SSF), midline shift (MS), comorbidity factors, pre-operative duration, duration of hospital stay at first surgery, pre-and post-operative Glasgow outcome score (GOS), bleeding in the surgical site, epidural collection, infection, CP area, new-onset seizure after CP, and hydrocephalus, and to examine potential predisposing factors.

Methods

Compliance with Ethical Standards

Ethical permission was obtained from Clinical Research Ethics Committe of University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital (approval number: 91- 2022, date: 11/5/2022).

Patient Selection

Patients who have undergone CP between 2016 and 2021 were retrospectively evaluated.

Inclusion Criteria

Decompressive surgery history, over the age of 18, SSF or trephined syndrome, midline brain shift, patients were included.

Exclusion Criteria

Cranioplasty patients with history of infections, seizure, and hydrocephalus, craniosynostosis, lineer skull fracture, lower Karnofsky performance score (<40) were excluded from the study.

Surgical Procedure

Following the application of appropriate prophylactic antibiotics and positioning of the patient appropriately, the surgical site was cleaned with baticon, the old incision line was opened sterilely, and the dura and layers were dissected. In cases with porencephalic cyst, the cyst was aspirated and duraplasty was performed. Tissue adhesive was used after controlling CSF leakage by applying positive end-expiratory pressure to the patients during the operation. The surgical site was washed with gentamicin and saline solution. If there was an autogenous bone, it was removed from its place in a sterile manner and re-planted after washing with gentamicin and saline solution. However, if the bone flap was severely resorbed or infected, CP was performed with titanium plaque or methyl methacrylate. Drains were used routinely in the epidural and subgaleal area.

We used Osirix MD to calculate the CP area according to the CT. The patients were followed up with CT in the early postoperative period, and EAFC that continued after the 10th day after CP were considered positive in these follow-ups (Figures 1-3).

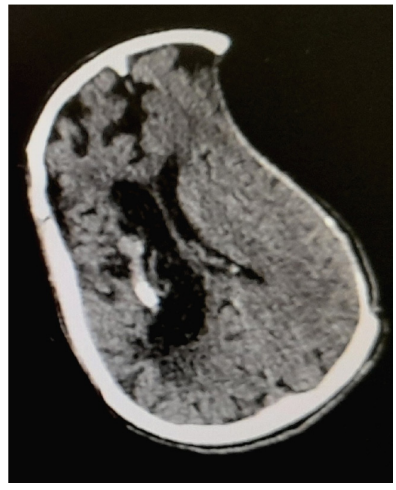

Figure 1. Preoperative CT
CT: Computed tomography

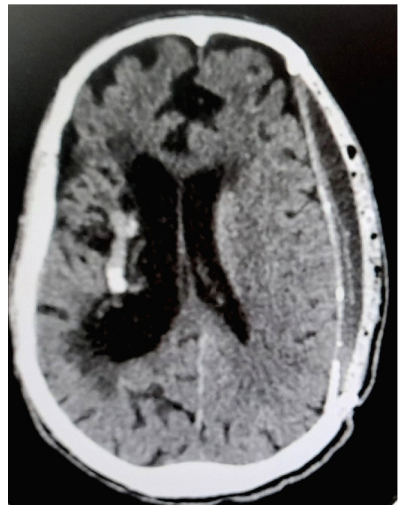

Figure 2. Postoperative CT with EAFC (+)
CT: Computed tomography, EAFC: Extra-axial fluid collection

