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## LETTER TO EDITOR

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EDITORIAL



# Luminescences of the 2023 Bethesda System for Reporting Thyroid Cytopathology, 3rd edition, in Thyroidology

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*Mater artium necessitas.* The Bethesda System for Reporting Thyroid Cytopathology (TBSRCT), *per se*, has still been crucial for Endocrine Pathologists, Endocrine Surgeons, Neck-Endocrine Surgeons, Endocrinologists, Head&Neck Surgeons, Laryngologists, Head&Neck Radiologists, Nuclear Medicine, and Thyroidologists, globally. The 2010 TBSRTC, 1st edition, was initially proposed in Bethesda, Maryland, USA, in 2007, providing Thyroidologists to utilize a standardized reporting system for thyroid fine-needle aspiration (FNA) [1]. The 2015 American Thyroid Association management guidelines have also endorsed wielding TBSRTC [2] through this delicate papillon endocrine gland [5-9]. Furthermore, a special 2½-hour symposium was moderated by Ali and Vielh at the 19th International Congress of Cytology, ICC, in Pacifico Yokohama, Japan on 28 May–01 June 2016 [10-12]. Subsequently, the 2017 TBSRTC, 2nd edition, was then published by amendment of indeterminate cytology [13]. However, (re)appraisal for atypia of undetermined significance (AUS) or follicular lesion of undetermined significance (FLUS), category III, has still been one of the most challenging issues in Thyroidology worldwide [14-21]. Currently, a 3rd edition of this lexicon, the 2023 TBSRTC, has been announced by Ali et al. after two former successful editions. This novel 2023 TBSRCT, 3rd edition, provides several key updates [22]:

**i)** Assignment of only a single name for each of the six-based diagnostic categories: (I) nondiagnostic; (II) benign; (III) atypia of undetermined significance (AUS) (by discontinuing the term follicular lesion of undetermined significance, FLUS); (IV) follicular neoplasm (FN) (by discontinuing the term suspicious for FN, SFN); (V) suspicious for malignancy (SM); and (VI) malignant.

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**ii)** Updating an implied risk of malignancy (ROM) for each of the six based categories, providing an average ROM for each category and the expected range of cancer risk. The estimated final ROM after excluding "Noninvasive Follicular Thyroid Neoplasm with Papillary Like Nuclear Features (NIFTP)" for each of the six categories has been updated based on the reported attenuating mean

**iii)** Subdividing category III, AUS, into two subgroups: (a) AUS-nuclear atypia (NA) or (b) AUS-other, based on the implied ROM and molecular profiling.

**iv)** Updating the new or revised disease nomenclatures in Thyroidology according to the recently published 2022 World Health Organization, WHO, Classification of Thyroid Neoplasms, including "thyroid follicular nodular disease" instead of nodular/multinodular goiter, "cribriform morular thyroid carcinoma," "high-grade follicular-derived carcinoma," "papillary thyroid carcinoma (PTC) subtypes" instead of PTC variants, and "oncocytic follicular lesions" instead of Hürthle cell lesions.

**v)** Intercalating brand fresh two chapters addressing clinical perspectives and imaging modalities (Chap. 13) and utilizing molecular and other ancillary tests (Chap. 14).

**vi)** Intercalating the novel pediatric ROMs and management algorithms for pediatric thyroid disease for the same six reporting categories for this age group.

One of the most luminescent novelties of the current and last edition is the subdivision of category III [22]. Of note, we emphasized in February 2021 whether it is essential to maintain AUS in TBSRTC, 1st and 2nd edition, as a unique category [20]. Afterward, we declared blurred lines for managing thyroid nodules in the era of category III in a possible forthcoming TBSRTC, 3rd edition, in October 2021. To this end, we postulated that the so-called subcategorization in category III, as (i) IIIA: AUS/FLUS without nuclear atypia (AUS/FLUS w/o NA) and (ii) IIIB: AUS/FLUS with nuclear atypia (AUS/FLUS w/ NA) [21]. Last but not least, we have currently recommended in a publication working with subsets to resolve the ongoing debate on 'indeterminate cytology', similar to 'intermediate suspicion' in Radiology, with a submission date of June 08, 2023 [23]. Evangely, just one month later, a 3rd and the last edition of this lexicon, the 2023 TBSRTC, was announced by Ali et al. after two former successful editions on July 08, 2023.

As two peas in a pod, the up-to-date 3rd edition announced and stated the subcategorization of category III: (i) AUS-NA and (ii) AUS-other, by confirming [22] our antecedent recommendations in our two former publications: (i) AUS w/ NA, and (ii) AUS w/o NA [20,21]. Evangely, the subcategorization has been announced after a long expectancy. NAs have non-negligible clues in thyroid nodules with indeterminate cytology, *hic et ubique terrarum. E fructu arbor cognoscitur.*.

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CASE REPORT



# Necrotizing soft-tissue infection of the upper extremity following a toothpick injury: Case report and a literature review

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**Abstract**

NSTIs (Necrotizing soft-tissue tissue infections) are severe surgical infections characterized by rapid spread over the superficial fascia and involve the subcutaneous tissue, fascia, and sometimes muscles. At the same time, the skin may appear intact at the beginning of the disease, which might lead to severe systemic complications that may end fatally for the patient. Early recognition and urgent surgical intervention with appropriate antibiotics and other supportive measures are the most important in treating these infections. The presence of comorbidities complicates treatment. Diabetes and heart diseases are the most common comorbidities in patients with NSTIs. Reminding clinicians about this infection is essential in order to recognize it and provide adequate and timely treatment quickly. To that end, we present a patient with NSTIs of the upper extremity after being pricked by a used toothpick.

**Keywords:** Soft-tissue; necrotizing soft-tissue infections; LRINEC; surgical exploration; toothpick; soft-tissue pathology

Zogic E, Plojovic H, Corovic M, et al. Necrotizing soft-tissue infection of the upper extremity following a toothpick injury: Case report and a literature review. *Cerasus J Med.* 2024;1(2):75-80.

## Introduction

Necrotizing soft tissue infections (NSTIs) are infections characterized by rapid and fulminant progression with life-threatening consequences such as multiorgan failure and a potentially fatal outcome. The main characteristic of these infections, in all anatomic locations, is that due to their rapid spread, which leads to the destruction of epidermal, dermal, subcutaneous, fascial, and sometimes muscle tissue with systemic effects on vital organs[1].This is a rare disease, but according to different authors, the incidence of NSTIs has increased in recent years and mainly reaches 1–4/100.000 persons per year. There are other data on mortality in the literature, but they have one thing in common: despite the available treatment methods, the mortality rate is high. Earlier studies reported mortality rates up to 70% [2]. The new studies report a mortality rate of up to 35%, an increase if the diagnosis is not made in time and in patients with comorbidities [3]. Diabetes mellitus (DM) is the most frequent comorbidity in patients with NSTIs [1,2]. Herein, we present a patient with NSTIs of the upper right extremity after contact with a wooden toothpick previously used by the patient.

## Case report

A 45-year-old previously healthy man was admitted to the Department of General Surgery, the General Hospital Novi Pazar, Serbia, after being treated by a physiatrist for pain, swelling, redness, and limited movement in his right hand. His symptoms appeared three days after accidentally puncturing himself with a used toothpick. He sought medical attention from a physiatrist, where he was treated for two days. On the 6$^{th}$ day, after a toothpick stab, a progressive worsening of symptoms led him to our outpatient clinic with a pronounced clinical picture of NSTIs.

Upon admission, the patient had swelling and pain throughout his right arm, from the hand to the shoulder, exhibiting a typical type of pain upon palpation, accompanied by redness and eschar. His movements were severely limited, almost impossible, and he experienced pain even at rest. In addition to local findings, the patient had a high fever. Blood pressure and oxygen saturation were within the normal limits.

Afterward, the patient was hospitalized, and a diagnostic workup was initiated, yielding the following laboratory findings [Table 1]. Based on the clinical findings and the Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) score outcomes (10), immediate surgical and conservative therapy was initiated with empirical broad-spectrum antibiotics (Ceftriaxone, Ciprofloxacin, and Metronidazole) until swab culture and sensitivity results were available, fluid replacement and other supportive therapy. The involvement of the skin, subcutaneous fat tissue, muscle fascia, and muscles was verified, and a cloudy fluid was observed seeping from the affected tissue after the skin incision (Figure 1). The patient underwent detailed surgical wound treatment under general anesthesia (Incision, debridement, drainage of contents, and establishing communication between affected tissue parts with the placement of sterile gauze soaked in antiseptics were performed). Of note, the *Enterococcus spp* was isolated from the wound swab on the 2$^{nd}$ day of hospitalization, and the antibiotherapy was altered based on its sensitivity to the Imipenem and Ciprofloxacin. On the 3$^{rd}$ day of hospitalization, a slight decrease in leukocytes and CRP was observed (Table 1). Although local infection symptoms persisted, laboratory findings showed initial improvement. The wound was dressed in antiseptics daily.

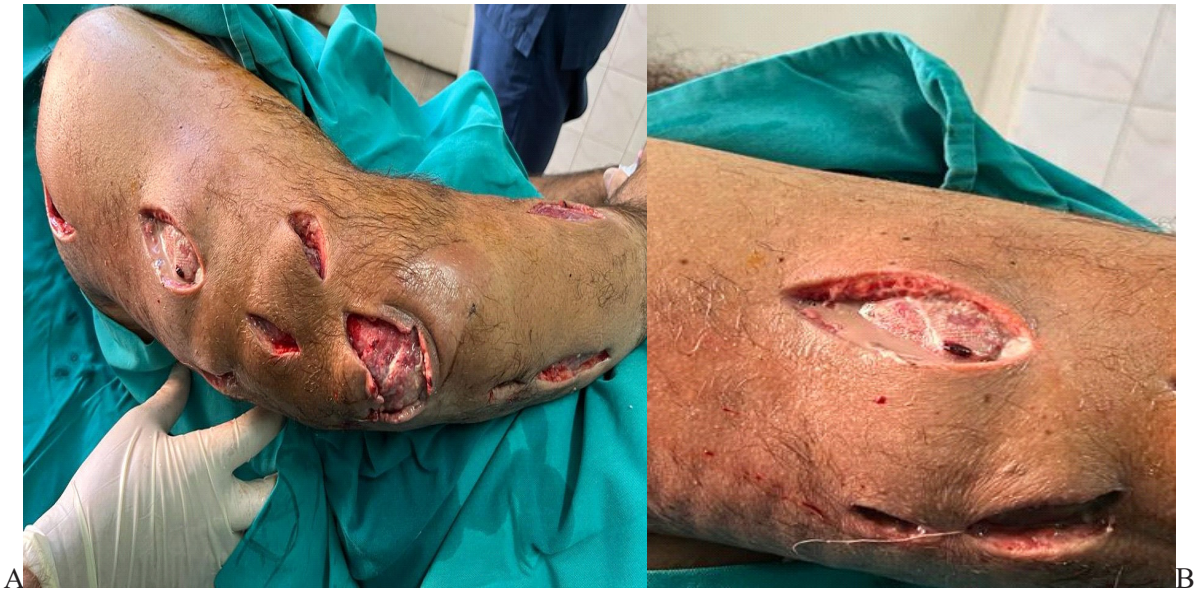
On the 5$^{th}$ day of hospitalization, the wound underwent a third surgical procedure (Figure 2). Subsequently, on the 7$^{th}$ day, the swelling and pain significantly regressed, and the patient became more mobile, with minimal discharge from the wound. Furthermore, a wound swab was repeated on the 12$^{th}$ day of hospitalization when *Klebsiella spp* was isolated, which led to antibiotic adjustment based on Colistin, Vancomycin, and Metronidazole findings for the next 10 days. In addition, daily dressing changes were done until complete healing was achieved. Moreover, on the 30 days of hospitalization, he was discharged in favorable general condition; his swelling and pain had significantly decreased, and hand mobility was almost

fully restored. The control wound swab was sterile. The patient was treated on an outpatient basis for another seven days, after which he was referred for physical therapy and scheduled for follow-up with a surgeon as needed.