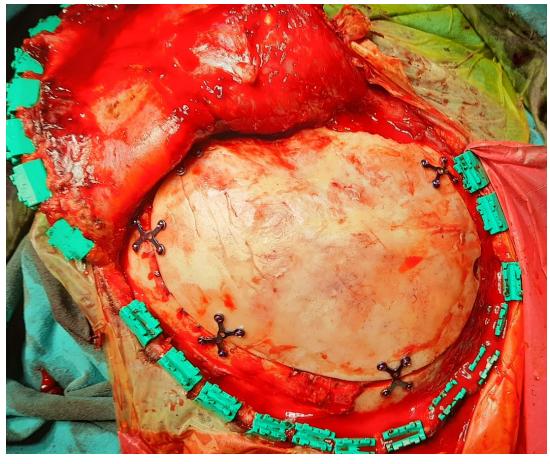

Figure 3. Cranioplasty restored bone flap with titanium screw and miniplate

Statistical Analysis

Statistical analysis was performed using the SPSS v20.0 software package (SPSS Inc., Chicago, IL, USA). Descriptive data were expressed in frequency, cross table, rate, arithmetic mean, and standard deviation. Data were analyzed with the Student's t-test and correlation. The groups were compared with test variables using independent samples t-test and multinominal logistic regression. A p-value of $p \leq 0.05$ was considered statistically significant.

Compliance with Ethical Standards

Ethical permission was obtained from Clinical Research Ethics Committe of University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital (approval number: 91-2022, date: 11/5/2022) and written informed consent was collected from all participants.

Results

A total of 106 patients, 70 male, and 36 female, with a mean age of 39.13±17.86 were included in the study. The number of patients with EAFC is 49 and the number of patients without EAFC is 57 (Table 1).

No significant relationship was found between EAFC and age, gender, first surgical diagnosis, the material used in CP, SSF, MS, comorbidity factors, pre-operative time, pre-and post-operative GOS, bleeding in the surgical site, epidural collection, infection, CP area and new-onset seizure after CP, and hydrocephalus. However, a positive relationship was found between the patients with a long hospital stay, surgical reoperation and reoperation time and EAFC development (Tables 1 and 2).

Discussion

While the rate of EAFC after CP ranged from 1.1% to 37.3% in a review of 636 patients by Shepetovsky et al. (7), Kim et al. (14) found this rate to be 41% in their study conducted with 117 patients (10). This rate was found as 46% in our study consisting of 106 patients.

Although EAFC is mostly asymptomatic, Jeong et al. (12) reported that 13 patients, among 65, who have undergone DC followed by CP had symptomatic EAFC, and therefore, surgical intervention was performed. Similarly, Lee et al. (15) reported in their study including non-traumatic patients that 22 of 59 CP patients developed EAFC and that surgical procedure was performed in 5 (22.7%) of those patients. Kim et al. (14) with a similar patient group reported that 48 of the 117 CP patients developed EAFC and 19 (38.8%) patients underwent surgical procedures. In our study, surgical procedures

Table 1. The age, gender, comorbidities, primary diseases, and comorbidity

	EAFC (+) (n=49) Mean ± SD	EAFC (-) (n=57) Mean ± SD	p-value
Age	41.44±17.2	37.14±18.2	0.217
Gender			0.504
Male	34	36	0.504
Female	15	21	0.504
Comorbidity			0.139
DM	1	0	0.431
HT	6	12	0.199
CAD	4	1	0.704
DM and HT	6	5	0.424
HT and CVD	2	1	0.667
HT, CVD, DM	1	0	0.283
No	29	38	0.433
Indication for craniectomy/craniotomy			0.872
Cerebral infarct	5	8	0.525
Trauma	20	21	0.529
Tumor	15	18	0.672
Aneuyrsm	3	0	0.06
ICH	5	7	0.872
Growing skull fractures	1	3	0.65

DM: Diabetes mellitus, HT: Hypertension, CAD: Coronary artery disease, CVD: Cerebrovascular disease, EAFC: Extra-axial fluid collection, SD: Standard deviation

Table 2. Peroperative and postoperative patient's status			
	EAFC (+) (n=49) Mean ± SD	**EAFC (-) (n=57) Mean ± SD**	**p-value**
GOS			
Preoperative GOS	4.06±0.89	4.22±0.73	0.295
Postoperative GOS	4.51±0.61	4.63±0.48	0.260
Hospital stay day	38.28±36.54	22.19±24.87	0.009
SSF and MS	0.93±1.73	0.57±1.32	0.229
Time interval between surgeries	215.51±284.28	226.26±509.36	0.89
Cranioplasty area			0.066
100 cm^2>	24	38	0.066
100 cm^2≤	25	19	0.068
Epidural air			0.130
(+)	42	42	0.130
(-)	7	15	0.124
Cranioplasty materials			0.561
Autogenous bone	26	31	0.594
MMA	17	16	0.595
Titanium	2	3	0.834
Combination	4	5	0.949
Reoperation	16	8	0.022
Reoperation time (month)	5.2±5.41	20.55±21.3	0.041

GOS: Glasgow outcome scores, cranioplasty materials, MMA: Methyl methacrylate, time interval between surgeries (day), hospital stay day, SSF: Sinking skin flap presence, MS: Midline shift, SD: Standard deviation, EAFC: Extra-axial fluid collection, N: number, Cranioplasty area, epidural air, reoperation and reoperation time (month). Independent samples t-test used between EAFC (+) and (-) groups, p-value, Mean

were performed in 16 of 49 patients who developed EAFC and the rate was found to be 32.6%. The evaluation of patients who underwent surgery showed that the rate of reoperation due to MS 6.2% (1/16), seizure (6.2%), ICH (6.2%), subgaleal effusion (6.2%), hydrocephalus (6.2%) and 68% (11/16) infection. In their study investigating the predisposing factors using parameters such as age, comorbidity, the material used, first diagnosis, GOS, and timing of CP which can be associated with infection after CP, Kim et al. (13), EAFC was considered as the only factor associated with infection. Although the risk of reoperation is statistically significant for EAFC group, infection rates was high but it was not significant for reoperation in our patient group (p=0.179). Although this situation gives rise to the thought of whether EAFC is a cause or result, we believe that EAFC becomes complicated by acting as a medium for the microorganism that may have an asymptomatic course.

In their study evaluating the relationship between age, gender, first diagnosis, CP timing, duration of surgery, bone flap length, CP material used, presence of shunt, epidural air, dural calcification, and the EAFC, Kim et al. (14) found a relationship between epidural air and dural calcification and EAFC. Lee et al. (15) examined the relationship between these parameters and EAFC, and found that EAFC is associated with male gender, epidural air, and dural calcification. Similarly, Jeong et al. (12) evaluated age, gender, first diagnosis, CP timing, CP material used, and CSF fistula during surgery in cases with EAFC grouped as symptomatic and asymptomatic, and found that the size of the bone flap and the presence of CSF fistula during CP were associated with symptomatic EAFC. Again, in the same study, they found that the presence of epidural air was 70% in the symptomatic EAFC group while 40% in the asymptomatic EAFC group, and reported that this was not associated with EAFC (12). In our study, presence of epidural air was 85.1% in EAFC (+) and 73.6% in EAFC (-) patients, and there was no statistical relationship between these groups. Although there is a statistically significant relationship in wide craniotomy defects in the study by Jeong et al. (12), no significant relationship was found with the CP area in our study, even though 25 of the 49 patients who developed had a CP area of more than 100 cm^2 (p=0.66). Epidural efusion may be an allergic reaction to the CP material (10), but we found no statistically difference between CP materials (p=0.56).

As dural calcification was observed in only 3 patients, no statistical evaluation could be performed. In our study, we evaluated that the duration of hospital stay before CP is associated with EAFC which is different from the literature. Decompressive craniotomy is performed frequently in trauma and ischemia cases, and the post-surgery intensive care and length of hospital stay are longer compared to other patient groups due to severe neurological deficits in patients (12). The mean hospital stay of our EAFC (+) patients is longer and statistically significant compared to the EAFC (-) patients (p=0.009). While Chun and Yi (16) found that the EAFC ratio was 7% in patients who have undergone CP within the first month, those who have undergone CP after 3 months had a ratio of 46.7%. They explained this situation with the resolution of brain edema and the increase in the permanent dead space in the late period (16). However, the CP procedure was performed between 3 and 6 months the earliest following the stabilization of the general status of our patients, and the patients with EAFC (n=26) (53.06%) were operated on within the 90 days-early periods. Although all EAFC (+) patients were operated on at an average of 215.51±284.82 days later, no statistically significant results were found. This suggested that other factors requiring a longer hospital stay should be examined rather than the duration.