**Table 1.** Laboratory findings.

| | 1st day of hospitalization | 3rd day of hospitalization | 7th day of hospitalization |
|---|---|---|---|
| WBC(/L) | $21.3x10^9$ | 16 | 12 |
| CRP (mg/L) | 321 | 251 | 101 |
| Glycemia (mmol/L) | 10.8 | 8 | 7 |
| Creatinin (µmol/L) | 169 | 153 | 123 |
| $Na^+$ (mmol/L) | 142 | 141 | 140 |
| Procalcitonin (ng/mL) | 4.2 | 3 | 0,5 |
| Hb (g/L) | 100 | 110 | 123 |

*WBC: white blood cell; CRP: C reactive protein; Hb: Hemoglobin



A B

**Figure 1.** A) Initial surgical treatment of the affected region; B) The cloudy liquid that oozes from the affected tissue.

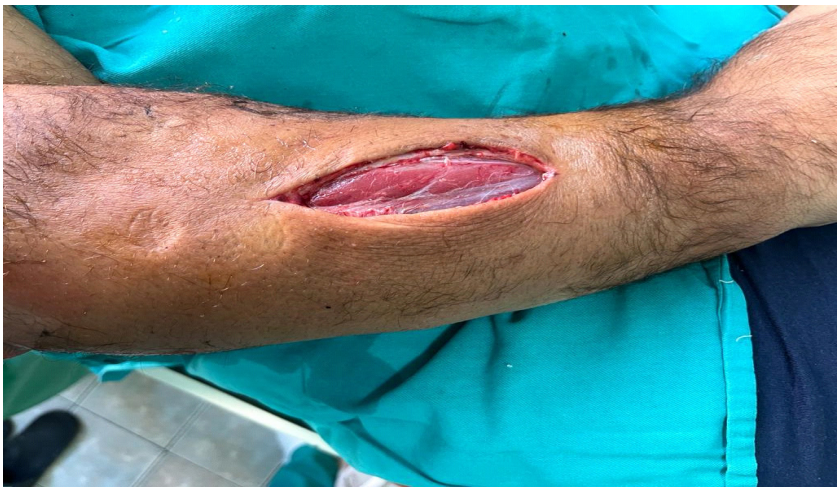


**Figure 2.** The affected region after the 3rd surgical debridement.

**Discussion**

Hand injuries caused by used toothpicks contaminated with human saliva can be equally serious as human bites [4]. According to literature data, toothpick-related injuries are estimated to be 3.6 per 100,000 persons and are believed to be underreported [5]. Several studies have stated that the majority of injuries caused by toothpicks involve ingestion [6]. Soft tissue infections remain crucial, like the tumoral conditions of these vital organ tissues of human beings, to date [7,8].The result of the one-year survey in the USA showed that 76% of all toothpick injuries involved extremities and trunks [6].The penetrating wound from a toothpick is tiny, and initial symptoms are subtle.

Moreover, the seemingly harmless tiny puncture wound is frequently overlooked by patients or missed during physical examination, making an accurate assessment of the severity of such an injury extremely challenging [4,5]. In the present work, our case with NSTIs of his upper right extremity after contact with a wooden toothpick previously utilized by himself. It is clear that in such situations, the wound may be insufficiently taken seriously and overlooked. Due to minor symptoms at the onset and delayed medical attention, an increase in the window between the injury and the first visit to the surgeon significantly provides time for the initial infection to develop into NSTIs.

NSTIs represent an aggressive surgical infection of the skin and soft tissues, which spreads along the fascia. In contrast, the tissue above it initially appears healthy, often leading to postponement of diagnosis and surgical intervention. It is frequently a life-threatening infection that requires urgent medical treatment, usually by a multidisciplinary team. The global incidence of NSTIs is reported as 0,4/100000 per year [1]. Despite an improvement in medical care, mortality was still reported very high [9]. Bodansky et al. [10] reported a recent increase in the incidence of NSTIs.

The most common sites of NSTIs are the anogenital region, lower limbs, and anterior abdominal wall, but they can occur on any body part [9]. The present case admitted us with an infection that affected his entire right upper extremity, with propagation to the back of the right shoulder. As such, health providers need to diagnose NSTIs promptly because these infections, besides antimicrobial therapy, necessitate surgical intervention. In addition to local warmth, the presence of erythema and ecchymosis, and tissue swelling, patients with NSTIs also experience a specific type of pain (disproportionate to palpation). Of note, it is also crucial to emphasize that in NSTIs, general symptoms such as elevated body temperature (fever) and hemodynamic instability in later stages are commonly present [1-5], which infections might lead to shock and sepsis with multiorgan failure and a potentially fatal outcome [1].The presented case revealed no difficulties in diagnosing NSTIs, as he was admitted to the outpatient clinic with a complete clinical picture of NSTIs, given that some time had already passed since the injury.

Based on the microorganisms isolated from wound swabs, NSTI commonly arises from a polymicrobial infection, including aerobic and anaerobic organisms, frequently associated with a breach in mucosal or cutaneous integrity [11,12]. Kim et al. stated that 73.9% had one or more identifiable pathogens [13].However, some studies report the prevalence of monomicrobial NSTIs at up to 60-80% [9]. As such, in monomicrobial NSTIs, *Staphylococcus aureus* (*S. aureus)* and *Streptococci* seem to be predominant pathogens [13]. Additionally, *Beta-hemolytic streptococcus* of serological group A is one of the most common organisms isolated in cases of NSTIs [9]. Eckmann et al. found methicillin-resistant *S. aureus* (MRSA) as a causative microorganism in 14.6% of complicated skin and soft tissue infections in many European countries [14]. Moreover, we reported that *S. aureus, Klebsiella spp,* and *Pseudomonas aeruginosa* were the most causative agents, with almost the same frequency [1]. Fungal infections are rare and primarily published as case reports [9,15]. According to Peetermans et al., up to 12% of patients with NSTI have a recurrent NSTI[16].

Various risk factors contribute to the progression of necrotizing fasciitis, such as immunosuppression, cancer, vascular disease, DM, alcoholism, obesity, chronic kidney diseases, liver cirrhosis, intravenous drug users, etc [1-9]. DM is the most associated co-morbidities with NSTI, with 22%–59% [17] and cardiovascular disease (9%–45%) [16].The incidence of *DM* in Tarchouli et al.'s [17] work was 38%, and cardiovascular diseases were 51%, where a higher mortality rate was recorded. Almost 25% of the cases with NSTI have no apparent predisposing factor [16]. Comorbidities can complicate the clinical picture and make treatment difficult [9].

NSTIs rise more frequently in men, accounting for up to 2/3 of all cases [9]. Although NSTIs do not have an age preference, data show that patients over 50 years of age have a worse prognosis [9]. Our case was immunocompetent, with an average body weight (BMI: 26), and without a medical history or clinical findings related to any chronic illness or alcoholism. NSTIs require immediate surgical intervention with antibiotic treatment against the causative pathogen, which increases the probability of a successful cure. Initial empiric pharmacological treatment with broad-spectrum antibiotics is aimed at the most common causative agents until the results of soft tissue Gram staining, culture, and sensitivity are obtained [18]. Due to the increasing uncritical use of antibiotics worldwide, there is a rising number of pathogenic microorganisms resistant to common antibiotics, representing a significant problem [19]. Urgent surgical treatment, which involves extensive removal of necrotic and devitalized tissue, is an essential indicator of favorable treatment outcomes. Initial surgical intervention performed after 24 hours from the onset of symptoms increases mortality. Treatment involves frequent and multiple surgical interventions during the treatment of NSTIs [1-6,9]. Literature data stated that all patients underwent up to 10 radical surgical debridements, averaging 2.5 [2]. The treatment of these infections with Hyperbaric Oxygen Therapy has not been definitively proven [9].We followed the same approach in the case of our patient, where Ceftriaxone, Ciprofloxacin, and Metronidazole were initially prescribed, and after isolating the pathogen, targeted antibiotic therapy was included. The first surgical intervention was performed within 24 hours, and three were conducted by the end of the hospitalization.

Different diagnostic procedures (radiological imaging modalities and laboratory tests) are used to diagnose this infection. For precisely this purpose, the LRINEC score was devised to aid clinicians in screening for NSTIs and stratifies patients into low, medium, or high risk of necrotizing fasciitis (NF), and six or higher were considered indicative of NF. To date, the highest sensitivity for the LRINEC of 89.9% was found in the original study. In recent years, the value of this score and its role as a scoring system has been the subject of ongoing controversy in many studies [20]. Regardless of the LRINEC score, surgical exploration is the only way to establish the diagnosis of necrotizing infection. Our patient had an LRINEC score of 10, which fits the high risk for necrotizing soft tissue Infection criteria.

## Conclusion

Consequently, the emergency department involves numerous patients who display signs and symptoms of an infection. Clinicians need to differentiate NSTIs, which necessitates surgical intervention promptly. Delays in appropriately addressing can lead to severe consequences, including limb loss, organ damage, and a significantly elevated risk of death. It is a significant challenge for physicians, especially those with limited encounters with this type of condition, to recognize this kind of infection. How to further enhance the early recognition and detection of this potentially fatal condition in the future remains a question. As a matter of fact, this issue merits further investigation.

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**Authors' contribution:** All authors have contributed equally.

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CERASUS JOURNAL OF MEDICINE

ORIGINAL ARTICLE

# Evaluation of satisfaction with general and spinal anesthesia in cesarean section surgery

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**Abstract**

**Objective:** We aimed to investigate the satisfaction of pregnant women scheduled for caesarean section with the anesthesia method applied after being informed about their preferred anesthesia method.

**Methods:** This study was conducted on patients who applied to the anesthesia outpatient clinic of our hospital in June-July-August 2023. A questionnaire was administered to the patients to inquire about their preoperative knowledge and fears about general and spinal anesthesia, and postoperative satisfaction with the type of anesthesia they preferred.

**Results:** Of the patients who underwent elective caesarean section,94.1% underwent regional anesthesia and 5.8% under general anesthesia.When the groups were evaluated in terms of anesthesia experience, there was a statistically significant difference between the groups($p=0.011$). The general anesthesia experience was significantly lower in the SS group compared to the GS and GG groups($p<0.05$).In addition, the experience of spinal anesthesia in the GS group was lower than the other groups and this difference was significantly different from the SS group($p<0.05$). A significant difference was found between the groups when the parameter of the method that the patients would prefer in case of reoperation was analysed($p<0.001$). When the groups were compared for subgroup analysis, "Spinal anesthesia preference" was statistically significantly higher in the SS and GS groups than in the GG group($p<0.05$). According to their new preferences after the information,92.3% of the SS group,77.8% of the GS group and 100% of the GG group stated that they were satisfied with the application.

**Conclusion:** Lack of information and having wrong information due to negative sensations from the environment cause patients to prefer general anesthesia. We think that if pregnant women are given good information in the preoperative period, their preference for spinal anesthesia, which is safer for themselves and their babies, in cesarean section surgeries and their satisfaction as a result of these preferences will increase.

**Keywords:** General anesthesia; spinal anesthesia; cesarean; satisfaction; postspinal headache

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## Introduction

Cesarean section is the most common obstetric surgical operation in Turkey as in the whole world. Cesarean section rates and rates in Turkey are increasing year by year. According to the Ministry of Health Statistics Yearbook 2021 data, 60% of all births in Turkey were performed by cesarean section [1].

In recent years, with the increase in the rate of cesarean section, there have been changes in the anesthesia method applied. Unlike other surgeries, in cesarean section surgeries, the anesthetist should choose the anesthesia method that is safest and comfortable for the mother, least depressant for the newborn and provides suitable working conditions for the surgeon by considering the physiological and anatomical changes that develop in the mother due to pregnancy and evaluating the factors that will affect the adaptation process of the mother in the postoperative period [2,3]. As defined in the American Society of Anesthesiologists (ASA) Guidelines for Obstetric Anesthesia, the choice of anesthesia technique for cesarean section should be based on anesthesia, maternal and fetal risk factors, the desire of the pregnant woman and the preference of the anesthetist [4]. In cesarean section anesthesia, both general and regional anesthesia can be preferred. Although regional anesthesia has been the most preferred method by both surgeons and anesthetists in recent years, especially in obstetric anesthesia, many patients in Turkey still prefer general anesthesia due to fear of regional blocks [5]. In order to increase the preference for regional anesthesia, adequate information should be provided preoperatively. In order for the patient to choose the appropriate method more easily, the anesthetist should definitely explain the anesthetic strategies to be applied and the advantages and disadvantages in detail [6]. Good preoperative information by the anesthetist is directly related to reducing preoperative fears and increasing satisfaction with the chosen anesthesia method intraoperatively and postoperatively.

In this study, we aimed to investigate the anesthesia method preferred by pregnant women undergoing cesarean section, their fears about the methods they preferred, whether their preferences changed after information and their satisfaction with the anesthesia method they preferred after surgery.

## Materials and Methods

This study was performed on patients who applied to the anesthesia outpatient clinic of our hospital in June-July-August 2023 after obtaining the permission of the Clinical Research Ethics Committee of Giresun Training and Research Hospital (no:20.11.2023/02). A questionnaire was administered to the patients in order to question their level of knowledge and fears about general and spinal anesthesia preoperatively and the degree of satisfaction with the type of anesthesia they preferred in the postoperative period.

The patients who came to the outpatient clinic were informed about the study and verbal and written informed consent was obtained from the patients who agreed to participate in the survey. The survey questions were asked by the anesthesia doctor and the answers obtained from the pregnant women were recorded by the same doctor. Pregnant women were informed that if there was a question they did not want to answer, that question would be skipped and they could terminate the questionnaire at any time. Pregnant women who were over 37 weeks of gestation and who were admitted to the anesthesia outpatient clinic in the preoperative period with the decision of cesarean section under elective conditions were included in the survey. Pregnant women who were taken urgently in this 3-month period, pregnant women who had communication problems even if they applied to the outpatient clinic electively, or pregnant women who were mentally unable to answer the questions were excluded from the study.

The first part of the questionnaire included the age and education level of the patients, their previous anesthesia experience, their anesthesia preference and whether they had information about this preference, the reasons for their preference for general or regional anesthesia and their fears. In the second part, after detailed information about anesthesia methods by the anesthesiologist, anesthesia method preferences were questioned.In the second part, their preferences were questioned after detailed information about anesthesia methods by the anesthesiologist. In the last part, the satisfaction of the patients with their postoperative anesthesia preferences (general and regional), their negative experiences, if any, and which method they would prefer if they were operated again were

questioned. The first two parts of the questionnaire were completed by one-to-one interview in the preoperative outpatient clinic room, and the last part of the questionnaire was completed by calling the patient by telephone in the first postoperative week. The results were recorded as 'yes/no'.

No guidance was given to the patients during the questioning. It was made clear to the patients that their preferred anesthesia method would be used unless there was a medical obstacle, such as upper respiratory tract infection, systemic disease or abnormal bleeding profile, but if there was a medical obstacle, the anesthesia method that was best for them and the baby would be chosen.

**Statistical analysis**

IBM-Statistical Package for Social Sciences (IBM-SPSS Inc., Chicago, IL, USA) 22.0 programme was used to analyse the data obtained in the study. The conformity of the data to normal distribution was analysed by "Kolmogorov Smirnov test". Continuous variables were expressed as mean ± standard deviation and categorical variables were expressed as number and percentage. 'One-Way ANOVA test' was applied in the analysis of continuous variables. Chi-square test or Fisher's exact test was used to analyse categorical variables. Statistical significance level was accepted as $p<0.05$.

**Results**

A total of 398 cesarean section operations were performed in the operating theatre of Giresun Gynaecology and Paediatrics Training and Research Hospital in June-July and August 2023. Of these patients, 105 of whom were decided to have a cesarean section under elective conditions, applied to the anesthesia clinic for preoperative evaluation. 3 patients were excluded from the study because they did not want to participate in the survey. A total of 102 patients were administered the study questionnaire.

Pregnant women were divided into groups according to the method they preferred and whether there was a change in their preference after the information. The group who preferred spinal anesthesia and whose preference did not change was named as SS, the group who preferred general anesthesia and whose preference changed towards spinal anesthesia after information was given was named as GS, and the group who preferred general anesthesia and whose preference did not change was named as GG. Pregnant women who preferred spinal anesthesia did not change their preference after information. The SS group consisted of 78 patients, the GS group consisted of 18 patients and the GG group consisted of 6 patients. During this period, 94.1% of the patients who underwent elective cesarean section were operated with regional anesthesia and 5.8% with general anesthesia.

Patients were evaluated according to age groups, educational status, experience of anesthesia in previous delivery, preferred anesthesia method and whether they had information about this method. There was no statistically significant difference between the age and education levels of the patients. When the groups were evaluated in terms of anesthesia experience, there was a statistically significant difference between the groups ($p=0.011$). When the anesthesia experience parameter was compared in subgroups, the general anesthesia experience was statistically significantly lower in the SS group compared to the GS and GG groups ($p<0.05$). In addition, the experience of spinal anesthesia in the GS group was lower than the other groups and this difference was statistically significantly different from the SS group ($p<0.05$) (Table 1). The number of patients who had no information about their preferred method was 13 in the SS group, 6 in the GS group and 2 in the GG group. The sources of information are given in detail in Table 1. In all groups, the source of information was mostly previous anesthesia experiences. The second most common source of information was the information obtained from gynaecologists.

The reasons of the patients who preferred spinal anesthesia are shown in Table 2. Among the patients who could select more than one option, 98.7% stated that they preferred spinal anesthesia because of the negative experiences they had heard about general anesthesia. The most common fear was that the anesthesia might be too much. The reasons of the patients who preferred general anesthesia are shown in Table 3. Again, in patients who could tick more than one option, the highest reasons for preference in both GS and GG groups were negative experiences from the environment, fear of paralysis and fear of postoperative headache.

**Table 1.** Demographic characteristics

| | | SS, (n=78) | GS, (n=18) | GG, (n=6) | p value |
|---|---|---|---|---|---|
| Age | | 30.22±4.45 | 31.06±5.16 | 29.67±5.28 | 0.837 |
| Education level | Primary School | 3(3.8%) | 3(16.7%) | 0(0%) | 0.084 |
| | Middle School | 13(16.7%) | 7(38.9%) | 1(16.7%) | |
| | High School | 28(35.9%) | 3(16.7%) | 3(50%) | |
| | University | 34(43.6%) | 5(27.8%) | 2(33.3%) | |
| Anesthesia experience | None | 13(16.7%)[a] | 3(16.7%)[a] | 1(16.7%)[a] | **0.011** |
| | General | 6(7.7%)[a] | 7(38.9%)[b] | 2(33.3%)[b] | |
| | Spinal | 56(71.8%)[a] | 6(33.3%)[b] | 3(50%)[a,b] | |
| | General+Spinal | 3(3.8%)[a] | 2(11.1%)[a] | 0(0%)[a] | |
| Information on anesthesia method | No information | 13(16.7%) | 6(33.3%) | 2(33.3%) | 0.707 |
| | Due to my previous anesthesia experience | 49(62.8%) | 9(50%) | 3(50%) | |
| | With the advice of my gynaecologist | 11(14.1%) | 1(5.6%) | 1(16.7%) | |
| | With experience recommendation from family or friends | 4(5.1%) | 2(11.1%) | 0(0%) | |
| | TV/internet research | 1(1.3%) | 0(0%) | 0(0%) | |

Variables were expressed as mean ± standard deviation or n (%). One-Way ANOVA test or Chi-square test was applied. Each identical superscript (a, b) indicates a subset of group categories that are not statistically significantly different from each other at the p: 0.05 level.

**Table 2.** Reasons for spinal anesthesia preference

| | SS, (n=78) |
|---|---|
| Due to previous experience | 39(50%) |
| Because of what I have heard about general anesthesia | 77(98.7%) |
| Fear of not waking up from general anesthesia | 64(82.1%) |
| Fear of too much anesthesia | 75(96.2%) |
| The desire to see your baby immediately when it is born | 54(69.2%) |
| The desire to be myself and be able to breastfeed your baby earlier | 69(88.5%) |
| With the advice of the gynaecologist | 70(89.7%) |
| Not wanting to suffer pain | 73(93.6%) |

Variables were expressed as n (%).

**Table 3.** Reasons for general anesthesia preference

| | GS, (n=18) | GG, (n=6) |
|---|---|---|
| Due to previous anesthesia experience | 8(44.4%) | 3(50%) |
| Because of the negative experiences I have heard from the environment about spinal anesthesia | 17(94.4%) | 6(100%) |
| Fear of paralysis after spinal anesthesia | 15(83.3%) | 6(100%) |
| Fear of headache after spinal anesthesia | 17(94.4%) | 6(100%) |
| With the recommendation of the gynaecologist | 16(88.9%) | 6(100%) |
| Due to unwillingness to suffer pain | 14(77.8%) | 5(83.3%) |
| For the reason that I don't want to see anything | 14(77.8%) | 4(66.7%) |

Variables were expressed as n (%).

**Table 4.** Postoperative period

| | | SS, (n=78) | GS, (n=18) | GG, (n=6) | p value |
|---|---|---|---|---|---|
| Negative effect | None | 72(92.3%) | 14(77.8%) | 5(83.3%) | 0.179 |
| | Headache | 2(2.6%)[a] | 1(5.6%)[a] | 0(0%)[a] | |
| | Backache | 1(1.3%)[a] | 1(5.6%)[a] | 0(0%)[a] | |
| | Panic attacks | 2(2.6%)[a] | 0(0%)[a] | 0(0%)[a] | |
| | Pain sensation | 1(1.3%)[a] | 1(5.6%)[a] | 0(0%)[a] | |
| | Shoulder pain | 0(0%)[a] | 1(5.6%)[a] | 0(0%)[a,b] | |
| | Trembling | 0(0%)[a] | 0(0%)[a,b] | 1(16.7%)[b] | |
| Satisfaction | Yes | 72(92.3%) | 14(77.8%) | 6(100%) | 0.123 |
| | No | 6(7.7%) | 4(22.2%) | 0(0%) | |
| Preferred in a new operation | Spinal | 72(92.3%)[a] | 14(77.8%)[a] | 0(0%)[b] | **<0.001** |
| | General | 6(7.7%)[a] | 4(22.2%)[a] | 6(100%)[b] | |

Variables were shown as n (%). Chi-square test was applied. Each same superscript (a, b) indicates a subset of group categories that are not statistically significantly different from each other at the p: 0.05 level.

Postoperative satisfaction and negative experiences, if any, of the patients who underwent surgery under spinal or general anesthesia according to their new preferences after information were evaluated. 92.3% of the SS group, 77.8% of the GS group and 100% of the GG group were satisfied with the procedure. When the reasons of the patients who were not satisfied were questioned, they stated the negative experiences they had. In the SS group, 2 patients reported postspinal headache, 1 patient reported backache, 2 patients reported panic attacks due to the sounds they heard from the environment, and 1 patient reported pain throughout the operation. In the GS group, one patient experienced postspinal headache, backache and shoulder pain, and 1 patient stated that they felt pain throughout the operation. No patient in the GG group had any negative experience. All patients were asked about the method they would prefer if they were operated again. There was a statistically significant difference between the groups when the parameter of the method that the patients would prefer if they were operated again was analysed ($p<0.001$). When the groups were compared for subgroup analysis, "Spinal anesthesia preference" was statistically significantly higher in the SS and GS groups than in the GG group ($p<0.05$) (Table 4).

**Discussion**

Obstetric anesthesia is an in-demand and satisfying subspecialty of anesthesiology. Its widespread acceptability and the use of regional anesthesia for delivery have made obstetric anesthesia an important part of many anesthetic practices [7]. In anaesthesia of non-obstetric patients, only one person's safety and optimal conditions are tried to be ensured, whereas in cesarean section, the safety of the mother and the fetus, which is affected by all kinds of changes occurring in the mother, must also be ensured. This gives cesarean anesthesia a distinct feature [8]. There is no ideal anesthetic method for all expectant mothers. The choice of anesthesia depends on the desire of the expectant mother, obstetric needs and the experience of the anesthetist [9].