Study Limitations

The main limitation of the current study is its retrospective and it is obvious that evaluations with larger series are needed. Despite these limitations the longer hospital stay is statistically significant a predisposition factor of EAFC. There are only a few series reporting EFCs following CP. We believe that using a shared definition of EAFC to get more efficient results will contribute to obtaining more valuable results in future studies.

Conclusion

Extra-axial fluid collection developing after the CP procedure is mostly asymptomatic and spontaneous resorption is observed frequently. Particularly in frail patients with a longer hospital stay, post-CP EAFC cases should be monitored closely due to the risk of re-surgery as a result of infection.

Ethics

Ethics Committee Approval: Ethical permission was obtained from Clinical Research Ethics Committe of University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital (approval no: 91-2022, date: 11.05.2022).

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

Peer-review: Internally peer-reviewed.

Authorship Contributions

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

Conflict of Interest: The authors have no conflicts of interest to declare.

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Case Report

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Giant Hydatid Cyst Originating from Psoas Muscle Extending to the Iliac Bone, Inguinal, and Femoral Canals: A Case Report and Current Literature Review

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Abstract

Retroperitoneal hydatid cysts are extremely rare and difficult to distinguish from other intra-abdominal pathologies, such as synovial sarcoma. In this study, we present a rare case of a complicated retroperitoneal hydatid cyst originating from the psoas muscle without any other focus. A 59-year-old male patient presented to the outpatient clinic with complaints of constipation and a feeling of gradually increasing swelling in the left lower quadrant of the abdomen and left groin area, progressing toward the left leg. In the examinations performed, a multiloculated giant hydatid cyst that filled the left pelvis in the retroperitoneal region, deviated the intra-abdominal organs to the right side, and extended to the left femoral and inguinal canals was detected. The patient underwent surgical excision and was followed up during the postoperative period. No evidence of recurrence was found at the patient's 3rd and 6th month follow-ups. Primary muscle hydatid cysts necessitate a distinct approach to treatment and management when compared with hydatid cysts in other bodily organs. While recurrences remain a potential concern after resection, it is noteworthy that the window for the formation of fertile cysts typically spans up to 10 months. Thus, it is advisable to conduct regular postoperative follow-up examinations during the first year following surgery to ensure comprehensive monitoring and care.

Keywords: Echinococcosis, cysts, psoas muscles, pelvis, retroperiton, bone

Introduction

Hydatid cyst is a parasitosis caused by Echinococcus granulosus helminth. It is endemic in many countries of the world, such as New Zealand, Africa, and Turkey, and maintains its importance for public health. It is a very difficult disease to diagnose and treat (1). Diagnosis is made by radiological imaging appropriate to the anatomical region where the disease is believed to be present and by performing an indirect hemagglutination test (IHA). Surgery is the mainstay of treatment. When a hydatid cyst is not treated, it can lead to complications such as anaphylactic shock, infection of existing cysts, and compression symptoms (2). In terms of location, the liver comes first with a rate of 50-70%, followed by the lung with a rate of 11-17%. The rate of localization in muscle and subcutaneous tissues is between 0.5 and 4.7%. In cases of hydatid cysts with retroperitoneal localization and muscle origin, i.v. contrast-enhanced magnetic resonance imaging (MRI) and computed tomography (CT) imaging are valuable in terms of differential diagnosis. In cases of hydatid cysts with atypical localization, the liver and lung should be investigated in terms of primary focus (3,4). In this article, we aim to underline the atypical localization of a hydatid cyst by presenting a case of a giant multiloculated cyst originating from the psoas muscle, located retroperitoneally, eroding the left iliac bone, and extending to the gluteal muscles.