General and regional anesthesia techniques are used in cesarean section anesthesia. The preference for regional anesthesia in cesarean section has increased significantly over the years. Gulhaş et al. retrospectively examined 2534 cases who underwent cesarean section between 2009 and 2011 from anesthesia follow-up forms and found that regional anesthesia method was applied to 74% of these patients and general anesthesia method was applied to 26%. In a study by Lai et al. [10] in Taiwan, in which 25.606 cases were evaluated, this rate was found to be 95%. Almost all cesarean sections performed in public hospitals in our city are carried out in our hospital. In our study, 94% of the patients were operated under regional anesthesia and we found that we were compatible with the literature in cesarean section anesthesia.

Although regional anesthesia has been the most preferred method by both surgeons and anesthesiologists in recent years, especially in obstetric anesthesia, many patients in Turkey still prefer general anesthesia because of fear of regional blocks [5]. Although this is the preference of patients, many studies in Turkey have shown that the rate of spinal anaesthesia is higher than general anaesthesia in caesarean section surgeries [11]. The majority of our patients had knowledge about spinal anaesthesia due to previous experience and 78 of 102 patients preferred spinal anaesthesia without any information.

Although most studies reported that maternal age did not affect the preference for regional and general anesthesia, in one study [12], the mean age of the subjects included in the study was found to be statistically significantly higher in the regional anesthesia group. No statistically significant difference was found in the mean age and education level of the mothers who participated in our study.

In patients undergoing general anesthesia, the most common preoperative anxiety is the fear of not waking up from anesthesia. In a study conducted by Shevde and Panagopoulos on 800 patients, 39% reported that they had no fear and 35% reported that they were afraid of "not waking up" [13]. Among the fears of our patients related with general anesthesia, fear of excessive narcosis and fear of not waking up were present in accordance with the literature. The reason for preferring spinal anesthesia was due to desire to remain conscious and to see the baby and, breastfeed.

Adequate information should be provided preoperatively to increase the preference for regional anesthesia. The anaesthetist should explain the anaesthesia strategies, advantages and disadvantages to the patient in detail and help the patient to choose the appropriate method [6]. A good preoperative information by the anesthetist is directly related with reducing preoperative fears and increasing intraoperative and postoperative satisfaction with the selected anesthesia method. The preference for general anesthesia was low among our patients. The reasons for the patients' preference for general anesthesia were negative experiences about spinal anesthesia, fear of paralysis and fear of postoperative headache. Our patients who came to the outpatient clinic were informed in detail by the anesthesiologist about the procedure, advantages and disadvantages of anesthesia methods. After the information, 18 of 24 patients who preferred general anesthesia changed their decision to spinal anesthesia. As the reason for the change, they stated that their fears were unfounded and that they had received wrong information.

The most common preoperative fears of patients who underwent regional anesthesia were reported being awake during surgery and experiencing pain during surgery [14]. In our study, when the 6 patients who preferred general anesthesia and whose decisions did not change despite being informed were questioned, they reported that they were 'afraid of being awake and having panic attacks' in accordance with the literature.

In studies conducted in cesarean section cases related with the choice of anesthesia technique, 80-96% of the patients who had previously experienced general and regional anesthesia reported that they were satisfied with regional anesthesia and would prefer it again in the next operation [15]. However, Afolabi et al. [16], who performed a meta-analysis of 29 studies, found that previous anesthesia experience was effective in the decision-making of pregnant women and that the majority of patients were prone to general anesthesia. Kızılkaya et al. compared spinal and general anesthesia methods and found no effect on satisfaction [17]. In our study, 92.3% of the patients who preferred spinal anesthesia and underwent spinal anesthesia and 77.8% of the patients who preferred general anesthesia but underwent spinal anesthesia after being informed reported that they were satisfied with spinal anesthesia and would prefer spinal anesthesia again if they had to undergo surgery again. All 6 patients who received general anesthesia reported that they were satisfied with general anesthesia and would prefer general anesthesia again.

Among the limitations of our study, we thought that it would not be correct to compare both groups in terms of postoperative satisfaction because of the low number of patients receiving general anesthesia. However, we believe that this is a good result for our hospital where regional anesthesia practice is high. Evaluation of the postop pain of the patients according to VAS (Visual Analogue Scale) scoring will be effective in the satisfaction rate. The fact that the pain related to the wound site was not evaluated in our study is our second limitation.

Despite its advantages, spinal anesthesia is not without potential complications. Some complications associated with spinal anesthesia include post dural puncture headache (PDPH), backache, hypotension, urinary retention, infection, bleeding and nerve injury. PDPH is one of the most common complications of spinal anesthesia and its frequency varies between 4% and 40% [18]. Various factors including patient characteristics, needle size, technique and the approach used affect the incidence of PDPH. In our study, the incidence of postop headache was found to be 3% among all patients who underwent spinal anesthesia and this is lower than the PDPH rates we have seen in the literature. We attribute this to the fact that we are a maternity hospital and our anesthetists have high experience in spinal anesthesia. The fact that our needles used were 25 gauge Quincke tipped needles is another important factor.

In conclusion, lack of information and having wrong information due to negative sensations from the environment cause patients to prefer general anesthesia. We think that by determining the preoperative concerns of pregnant women about anesthesia and providing more effective information, pregnant women's preference for spinal anesthesia, which is safer for themselves and their babies in cesarean section operations, can

be increased and their satisfaction can be increased by providing a better experience.

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ORIGINAL ARTICLE

# Relationship between low back, shoulder, and elbow pain in hazelnut workers and their harvestıng methods, physical activity status and healthy lifestyle

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**Abstract**

**Objective:** The aim of the study to evaluate the sociodemographic characteristics, hazelnut harvesting methods and duration, physical activity status, and healthy lifestyle behaviors of patients who have engaged in hazelnut harvesting and presented with complaints of low back, shoulder, and elbow pain for the first time at clinic . The goal is to assess whether these factors are influential in the emergence of disorders related to the reported complaints.

**Methods:** It is a cross-sectional study conducted on a total of 124 people between the ages of 20-65 years who applied to the Physical Medicine and Rehabilitation Clinic with complaints of low back, shoulder and elbow pain during the period of September - November 2020. Since the most common diagnoses were lumbar strain-sprain, subacromial impingement syndrome and lateral epicondylitis, patients with other diagnoses were excluded from the study. A total of 124 patients' data were analysed. Data were collected by a single physician through a questionnaire interview. The questionnaire consisted of 3 sections; sociodemographic characteristics, harvesting methods and additional tasks and IPAQ Short Form.

**Results:** Of the study participants, 63 (50.8%) presented to the clinic with low back pain and 66 (53.2%) were diagnosed with lumbar strain-sprain. This was followed by 38 (30.6%) with shoulder pain and 34 (27.4%) were diagnosed with subacromial impingement syndrome. There was no significant difference between clinical diagnosis and age and sex.

**Conclusions:** Although sociodemographic characteristics, hazelnut harvesting methods and duration were not statistically associated with clinical diagnoses, the most common diagnosis was lumbar strain-sprain. In order to minimize the negative impact of the hazelnut harvesting on the musculoskeletal system, education and preventive measures can be provided to individuals engaged in hazelnut harvesting.

**Keywords:** hazelnut; agriculture; musculoskeletal disorders

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## Introduction

Agriculture is the second-largest employment sector in Turkey and globally. There are 1.1 billion agricultural workers in the world. According to the May 2018 data from the Turkish Statistical Institute [TURKSTAT], 18.8% of the total employed population (32 million 274 thousand) in Turkey works in the agricultural sector [1]. Hazelnut orchards hold significant importance among cultivated agricultural lands in Turkey. Approximately 80% of the total global hazelnut orchard area is located in our country. Approximately 60% of the hazelnut orchards in Turkey are located in the Black Sea region, of which approximately 18% is in Giresun province. Giresun province second-highest hazelnut-producing province after Ordu. Consequently, there is a intense workload for hazelnut production and harvesting throughout the province. [2].

The agricultural sector requires human labor as well as machine power, and physical processes such as harvesting, hoeing, sorting and other tasks that demand physical strength can have negative effects on the musculoskeletal system. Although there are publications supporting this issue in the literature [3-5], there are no publications on skeletal-muscular system problems that can be seen in agricultural workers who pick hazelnuts.

Conditions like subacromial impingement syndrome, lateral epicondylitis, medial epicondylitis and lumbar strain-sprain are disorders that can lead to shoulder, elbow and low back pain problems. These conditions can be diagnosed clinically and may arise from acute or repetitive traumas, such as those experienced by hazelnut workers, causing pain and loss of work capacity. These are significant conditions that can be observed in agricultural workers [6-9].

The level of physical activity in people's daily lives affects health in many ways. Restriction in physical activity leads to obesity and causes many health problems [10]. It is also known that unconscious physical activity can have negative effects on the musculoskeletal system [11]. Improving health can be achieved by individuals taking responsibility for their health, managing and controlling it and reaching their full health potential.

Indicators of this process include health responsibility, physical activity, nutrition, mental development, interpersonal relationships and stress management. Working and workplace conditions, including the physical, psychosocial and organizational environment, directly shape employee health, health behaviors and safety [12].

It can be concluded that musculoskeletal system problems, as indicated in the literature for other agricultural workers, may also develop in hazelnut workers, especially considering the method and duration of hazelnut harvesting. Unconsciously or consciously engaging in this physical activity, particularly in the context of hazelnut harvesting, may lead to repetitive or acute traumas. This could result in complaints such as shoulder pain, elbow pain, and low back pain.

In our study, we aimed to evaluate the sociodemographic characteristics, hazelnut harvesting methods and duration, physical activity status and healthy lifestyle behaviors of hazelnut harvesting patients who were admitted to Giresun University Prof. Dr. A. İlhan Özdemir Training and Research Hospital Physical Medicine and Rehabilitation Clinic for the first time with complaints of low back, shoulder and elbow pain and diagnosed with lumbar strain-sprain, subacromial impingement syndrome and lateral epicondylitis. The aim is to evaluate whether these factors are effective in the occurrence of the disorders related to the reported complaints.

## Material-Method

This study is a cross-sectional study conducted in individuals between the ages of 20-65 who were hazelnut workers and applied to Physical Medicine and Rehabilitation Clinic of Giresun University Prof. Dr. A. Ilhan Ozdemir Training and Research Hospital with

low back, shoulder and elbow pain.

The study was conducted on individuals who were engaged in hazelnut harvesting between September and November 2020 and who applied to the Physical Medicine and Rehabilitation Clinic with complaints of low back, shoulder and elbow pain and agreed to participate in the study. The most common diagnoses were lumbar strain-sprain, subacromial impingement syndrome and lateral epicondylitis..Patients with other diagnoses were excluded from the study and a total of 124 individuals were included.

The data of the study were collected by a single physician through a face-to-face questionnaire interview in the Physical Medicine and Rehabilitation Clinic of Giresun University Prof. Dr. A. Ilhan Ozdemir Training and Research Hospital. The physician performed a physical examination of the patient and made a clinical diagnosis. The diagnosis of low back strain was based on pain in the lumbar region which increased especially with coughing and lumbar flexion, tenderness in the paravertebral muscles with palpation. Negative straight leg raising test, absence of neurological deficit and urinary-fecal incontinence also supported our diagnosis.

The diagnosis of subacromial impingement syndrome was made on the basis of physical examination and ultrasonography(USG). The diagnosis was made with pain in the deltoid insertion site, positive Neer and Hawkins-Kennedy tests, pain in shoulder abduction and USG findings (subacromial bursa lateral to the impingement site, bundling in the coracoacromial arch, subdeltoid bursa, swelling in the coracoacromial ligament). Bone pathologies were excluded after anterior and posterior shoulder X-rays of all patients. [13].

The diagnosis of lateral epicondylitis was made on the basis of tenderness on palpation over the lateral epicondyle, pain in the lateral elbow area, pain over the lateral epicondyle with resistance to wrist and/or middle finger extension, and a positive Cozen's test. [14].

The questionnaire form was prepared in accordance with the purpose of the study, utilizing the literature and clinical experience, and consisting of three sections as a result of preliminary interviews with hazelnut workers before starting the study and observation of harvesting methods.

In the first section of the questionnaire form, the participants' sociodemographic characteristics are included, such as age, sex, occupation, education level, income status, physician-diagnosed chronic diseases, height, weight, and income level, among others. In the second section, details about hazelnut harvesting methods, duration, and additional tasks (such as removing weeds in the orchard) are included.

The third section of the questionnaire includes the International Physical Activity Questionnaire Short Form (IPAQ Short Form). The International Physical Activity Questionnaire (IPAQ) was developed to assess the physical activity levels of participants aged 15-65 [15]. In Turkey, a validity and reliability study for IPAQ was conducted by Öztürk in 2005 among university students, and later in 2007, Karaca and Turnagöl conducted a validity and reliability study among working individuals [16].

The IPAQ Short Form provides information about the time spent on walking, moderate-intensity, and vigorous-intensity activities, as well as the time spent sitting. The calculation of the total score of the short form includes the sum of duration (minutes) and frequency (days) of walking, moderate to vigorous activity and vigorous activity. According to the numerical data obtained, three levels were defined as inactive, minimally active and very active.

The dependent variables in our study are clinical diagnosis, physical activity status, and healthy lifestyle behaviors. The independent variables include sociodemographic characteristics (age, sex, occupation, education level, income status, physician-

**Table 1: Some sociodemographic characteristics of the study group**

| FEATURE | n | % | TOTAL |
|---|---|---|---|
| **Sex** | | | |
| Female | 46 | 37.1 | 124 |
| Male | 78 | 62.9 | |
| **Age** | | | |
| Under 50 years old | 65 | 52.4 | |
| 50 years and older | 59 | 47.6 | |
| **Body Mass Index** | | | |
| Normal | 41 | 33.1 | 124 |
| Overweight | 57 | 46.0 | |
| 1st, 2nd and 3rd degree obese | 26 | 21.0 | |
| **Occupation** | | | |
| Non-farming | 63 | 50.8 | 124 |
| Farming | 61 | 49.2 | |
| **Physician Diagnosed Chronic Disease Status** | | | |
| No | 80 | 64.5 | 124 |
| Yes | 44 | 35.5 | |
| **Reason for Application to Clinic** | | | |
| Shoulder pain | 38 | 30.6 | 124 |
| Low back pain | 63 | 50.8 | |
| Elbow pain | 23 | 18.5 | |
| **Clinical Diagnosis** | | | |
| Subacromial impingement syndrome | 34 | 27.4 | 124 |
| Lumbar strain-sprain | 66 | 53.2 | |
| Epicondylitis | 24 | 19.4 | |
| **Hazelnut Harvesting Methods** | | | |
| From the branch | 11 | 8.9 | 124 |
| From the ground | 93 | 75.0 | |
| Branch and ground | 20 | 16.1 | |
| **Daily Picking Time** | | | |
| 8 hours or less | 93 | 75.0 | 124 |
| Over 8 hours | 31 | 25.0 | |
| **Number of Days Hazelnut Picking** | | | |
| 10 days and less | 45 | 36.3 | 124 |
| Over 10 days | 79 | 63.7 | |
| **Hazelnut Carrying Status** | | | |
| Yes | 89 | 71.8 | 124 |
| No. | 35 | 28.2 | |
| **Removing weeds in orchards** | | | |
| Yes | 89 | 71.8 | 124 |
| No. | 35 | 28.2 | |

**Table 2: Association of clinical diagnosis with some sociodemographic characteristics**

| FEATURE | CLINICAL DIAGNOSIS | | | TOTAL | $X^2$ | P |
|---|---|---|---|---|---|---|
| | Subacromial impingement syndrome n(%) | Lumbar Strain-Sprain n(%) | Epicondylitis n(%) | | | |
| **Sex** | | | | | | |
| Female | 15(32.6) | 26(56.5) | 5(10.9) | 46(100.0) | 3.588[a] | 0.166 |
| Male | 19(24.4) | 40(51.3) | 19(24.4) | 78(100.0) | | |
| **Age** | | | | | | |
| Under 50 years old | 17(26.2) | 38(58.5) | 10(15.4) | 65(100.0) | 1.896[a] | 0.388 |
| 50 years and older | 17(28.8) | 28(47.5) | 14(23.7) | 59(100.0) | | |
| **Body Mass Index** | | | | | | |
| Normal | 12(29.3) | 20(48.8) | 9(22.0) | 41(100.0) | 0.697[a] | 0.952 |
| Overweight | 15(26.3) | 31(54.4) | 11(19.3) | 57(100.0) | | |
| 1st, 2nd and 3rd degree obese | 7(26.9) | 15(57.7) | 4(15.4) | 26(100.0) | | |
| **Occupation** | | | | | | |
| Non-farming | 13(20.6) | 39(61.9) | 11(17.5) | 63(100.0) | 4.200[a] | 0.122 |
| Farming | 21(34.4) | 27(44.3) | 13(21.3) | 61(100.0) | | |
| **Physician Diagnosed Chronic Disease Status** | | | | | | |
| No | 24(30.0) | 40(50.0) | 16(20.0) | 80(100.0) | 1.037[a] | 0.595 |
| Yes | 10(22.7) | 26(59.1) | 8(18.2) | 44(100.0) | | |
| **Reason for Application to Clinic** | | | | | | |
| Shoulder pain | 34(89.5) | 4(10.5) | 0(0.0) | 38(100.0) | 221.290[a] | **<0.001** |
| Low back pain | 0(0.0) | 62(98.4) | 1(1.6) | 63(100.0) | | |
| Elbow pain | 0(0.0) | 0(0.0) | 23(100.0) | 23(100.0) | | |
| **Hazelnut Harvesting Methods** | | | | | | |
| From the branch | 3(27.3) | 6(54.5) | 2(18.2) | 11(100.0) | 0.823[a] | 0.935 |
| From the ground | 24(25.8) | 51(54.8) | 18(19.4) | 93(100.0) | | |
| Branch and ground | 7(35.0) | 9(45.0) | 4(20.0) | 20(100.0) | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Daily Picking Time** | | | | | | |
| 8 hours or less | 24(25.8) | 50(53.8) | 19(20.4) | 93(100.0) | 0.595[a] | 0.743 |
| Over 8 hours | 10(32.3) | 16(51.6) | 5(16.1) | 31(100.0) | | |
| **Number of Days Hazelnut Picking** | | | | | | |
| 10 days and less | 10(22.2) | 26(57.8) | 9(20.0) | 45(100.0) | 0.986[a] | 0.611 |
| Over 10 days | 24(30.4) | 40(50.6) | 15(19.0) | 79(100.0) | | |
| **Hazelnut Carrying Status** | | | | | | |
| Yes | 24(27.0) | 46(51.7) | 19(21.3) | 89(100.0) | 0.812[a] | 0.666 |
| No | 10(28.6) | 20(57.1) | 5(14.3) | 35(100.0) | | |
| **Removing weeds in orchards** | | | | | | |
| Yes | 25(28.4) | 46(52.3) | 17(19.3) | 88(100.0) | 0.160[a] | 0.923 |
| No | 9(25.0) | 20(55.6) | 7(19.4) | 36(100.0) | | |

**Table 3: Association of physical activity status with some sociodemographic characteristics**

| FEATURE | Physical activity status | | | TOTAL | $X^2$ | P |
|---|---|---|---|---|---|---|
| | Inactive n(%) | Low Activity n(%) | Sufficient Active n(%) | | | |
| **Sex** | | | | | | |
| Female | 3(6.5) | 29(63.0) | 14(30.4) | 46(100.0) | 0.014[a] | 0.993 |
| Male | 5(6.4) | 50(64.1) | 23(29.5) | 78(100.0) | | |
| **Age** | | | | | | |
| <50 years | 1(1.5) | 41(63.1) | 23(35.4) | 65(100.0) | 6.528[a] | **0.038** |
| ≥50 years | 7(11.9) | 38(64.4) | 14(23.7) | 59(100.0) | | |
| **Body Mass Index** | | | | | | |
| Normal | 2(4.9) | 22(53.7) | 17(41.5) | 41(100.0) | 5.372[a] | 0. 251 |
| Overweight | 3(5.3) | 39(68.4) | 15(26.3) | 57(100.0) | | |
| 1st, 2nd and 3rd degree obese | 3(11.5) | 18(69.2) | 5(19.2) | 26(100.0) | | |
| **Occupation** | | | | | | |
| Non-farming | 7(11.1) | 34(54.0) | 22(34.9) | 63(100.0) | 7.326[a] | **0. 026** |
| Farming | 1(1.6) | 45(73.8) | 15(24.6) | 61(100.0) | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Physician Diagnosed Chronic Disease Status** | | | | | | |
| No | 6(7.5) | 47(58.8) | 27(33.8) | 80(100.0) | 2.410[a] | 0. 300 |
| Yes | 2(4.5) | 32(72.7) | 10(22.7) | 44(100.0) | | |
| **Reason for Application to Clinic** | | | | | | |
| Shoulder pain | 2(5.3) | 27(71.1) | 9(23.7) | 38(100.0) | 2.216[a] | 0. 696 |
| Low back pain | 4(6.3) | 40(63.5) | 19(30.2) | 63(100.0) | | |
| Elbow pain | 2(8.7) | 12(52.2) | 9(39.1) | 23(100.0) | | |
| **Clinical Diagnosis** | | | | | | |
| Subacromial impingement syndrome | 1(2.9) | 24(70.6) | 9(26.5) | 34(100.0) | 3.293[a] | 0.510 |
| Lumbar strain-sprain | 5(7.6) | 43(65.2) | 18(27.3) | 66(100.0) | | |
| Epicondylitis | 2(8.3) | 12(50.0) | 10(41.7) | 24(100.0) | | |
| **Hazelnut Harvesting Methods** | | | | | | |
| From the branch | 1(9.1) | 7(63.6) | 3(27.3) | 11(100.0) | 2.455[a] | 0. 653 |
| From the ground | 7(7.5) | 60(64.5) | 26(28.0) | 93(100.0) | | |
| Branch and ground | 0(0.0) | 12(60.0) | 8(40.0) | 20(100.0) | | |
| **Daily Picking Time** | | | | | | |
| ≤8 hours | 7(7.5) | 61(65.6) | 25(26.9) | 93(100.0) | 1.964[a] | 0. 375 |
| >8 hours | 1(3.2) | 18(58.1) | 12(38.7) | 31(100.0) | | |
| **Number of Days Hazelnut Picking** | | | | | | |
| ≤10 days | 7(15.6) | 24(53.3) | 14(31.1) | 45(100.0) | 10.306[a] | **0. 006** |
| >10 days | 1(1.3) | 55(69.6) | 23(29.1) | 79(100.0) | | |
| **Hazelnut Carrying Status** | | | | | | |
| Yes | 6(6.7) | 58(65.2) | 25(28.1) | 89(100.0) | 0.470[a] | 0. 791 |
| No. | 2(5.7) | 21(60.0) | 12(34.3) | 35(100.0) | | |
| **Removing weeds in orchards** | | | | | | |
| Yes | 5(5.7) | 60(68.2) | 23(26.1) | 88(100.0) | 2.622[a] | 0.269 |
| No. | 3(8.3) | 19(52.8) | 14(38.9) | 36(100.0) | | |
| **Total** | 8(6.5) | 79(63.7) | 37(29.8) | | 124(100.0) | |

diagnosed chronic diseases, height, weight, among others), hazelnut harvesting methods, duration, and additional tasks.

The data obtained were transferred to a computer and analyzed using the IBM SPSS software package (version 20.0). Descriptive statistics were presented as frequencies, percentages, median (min-max), and mean±standard deviation. Chi-square analysis was conducted for the univariate analysis of dependent and independent variables in categorical data.