Case Presentation

A 59-year-old male patient was admitted to the outpatient clinic with complaints of pain in the left lower

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quadrant of the abdomen, abdominal fullness, and constipation. He also complained of swelling and tingling in his left leg. In his history, it was learned that the swelling in the abdomen gradually increased and progressed from the left inguinal region to the leg. During the examination, a hard-consistent mass lesion starting from the upper flank region of the left abdomen and extending to the midline was palpated. On palpation, the mass lesion was pushing up the anterior abdominal wall and was immediately felt under the skin. The mass lesion was progressing toward the pelvis. The mass filled the femoral and inguinal canals on the lower side and progressed from the thigh region to the left lower extremity.

In the abdominal ultrasonography (USG), a multiloculated cystic lesion progressed toward the femoral and inguinal canals and filled both canals. In the left lower quadrant of the abdomen, anterior to the iliac muscle, a cystic lesion with a size of approximately 77x90 mm, with macrolobule contours, containing multiloculated cystic foci, and with no significant blood flow in Doppler USG, with dense content, was detected (Figure 1). Initially, the pre-diagnosis of retroperitoneal sarcoma and hydatid cyst was considered, and an i.v. contrast-enhanced CT of the entire abdomen and pelvis was performed (Figure 2A). In the MRI examination, hypointense on T1-weighted images, hyperintense on T2-A images, and non-contrast-enhancing, multilocus cystic lesions on post-contrast images were observed (Figure 2B). In the results, hydatid disease was thought to be more prominent, and an IHA test was performed. The IHA titer was found to be 1/2560 positive in blood tests, and surgery was decided.

Considering the pelvic extent of the mass, the transperitoneal approach was preferred for this type of surgery. During laparotomy, it was observed that the giant mass started from the retroperitoneum and pushed the sigmoid colon and rectosigmoid junction up to the anterior abdominal wall, causing partial obstruction. In the dissection, it was observed that the hydatid cyst lesions originated from the psoas muscle. The psoas muscle was dissected up to the paravertebral area, and the mass lesion was separated from the psoas muscle and paravertebral area. The mass filled the pelvis on the iliac bone and entered the gluteal muscle group by eroding the bone from the posterior. The mass lesion was separated by posterior dissection and removed from the gluteal muscle group. Multiple cystic lesions were detected in the inguinal and femoral canals of the patient with a left inguinal hernia. Cystic lesions were excised, preserving the femoral vein, artery, and nerve. The inguinal canal was dissected,

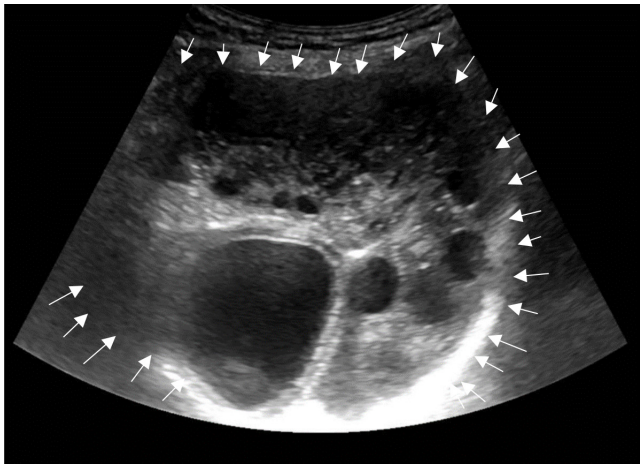

Figure 1. Multiloculated cystic lesion on USG (little white arrows)
USG: Ultrasonography