The study protocol and design were approved by the Clinical Research Ethics Committee of Giresun University (Decision date: 4 September 2020 number KAEK-13)

**Results**

The mean age of the participants was 48.9±1.1 years (min=18, max=80) and 78 (62.9%) of them were male. The mean body mass index (BMI) of the research group was determined to be 26.7302±4.35 (min=16.90, max=47.75). 63 (50.8%) of the participants were not farmers. While 80 (64.2%) of the study group did not have a physician-diagnosed disease, 63 (50.8%) of the study group applied to the clinic due to low back pain and 66 (53.2%) were diagnosed with lumbar strain-sprain. During the hazelnut harvesting season, 93 (75% ) of the study group worked for 8 hours or less per day, and 79 (63.7% ) indicated picking hazelnuts for 10 days or more. Additionally, 89 (71.8%) of the participants reported engaging in both hazelnut carrying and removing weeds activities. The distribution of the study group's demographic characteristics is provided in Table 1.

Among the study participants, those who applied to the clinic with low back pain were diagnosed with lumbar strain-sprain (X2 : 221,290a ;p<0.001), while there was no significant difference between clinical diagnosis and other characteristics. The relationship between clinical diagnosis and some sociodemographic characteristics of the study group is given in Table 2.

In our study, those under 50 years of age were more likely to have sufficient physical activity compared to those aged 50 and above. Similarly, non-farmers were more likely to have sufficient physical activity compared to farmers. Additionally, those who picking hazelnuts for 10 days or less were not physically active compared to those who did not picking. The relationship between physical activity status and some sociodemographic characteristics of the study group is given in Table 3.

**Discussion**

According to the results of our study, among hazelnut workers, 50.8% presented to the clinic with the complaint of low back pain. This was followed by 30.6% with shoulder pain and 18.5% with elbow pain. The prevalence of low back pain as the primary complaint is consistent with other studies in the literature. In a study conducted by Thetkathuek et al. among Cambodian fruit farm workers, the prevalence of low back pain was 41.3%, ranking first [17]. Momeni et al. reported the most common musculoskeletal problems among Iranian farmers as low back pain (59.3%), knee pain (36.9%), back pain (36.6%), neck pain (36.5%), and shoulder pain (36.2%) [18]. In a study by Min et al. evaluating the prevalence of musculoskeletal pain in Korean farmers, low back pain (63.8%) ranked first, followed by leg/foot pain (43.3%) and shoulder pain (42.9%) [19]. Taking our study and other research into account, it is evident that in hazelnut harvesting, as in all agricultural activities, risk factors such as repetitive movements, heavy lifting, and working in incorrect postures facilitate the emergence of musculoskeletal symptoms.

Of the patients included in the study, 53.2% were diagnosed with lumbar strain-sprain, 27.4% with subacromial impingement syndrome and 24% with epicondylitis. The most common diagnosis was lumbar strain-sprain in both sexes and in individuals under and over 50 years of age. There was no significant difference between clinical diagnosis and age and sex. Osborne et al. did not find a relationship between age and the high prevalence of musculoskeletal disorders [20]. Similarly, Min et al. did not find a significant difference in musculoskeletal pain between those under 65 and those over 65, except for leg/foot pain, but they reported a significant association between female sex and musculoskeletal pain [5]. In contrast, a study by Jain et al. found an association between age (>25), sex (male), and the frequency of musculoskeletal symptoms [20].

In our study, no significant difference was found between body mass index (BMI) and clinical diagnosis. Kee et al. did not find a consistent relationship between body weight and the prevalence of musculoskeletal disorders. However, they observed lower rates of musculoskeletal symptoms in individuals weighing ≥70 kg compared to other groups, interpreting this as an advantage due to having more muscle strength in lifting and carrying heavy loads [21].

In another study, BMI was reported as a significant risk factor for the use of sick leave due to low back disorders. The authors explained this finding by suggesting that obese individuals with low back problems may experience difficulty in maintaining work continuity [22].

Momeni et al. identified body weight as a significant factor for musculoskeletal symptoms in some body regions such as the back, low back, and knees. It was shown that musculoskeletal symptoms were more common in individuals with a body weight >70 kg [18].

In our study, the most common diagnosis was lumbar strain-sprain in those with a daily working time of 8 hours or less and those with a daily working time of more than 8 hours. The second most common diagnosis was subacromial impingement syndrome and the third most common diagnosis was lateral epicondylitis. Similar rankings of clinical diagnoses were observed between those working 10 days or less and those working more than 10 days. There was no significant difference in clinical diagnoses based on daily working hours and the number of days of hazelnut picking.

Osborne et al. found a statistically higher prevalence of musculoskeletal disorders in farmers with longer daily working hours [5]. Similarly, Fethke et al. observed a statistically significant relationship between the weekly average hours spent on several agricultural activities and musculoskeletal pain. The weekly average hours spent milking animals were associated with both neck/shoulder pain and elbow/wrist/hand pain. In addition, the weekly average hours spent on maintenance and repair of equipment was associated with low back pain [9]. In contrast, Kaewdok et al. did not find a statistically significant relationship between working hours and musculoskeletal disorders [23].

The National Institute for Occupational Safety and Health reported that repetitive work, overexertion and incorrect working postures cumulatively affect musculoskeletal symptoms in the arm/wrist/hand region. They also reported that the neck/shoulder region is affected by incorrect working postures and the lumbar region is affected by lifting, heavy physical work or systemic vibrations [24]. In a review by Kumaraveloo et al. examining agriculture and musculoskeletal disorders, incorrect working posture was reported as the most common physical risk factor [25].

When removing weeds, hazelnut picking and hazelnut carrying were evaluated, the most common clinical diagnosis was lumbar strain-sprain in those who did and those who did not do these jobs. There was no statistically significant difference between the two groups. Removing weeds, hazelnut picking, and hazelnut carrying in sloping terrain involve challenging agricultural activities that require leaning forward, kneeling, and repetitive upper extremity and trunk movements. In a study by Kee and Haslam, the prevalence of musculoskeletal disorders in the shoulder, knee and lumbar regions was associated with frequent use of these regions. This relationship was explained by three reasons: less machinery use compared to developed countries, prolonged working in a bent posture during harvesting, and poor working posture such as squatting/kneeling during activities such as removing weeds and picking fruits from the ground [21]. Kang et al. reported that approximately 60% of farmers perform repetitive hand or wrist movements (>30/day) and that bending or turning the trunk and squatting or kneeling are common ergonomic risk factors [26].

In our study, patients under the age of 50 had sufficient physical activity compared to those over 50. Aging is associated with negative effects on various physiological systems, such as loss of muscle mass, decreased balance ability, and reduced muscle strength and endurance. Additionally, there is an increase in the frequency of non-communicable chronic diseases. All these factors lead to physical inactivity in elderly individuals [27]. We think that the difference between the two groups in our study is due to these reasons.

In our study, the most common diagnosis in farmers and non-farmers was lumbar strain-sprain. Studies in the literature have reported a higher prevalence of neck and shoulder pain in farmers compared to non-farmers [5]. In our study, non-farmers had more adequate physical activity than farmers. In Giresun province, non-farmers usually do hazelnut picking as an additional job in addition to their main occupation. While farmers increase their activity levels only during the hazelnut harvesting season, non-farmers have a certain level of physical activity even before the hazelnut harvesting season. This situation could be a reason explaining the difference observed between the two groups.

This study has several limitations. First, this study did not include the occupational groups of non-farmers. It could not be evaluated whether these occupations cause low back, shoulder and elbow pain. Second, It could not be determined how long the patients' complaints lasted before they applied to the clinic. However, it can be estimated that the longest period was 3 months based on the date of hazelnut harvest. And, since the most common diagnoses were lumbar strain-sprain, subacromial impingement syndrome and lateral epicondylitis, patients with other diagnoses were not included in the study and could not be analyzed.

In conclusion, although sociodemographic characteristics, methods and duration of hazelnut harvesting were not statistically related to clinical diagnoses, the most common diagnosis was lumbar strain-sprain. The hazelnut harvesting process involves working in a sloped terrain, requiring poor posture, repetitive activities, and lifting and carrying heavy loads. To minimize the impact of these conditions on the musculoskeletal system, individuals engaged in hazelnut harvesting could be provided with education and preventive measures.

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CERASUS JOURNAL OF MEDICINE

ORIGINAL ARTICLE



# Phototherapy in pediatric patients: 5-years single center experience

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**Abstract**

**Objective**: Phototherapy is a treatment option that has been used for many years in the treatment of various skin diseases. While it has more widespread use in adult patients, its use is more limited in the pediatric age group due to the long-term risk of skin cancer. In our study, we would like to present the data of pediatric patients we treated in our phototherapy unit for 5 years.

**Methods:** Medical records of pediatric patients treated in our phototherapy unit between 01. January 2018 and 31 December 2022, were retrospectively reviewed. Age, gender, skin type, diagnosis, treatment duration, total number of sessions, cumulative doses, frequency of regularly treated patients, side effects, treatment response, and months of treatment were recorded.

**Results:** During this period 688 patients received phototherapy. Thirty-three (4.4%) of these patients were under the age of 18. Median age was 15 (3-17), female to male ratio was 19/14. Psoriasis (54.5%) was the most common diagnosis. Other diagnoses were vitiligo (18.2%), atopic dermatitis (15.2%), pityriasis lichenoides chronica (6.1%), alopecia totalis (3%), and pityriasis rubra pilaris (3%). 27 (81.8%) patients received cabin nbUVB, 5 (15.2%) local nbUVB, 1 local topical PUVA (3%). Side effects were observed in 4 patients (12.1%). Erythema was observed in 2 patients (6.1%), itching and dryness were observed in 1 patient (3.0%), and vesicular eruption on the face was observed in 1 patient (3.0%). Complete recovery was observed in 4 patients (12.9%), and partial recovery was observed in 11 patients (35.5%), while 16 patients (51.6%) did not benefit from the treatment.

**Conclusion:** Phototherapy was most commonly used in patients with psoriasis in the pediatric age group. The incidence of side effects was lower than similar studies in the literature. However, response rates to treatment were lower than those reported in the literature.

**Keywords:** Phototherapy; narrowband UVB; PUVA; childhood

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## Introduction

Phototherapy has been used as a treatment option for a wide range of skin diseases since 1988 [1]. While it is more commonly used in adult patients, its use in the pediatric population is more limited due to insufficient long-term safety data and concerns about the risk of skin cancer [2,3]. Therefore, it is preferred for patients who do not respond to topical treatments or cannot receive systemic therapy due to side effects [4]. Phototherapy is most commonly used for the treatment of inflammatory skin diseases such as psoriasis, vitiligo, and atopic dermatitis in the pediatric population [3,4].

There are a limited number of studies presenting experiences of phototherapy in pediatric patient groups. Therefore, we aimed to retrospectively analyze data from pediatric patients treated in our phototherapy unit over a period of 5 years to identify similarities and differences with studies presented in the literature.

## Methods

After obtaining ethical approval (Giresun Training and Research Hospital Clinical Research Ethics Committee. Approval Number: KAEK-70/Decision Number: 27.03.2023/08) and institutional permissions, we retrospectively reviewed the medical records of patients under 18 years of age who started treatment in our phototherapy unit and those whose treatment was discontinued for any reason between January 1, 2018, and December 31, 2022. The study was conducted in accordance with the principles of the Helsinki Declaration. Patient demographics, including age, gender, skin type, diagnoses, rates of patients receiving narrow-band ultraviolet B (nbUVB) and psoralen ultraviolet A (PUVA) phototherapy, rates of patients receiving local and cabin phototherapy, treatment durations, total number of sessions, cumulative doses, presence of side effects, rates of regular attendance to treatment sessions, and the months during which treatment was received, were recorded.

Patients who achieved complete resolution of all lesions with treatment were considered to have achieved a complete response. In patients with psoriasis, pityriasis lichenoides chronica (PLC), pityriasis rubra pilaris (PRP), and atopic dermatitis, improvement of 75% or more in lesions was considered a partial response, while in vitiligo patients, repigmentation of 50% or more of the lesions, and in alopecia areata patients, hair regrowth in more than 50% of the alopecic areas, were considered partial responses [5].

In our phototherapy unit, we utilize the Waldman UV 7002 cabin for UVA/dbUVB and the Waldman 182 for local nbUVB and UVA treatments (Waldman, 9W. Century Drive, Wheeling, IL 60090, USA). Treatment protocols for patients were planned by entering diagnosis and Fitzpatrick skin type data into the device's software program. In case of side effects or treatment interruptions, the energy provided could also be manually adjusted.

The normality of the obtained numerical data was examined using visual methods (histograms and probability plots) and analytical methods (Kolmogorov-Smirnov test). Since numerical ordinal data such as age, cumulative dose of dbUVB, and number of phototherapy sessions did not follow a normal distribution, median and minimum-maximum range were used for descriptive statistics analysis. Percentages were calculated for categorical variables.

## Results

Between January 1, 2018, and December 31, 2022, a total of 688 patients received phototherapy in our unit. Among these patients, 33 (4.4%) constituted the under 18 age group. The median age of patients under 18 was 15 years (range: 3-17). Of these patients, 16 (48.5%) had Fitzpatrick skin type 2, and 17 (51.5%) had Fitzpatrick skin type 3. Among them, 19 (57.6%) were female, and 14 (42.4%) were male. The most common diagnosis of these patients was psoriasis, with 18 patients (54.5%). Six patients (18.2%) had vitiligo, 5 patients (15.2%) had atopic dermatitis, 2 patients (6.1%) had pityriasis lichenoides chronica (PLC), 1

patient (3%) had alopecia totalis, and 1 patient (3%) had pityriasis rubra pilaris (PRP).

Of the patients, 27 (81.8%) received cabin nbUVB phototherapy, while 5 (15.2%) received local nbUVB phototherapy (3 for psoriasis, 1 for vitiligo, and 1 for PRP). Only one patient (3%) received local PUVA therapy, a 12-year-old girl diagnosed with alopecia totalis. Due to the lack of improvement with treatment, the therapy was discontinued after 16 sessions (cumulative dose: 36.53 j/cm$^2$) for this patient.

The median total cumulative dose achieved by patients receiving nbUVB phototherapy was 10.4 j/cm$^2$ (range: 0.19-67.1), with a median total number of sessions 24.5 (range: 1-78). Among the patients, 78.8% (26 patients) completed at least 12 sessions of treatment, while 21.2% (7 patients) had their treatment discontinued before completing 12 sessions. Of the total, 16 patients (48.5%) attended their sessions regularly without interruption, whereas 17 patients (51.5%) either missed sessions or had irregular attendance during their treatment course.

All patients initially started treatment with three sessions per week. However, during the course of treatment, the therapy frequency was reduced to twice a week for 4 patients (12.1%), and subsequently, one patient's (3%) treatment was reduced to once a week before being discontinued. While 27 patients (81.8%) completed one treatment cycle, 6 patients (18.2%) received a second treatment cycle after their initial treatment was discontinued.

Four patients received phototherapy in combination with systemic treatment (12.1%). One patient received acitretin, one patient received azithromycin, and two patients received systemic steroid along with phototherapy. The 12-year-old male patient who received acitretin had a diagnosis of psoriasis. After receiving 6 sessions of cabin-type nbUVB therapy, the patient experienced partial improvement but discontinued treatment due to social reasons. The first patient who received systemic steroid was a 4-year-old girl diagnosed with vitiligo. Despite undergoing 54 sessions of nbUVB phototherapy, the patient did not benefit from the treatment. The other patient receiving systemic steroid was a 1-year-old girl diagnosed with atopic dermatitis. After receiving 8 sessions of treatment, she discontinued phototherapy due to non-attendance, also showing only partial response to treatment. The 16-year-old female patient diagnosed with PLC and receiving azithromycin did not benefit from 61 sessions of nbUVB phototherapy.

Four patients (12.1%) experienced side effects. Among these, two patients (6.1%) reported erythema, one patient (3.0%) reported itching and dryness, and one patient (3.0%) exhibited vesicular eruption on the face. Treatment was discontinued in two patients (6.1%) due to side effects (Table 1).

Upon examining the distribution by month, it was observed that more pediatric patients underwent phototherapy in July and August compared to other months (Figure 1).

Upon examining the rates of benefit obtained from the treatment, data from 31 patients were available. Full recovery was observed in 4 patients (12.9%), partial improvement was noted in 11 patients (35.5%), while 16 patients (51.6%) did not benefit from the treatment. Data on treatment response were not available for 2 patients.

When analyzing treatment responses according to diagnostic groups, complete response was only achieved in the psoriasis group (23.5% - 4 patients), while partial response was observed in 7 patients (41.2%). In the vitiligo group, partial response was seen in 1 patient, in the atopic dermatitis group, partial response was observed in 2 patients, and in one PRP-diagnosed patient, partial response was noted. However, none of the patients diagnosed with alopecia totalis and PLC benefited from the treatment (Table 2).

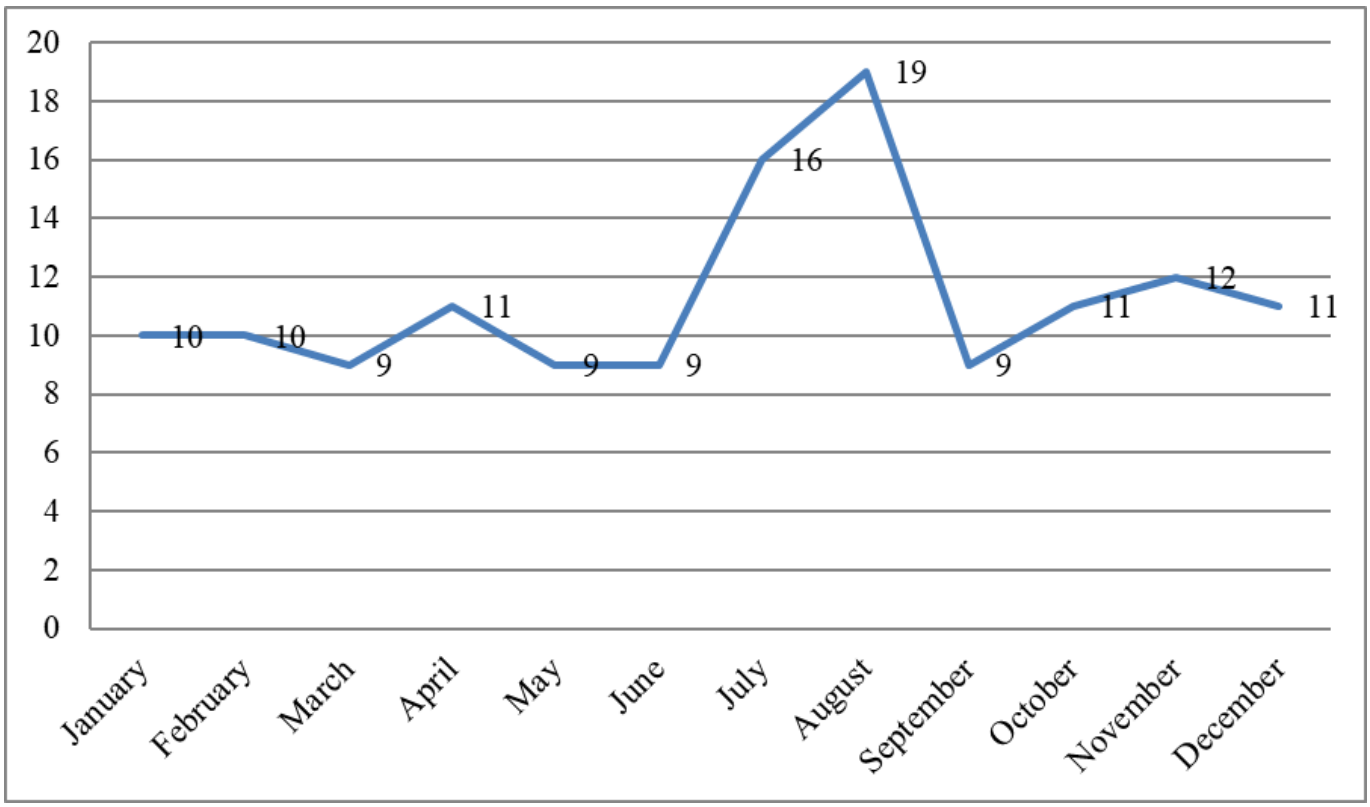


**Figure 1:** Number of patients receiving phototherapy by month

**Table 1:** Demographic data of pediatric patients receiving phototherapy

| Demographic data of pediatric patients receiving phototherapy | | |
|---|---|---|
| Age (year) -median (minimum-maximum) | | 15 (3-17) |
| Gender | Female | 19 (57.6%) |
| | Male | 14 (42.4%) |
| Fitzpatrick skin photo type | 2 | 16 (48.5%) |
| | 3 | 17 (51.5%) |
| Diagnoses | Psoriasis | 18 (54.5%) |
| | Vitiligo | 6 (18.2%) |
| | Atopic dermatitis | 5 (15.2%) |
| | Alopecia totalis | 1 (3%) |
| | Pityriasis lichenoides chronica | 2 (6.1%) |
| | Pityriasis rubra pilaris | 1 (3%) |

| | | |
|---|---|---|
| Phototherapy type | Cabin nbUVB | 27 (81.8%) |
| | Local nbUVB | 5 (15.2%) |
| | Local PUVA | 1 (3.0%) |
| nbUVB cumulative dose –joule/cm$^2$ -median (minimum-maximum) | | 10.4 (0.19-67.1) |
| nbUVB total number of sessions -median (minimum-maximum) | | 24.5 (1-78) |
| PUVA cumulative dose – joule/cm$^2$ | | 36.53 |
| PUVA total number of sessions -median | | 16 |
| Number of patients treated regularly without interruption of treatment regularly- n (%) | | 16 (48.5%) |
| Number of patients who interrupted their treatment / could not receive regular treatment- n (%) | | 17 (51.5%) |
| Number of courses | **Patients received 1 course of treatment - n (%)** | 27 (81.8%) |
| | **Patients received 2 courses of treatment - n(%)** | 6 (18.2%) |
| Number of treatments per week | **3 per week –n (%)** | 33 (100%) |
| | **2 per week- n(%)** | 4 (12.1%) |
| | **1 per week- n (%)** | 1 (3%) |
| Adverse effects- n(%) | | 4 (12.1%) |
| – Erythema-n(%) | | 2 (6.1%) |
| – Pruritus and xerosis-n(%) | | 1 (3%) |
| – Vesicles on face-n(%) | | 1 (3%) |

**nbUVB:** narrow band ultraviolet B**, PUVA:** Psoralen ultraviolet A

**Table 2:** Phototherapy response rates according to diagnoses

| Response rate (number of patients whose data were accessed / total number of patients) | Complete recovery (%) | Partial recovery n (%) | No benefit n (%) |
|---|---|---|---|
| Psoriasis (17/18) | 4 (23.5%) | 7 (41.2%) | 6 (35.3%) |
| Vitiligo (5/6) | 0 | 1 (20%) | 4 (80%) |
| Atopic dermatitis (5/5) | 0 | 2 (40%) | 3 (60%) |
| Alopecia totalis (1/1) | 0 | 0 | 1 (%100) |
| Pityriasis rubra pilaris (1/1) | 0 | 1 (100%) | 0 |
| Pityriasis lichenoides chronica (2/2) | 0 | 0 | 2 (100%) |

**Table 3:** Comparison of treatment response rates reported in the literature

| | Psoriasis % (n) | Vitiligo % (n) | Atopic dermatitis % (n) | Alopecia areata % (n) | Pityriasis lichenoides chronica % (n) | Pityriasis rubra pilaris % (n) |
|---|---|---|---|---|---|---|
| Our study | 64.3% (9) | 20% (1) | 33.3% (1) | 0 | 0 | 100% (1) |
| Slimani et al [2] | 73% | 50% | 68% | - | - | - |
| Ersoy-Evans et al [8] | 92.9% (26)-nbUVB<br>83.8% (5)-PUVA<br>93.3% (28)-UVB | 50% (4)-nbUVB<br>57% (4)-PUVA | - | - | 83.3% (10) | - |
| Jury et al [10] | 63% (22) | | 68% (17) | 0 | 100% (2) | 100% (1) |
| Brazelli et al [9] | | | | | 100% (5) | |
| Brazelli et al [12] | | 80% (8) | | | | |
| Pavlovsky et al [11] | 92% (73) | | 69% (25) | | | |

**nbUVB:** narrow band ultraviolet B, **PUVA:** Psoralen ultraviolet B, **UVB:** Ultraviolet B

**Discussion**

Phototherapy is a convenient and effective treatment option. It serves as a safe therapeutic alternative, particularly for patients who cannot undergo systemic treatment due to potential side effects or do not respond to topical therapies [6]. While more commonly preferred in adult patients, phototherapy can also be used in pediatric dermatology for the treatment of various skin conditions such as psoriasis, vitiligo, atopic dermatitis, and mycosis fungoides. In pediatric dermatology, devices incorporating UVB and UVA wavelengths are primarily used for treatment [4,7].