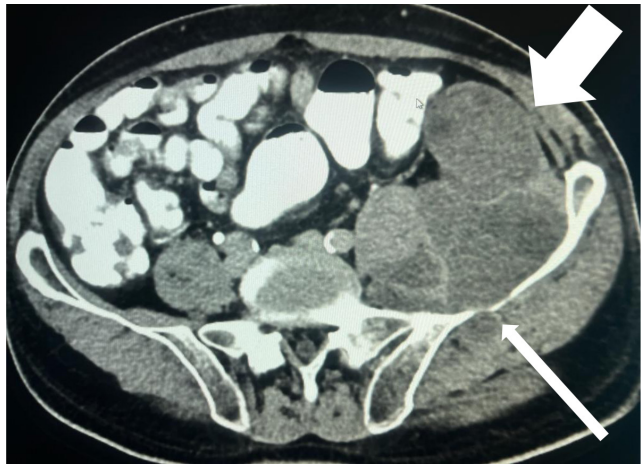

Figure 2A. Septal cystic mass (thick white arrow) that erodes the bone structure within the iliacus muscle (thin white arrow) on axial CT
CT: Computed tomography

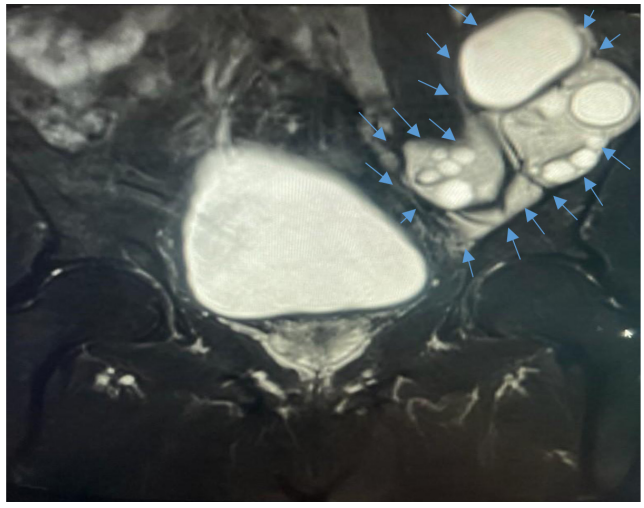

Figure 2B. Multiloculated septal cystic mass in the iliac muscle on coronal section T2-A MRI (little blue arrows)
MRI: Magnetic resonance imaging

the cord and vascular structures were preserved, and cystic lesions were excised from the inguinal canal into the abdomen. Because of the diagnosis of a hydatid cyst, each cystic lesion was filled with hypertonic 3% serum saline, and after waiting for 5 minutes, excision was initiated. All cystic masses were resected without perforation. The operation area was washed with 5 L of body-temperature isotonic fluid, and a drain was placed in the retroperitoneal area. The left and sigmoid colons were brought to their anatomical positions, and the peritoneum was repaired to ensure retroperitoneal integrity and isolation.

The resection specimen was examined under a microscope in the pathology laboratory using hematoxylin/eosin and Periodic acid-Schiff (PAS) dye. A diagnosis of a hydatid cyst originating from Echinococcus granulosus was made. Histopathological examination revealed that the cysts consisted of a cellular germinal membrane, a thick PAS-positive cell-free homogeneous pink-colored laminated layer, and an outer adventitial layer (Figures 3A and 3B). Germinative vesicles were observed in the cysts. An increase in connective tissue and inflammatory cells was observed around the membrane of some cysts (Figure 3C).

No lesion was detected in the early postoperative control abdominal CT (Figure 4). Benzimidazole group Albendazole 400 mg 2x1 treatment was started in the patient in the postoperative period. It was observed that the swelling in the left leg of the patient regressed, and the tingling complaint of the patient disappeared in the first week postoperatively. The patient did not have any constipation complaints anymore.

In the 3rd postoperative month, the entire abdomen of the patient was checked with USG, and no cystic lesion was found. In the 6th postoperative month, the patient

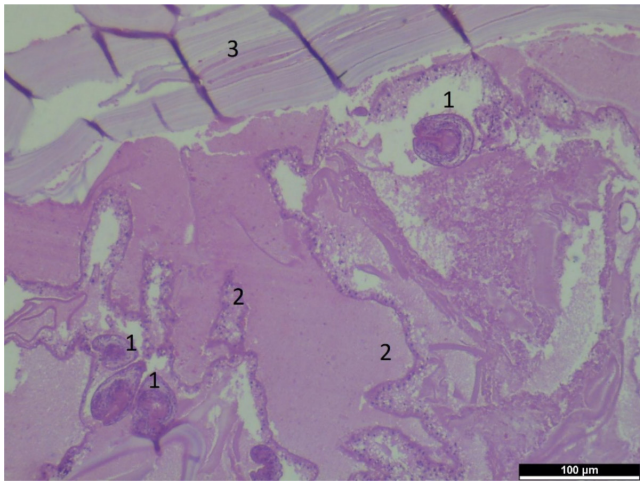

Figure 3A. Microscopic image of hydatid cyst, protoscolices (1), germinal layer (2) followed by laminated layer (3) (H&E-Original magnification ×40)

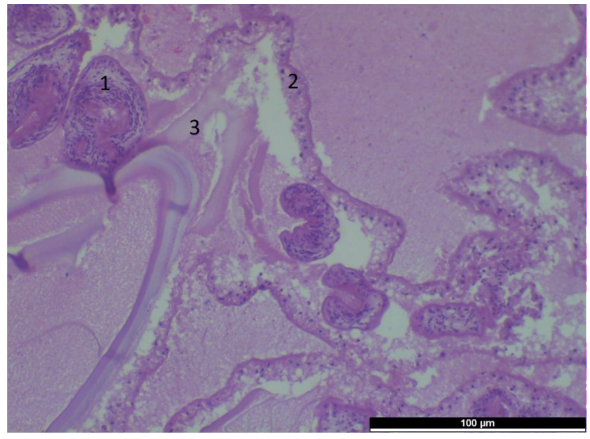

Figure 3B. Protoscolices (1), germinal layer (2), laminated layer (3) (H&E-Original magnification ×100)

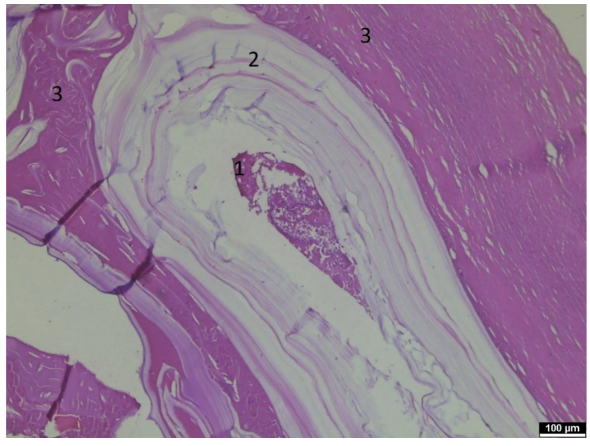

Figure 3C. Germinal layer (1), laminated layer (2), adventitia (1) (H&E-Original magnification ×40)

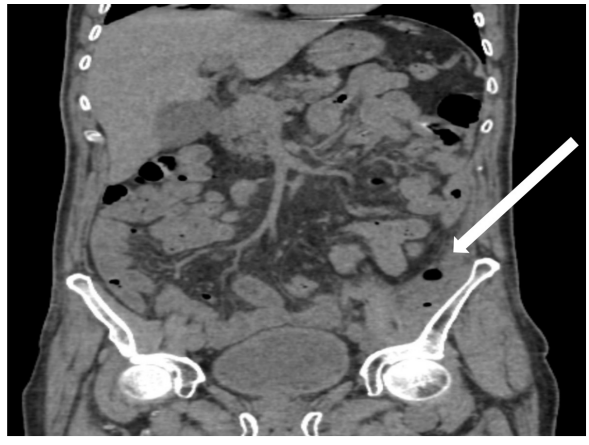

Figure 4. No postoperative residue was observed in the coronal section CT examination (white arrow)
CT: Computed tomography

was evaluated with an ultrasound of the entire abdomen, i.v. contrast-enhanced abdominal and pelvic CT, and chest X-ray examinations. No cystic lesions were found in the examinations. Because of the high risk of recurrence in the first 10 months, clinical follow-up was planned for the patient every 3 months for the first year.

Discussion

Hydatid cysts are usually located first in the liver, second in the lungs, and rarely in the brain (5). Muscle involvement in hydatid cysts is rare and has rarely been reported in the literature as case reports. It is thought that the reason why muscle involvement of hydatid cysts is rare is due to the amount of lactic acid in the muscle and the contraction of the muscles, preventing the growth of the cysts in the striated muscles (6). However, primary hydatid cysts of muscle origin are known to involve the pectoralis major, sartorius, quadriceps, and gluteus muscles (7-9). Cases of hydatid cysts in the retroperitoneum often have another primary focus. Therefore, when a hydatid cyst is detected in the retroperitoneum, it is useful to seek another focus with radiological examinations showing liver, lung, and brain tissue. Cases of primary hydatid cysts originating from the retroperitoneal muscles are even rarer (10,11). Such lesions may progress in the inguinal canal and mimic an irreducible inguinal hernia (12). In the case we are presenting, another focus was investigated preoperatively with cranial MRI and whole abdomen, pelvic, and thorax CT scans, and no focus was found other than the retroperitoneum. In this study, we observed that the hydatid cyst filled the inguinal canal and could not be reduced from the inguinal canal in the testicular examination. At the same time, the situation was the same in the femoral canal.

The components of the hydatid cyst are formed by an inner, thin germinal layer and an outer, thick laminated layer. The outermost layer is the adventitia. The adventitia layer forms as a fibroinflammatory response and attempts to limit the cyst. Degeneration and calcification can be observed in long-lasting cases. Cysts filled with protoscolex may be observed, indicating that the cyst attached to the germinal layer is fertile. In this study, the hydatid cyst showed the characteristics of a fertile cyst, and calcification was observed in some cysts in the resection material. While the probability of fertilization of lung hydatid cysts is 55%, it is 45% for liver hydatid cysts (13).

Hydatid cyst treatment usually includes surgery, medication, or a combination of both. For hydatid cysts with muscle involvement, the treatment process may differ from cysts in other organs. The treatment of hydatid cysts with muscle involvement may vary depending on the size and location of the cyst and the general health status of the patient. In cases where surgical intervention is not appropriate or to prevent postoperative recurrence, antiparasitic drugs such as albendazole or mebendazole are used. These medications can help shrink the cyst by preventing the parasite from growing and reproducing. Muscle cysts that are small and suitable for placement can be surgically removed. The operation can be performed with open or laparoscopic surgery, depending on the region and size of the cyst (14,15).

In this study, midline incision and transperitoneal approaches were preferred because of the localization of hydatid cysts. Albendazole treatment was started from the moment the patient was diagnosed in the pre-operative period, and it continued to be used in the postoperative period.

In conclusion, primary muscle hydatid cysts present a unique clinical challenge, necessitating a tailored approach to treatment and management compared with hydatid cysts in other organs. Although the risk of recurrence exists following surgical resection, it is important to emphasize that the fertile cyst formation period typically spans up to 10 months. Consequently, conducting regular postoperative follow-up examinations within the first year is paramount to ensuring diligent monitoring and comprehensive care for patients with primary muscle hydatid cysts.

Ethics

Informed Consent: Informed consent was obtained.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: K.G., D.D., A.M., Design: K.G., D.D., A.M., Data Collection or Processing: K.G., D.D., A.M., F.M.I., Literature Search: K.G., Writing: K.G., D.D., A.M., F.M.I.

Conflict of Interest: The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article. All authors have read and confirmed that they meet the ICMJE criteria for authorship.

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