There is a limited amount of literature available on the use of phototherapy in the pediatric population. All published data are derived from retrospective studies. There are no prospective randomized controlled trials conducted on this subject. Additionally, there is no treatment guideline available specifically for pediatric phototherapy protocols. Therefore, treatment parameters and dosages have not been standardized in the pediatric age group [8].

One of the largest and most recent studies examining phototherapy in the pediatric age group was published by Slimani et al. in 2020. In this study, medical records of 90 pediatric patients were retrospectively analyzed covering 36 years of data [2]. While patients under the age of 16 were included in Slimani et al.'s study, our study included patients under the age of 18. In Slimani et al.'s study, 38% of patients received treatment for generalized psoriasis, 14% for palmoplantar psoriasis, 19% for vitiligo, 11% for atopic dermatitis, 9% for pruritus/prurigo, and 9% for alopecia areata. The distribution of diagnoses among patients in our study was similar to their findings. However, none of our patients received phototherapy for pruritus, unlike in Slimani et al.'s study. The mean cumulative treatment dose and mean number of sessions for patients receiving nbUVB therapy were reported as 10.8 j/cm2 and 20, respectively, in Slimani et al.'s study. In our study, the median cumulative dose was 10.4 j/cm2 (range: 0.19-67.1), and the median number of sessions was 24, which were comparable results. In Slimani et al.'s study, 14% of patients (approximately 12 patients) received local PUVA therapy, whereas only one of our patients received local PUVA therapy. There were no patients receiving systemic PUVA therapy in both studies. Additionally, in Slimani et al.'s study, mild erythema was observed in 15% of patients as a side effect, while this rate was slightly lower in our study (6.1%). In Slimani et al.'s study, 32% of patients discontinued their treatment, whereas 78.8% of our patients received at least 12 sessions of treatment, and 21.2% (7 patients) discontinued treatment before completing 12 sessions.

The largest study conducted in our country about this topic was carried out by Ersoy Evans et al. in 2008 [5]. In this study, the data of pediatric patients under the age of 18 receiving phototherapy over a period of 20 years were examined, and 113 patients were included in the study. The distribution of diagnoses among patients in Ersoy Evans et al.'s study showed similarities to our study. Psoriasis was reported as the most frequent diagnosis, as in our study (53.5%). However, unlike our study, there were also patients diagnosed with mycosis fungoides, lichen planus, and parapsoriasis in their study. Additionally, unlike our study, 21% of the patients received systemic PUVA therapy. In this study, the mean or median number of sessions for treatment response was also calculated. These numbers were reported as 16±6.6 sessions for psoriasis (nbUVB), 14 sessions (range: 9-107) for vitiligo (nbUVB), and 22 sessions for PLC (nbUVB).

In the present study, the highest response rate to treatment was observed in the psoriasis patient group (64.3%). Comparative results of phototherapy response rates in pediatric patient groups reported in the literature are provided in Table 5 [2, 5, 9-12]. Compared to other studies, we found lower treatment success rates in our patients. Possible reasons for this could include our smaller sample size; the retrospective nature of the study, which relied on patient files and statements for data collection, thus not accessing the true data of each patient; initiating treatment based on skin type rather than minimal erythema dose and minimal phototoxic dose; the need to reduce the energy given due to the fact that 51.5% of patients interrupted treatment at least once, and the time it takes to reach the maximum energy level.

The most commonly observed side effect of phototherapy is mild self-limiting erythema. In addition to this, xerosis, pruritus, and gastrointestinal symptoms in PUVA recipients are other possible side effects. Long-

term side effects include carcinogenesis, cataracts, lentigines, and photoaging. The relationship between UV exposure and skin cancer has been demonstrated in many studies. The carcinogenic risk of PUVA therapy is higher compared to UVB phototherapy [13]. In our study, we observed side effects in 4 patients (12.1%). Treatment was discontinued in 2 patients due to side effects (6.1%). In the study by Ersoy Evans et al., side effects were observed in 75.6% of patients receiving dbUVB (51.6% erythema, 18% pruritus, 9% burning) [5]. In the study by Jury et al., erythema was observed in 30% of cases, while vesicular eruptions were detected in 5 patients (6.4%) (2 hydroa vacciniforme, 2 herpes, 1 varicella reactivation) [10]. In the study by Slimani et al., mild erythema was observed in 15% of patients [2]. The incidence of side effects in our study was lower compared to other studies. We could not access long-term side effect data as patients did not attend follow-up visits.

The main limitation of our study is its retrospective nature, which prevented us from accessing complete patient data. Since we did not measure treatment responses using quantitative methods such as the affected body surface area or PASI response, we could not obtain objective data in this regard. Additionally, our clinic is relatively new compared to other clinics, so we only have data spanning a period of 5 years. Therefore, the number of patients in our study is lower compared to other large-scale studies.

## Conclusion

Phototherapy has been most commonly administered in pediatric patients diagnosed with psoriasis. The frequency of observed side effects was found to be lower compared to similar studies in the literature. However, treatment response rates were also determined to be lower compared to similar studies. We believe that prospective, larger-scale, and multicenter studies are needed to determine the long-term efficacy and side effects of phototherapy in pediatric patients.

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**Authors' contribution:** Surgical and Medical Practices: I.D.O., B.A., Concept: I.D.O., B.A., Design: I.D.O., B.A., Data Collection or Processing: I.D.O., B.A., Analysis or Interpretation: I.D.O., Literature Search: I.D.O., Writing: I.D.O.

**Ethical Declaration:** The permission for this study has been obtained from the Giresun Training and Research Hospital Ethics Committee with decision number 27.03.2023/08.

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CERASUS JOURNAL OF MEDICINE

ORIGINAL ARTICLE



# Evaluation of vaccine hesitancy/refusal in Giresun province

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**Abstract**

**Objective**

This study aimed to determine the frequency of vaccine hesitancy/refusal specifically in the province of Giresun, identify the related factors behind these behaviors, and determine the factors that could influence families in making these decisions.

**Methods**

This is a decriptive study. The data for this study were obtained from 'Vaccine Refusal Form' filled in by family physicians and 'Vaccination Refusal Reasons Survey' prepared by the Public Health Services Department of the Giresun Provincial Health Directorate is also filled out by families and sent to the Directorate at the end of each month along with the refusal forms. The study encompassed data from the years 2019 to 2023 inclusive.

**Results**

The number of infants/children who had not received at least one vaccine due to family refusal was 98 in 2019, and this number increased each year, reaching 99, 184, 213, and 317 in the subsequent years. These children including 431 girls (47,3%) and 480 boys (52.7%). According to the live birth data and Birth Notification System information released for Giresun province, the rate of vaccine hesitancy/refusal calculated was 2.3% in 2019 and increased each year to 2.5%, 4.8%, 5.7%, and 8.9% for the years 2020, 2021, 2022 and 2023, respectively. 43.9% of the mothers and 51.7% of the fathers were university graduates. The majority of mothers were housewives (70.8%), followed by teachers (9.0%). Among fathers, 37.9% were industrial workers, 13.2% were religious officials, 13.2% were self-employed, and 9.9% were teachers.

**Conclusion**

Vaccine hesitancy/refusal is emerging as a problem growing day by day, and remains significant regardless of the education level and occupation of those who engage in it. Policies that can prevent misinformation on this subject should be developed and implemented swiftly.

**Keywords:** Vaccine hesitancy; vaccine refusal; Giresun

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## Introduction

Providing immunizations is an essential health service aimed at preventing babies, children, or adults from contracting infections by vaccinating them before the period of highest risk [1]. Through vaccination, between 3.5 to 5 million deaths caused by diseases like diphtheria, tetanus, pertussis, influenza, and measles are prevented each year. In 2022, 12.9 million children worldwide did not receive any vaccination. [2].

In recent years, there has been a significant increase globally in parents opting not to vaccinate their children. Consequently, there has been a rise in childhood infectious diseases. Due to these developments, the World Health Organization (WHO) has made the issue of vaccination a priority. It established the 'Vaccine Hesitancy Working Group' in 2012 to conduct research. According to the report prepared by the group, there are two main attitudes related to why people do not get vaccinated. The first is 'vaccine hesitancy,' which involves delaying becoming vaccinated or refusing to accept one or more vaccines. The second is 'vaccine refusal,' characterized by the deliberate non-acceptance of all vaccines [3].

In Türkiye, especially in the last decade, similar processes have been experienced regarding vaccine refusal. According to the 2018 data of the Türkiye Demographic and Health Survey (TDHS), 2% of children aged 12-23 months and 3% of children aged 24-35 months have never been vaccinated. Among children aged 24-35 months, the proportion of those who received all basic vaccines is 72% [4]. In recent years, vaccination rates have been declining due to false reports and negative rumors surrounding vaccination programs [5].

According to the Family Medicine Information System data of the Ministry of Health while the vaccination rates in Türkiye are at 99.5% for DaBT 3, 98.1% for BCG, and 99.3% for HBV, the vaccination rates for MMR and KPA Booster are 95.2% and 95.3%, respectively [6]. One of the objectives of the Expanded Immunization Program, which constitutes the basis of vaccination services in Türkiye, is to achieve and maintain a 95% vaccination rate nationwide for each antigen using effective vaccines [1]. In light of the current situation, it is clear that there might be challenges in achieving this goal for some antigens. Vaccine hesitancy and refusal can be considered major obstacles to reaching the target vaccination rates.

This study aimed to determine the frequency of vaccine hesitancy/refusal specifically in the province of Giresun, identify related factors behind these behaviors, and determine the factors that could influence families in making these decisions.

## Materials and Methods

This study is a descriptive study was conducted among families living in Giresun province who exhibit vaccine hesitancy/refusal behavior. The permission for this study has been obtained from the Giresun Training and Research Hospital Ethics Committee with decision number 20.11.2023/23.

According to practices of the Turkish Ministry of Health, when it is time for a child to be vaccinated, their registered physician contacts their family to arrange to administer the vaccine. However, if a family refuses vaccination, and as a result, the family physician cannot administer the vaccine, they are required to fill out and have signed a 'Vaccine Refusal Form'. These forms, documenting the refusal, are sent to the Giresun Provincial Health Directorate at the end of each month. Families refusing vaccination can be identified through these forms.

In addition to the vaccination refusal form, since 2019, a 'Vaccination Refusal Reasons Survey' (including data about gender, identity of the family member refusing vaccination, mother's education level, father's education level, mother's occupation, father's occupation, average monthly household income, type of vaccine refused, reasons for vaccine refusal) prepared by the Public Health Services Department of the Giresun Provincial Health Directorate is also filled out by families and sent to the Directorate at the end of each month along with the refusal forms. These surveys have been archived by the Giresun Provincial Health Directorate since 2019.

The data for this study were obtained from these two forms using archival scanning methods. The study encompassed data from the years 2019 to 2023 inclusive. It was considered vaccine hesitancy/refusal if at least one vaccine dose has not been administered

despite being due according to the vaccination schedule. The total number of live births, which was used in calculating the vaccine refusal rates for the years 2019, 2020, 2021, and 2022 (4237, 4002, 3801 and 3742, respectively) was obtained from Turkish Statistical Institute (TSI). The data for the number of live births in the year 2023 (3546) was based on the Birth Notification System, since this number has not yet been disclosed by TSI.

As descriptive statistics, qualitative data were given in numbers and percentages.

**Results**

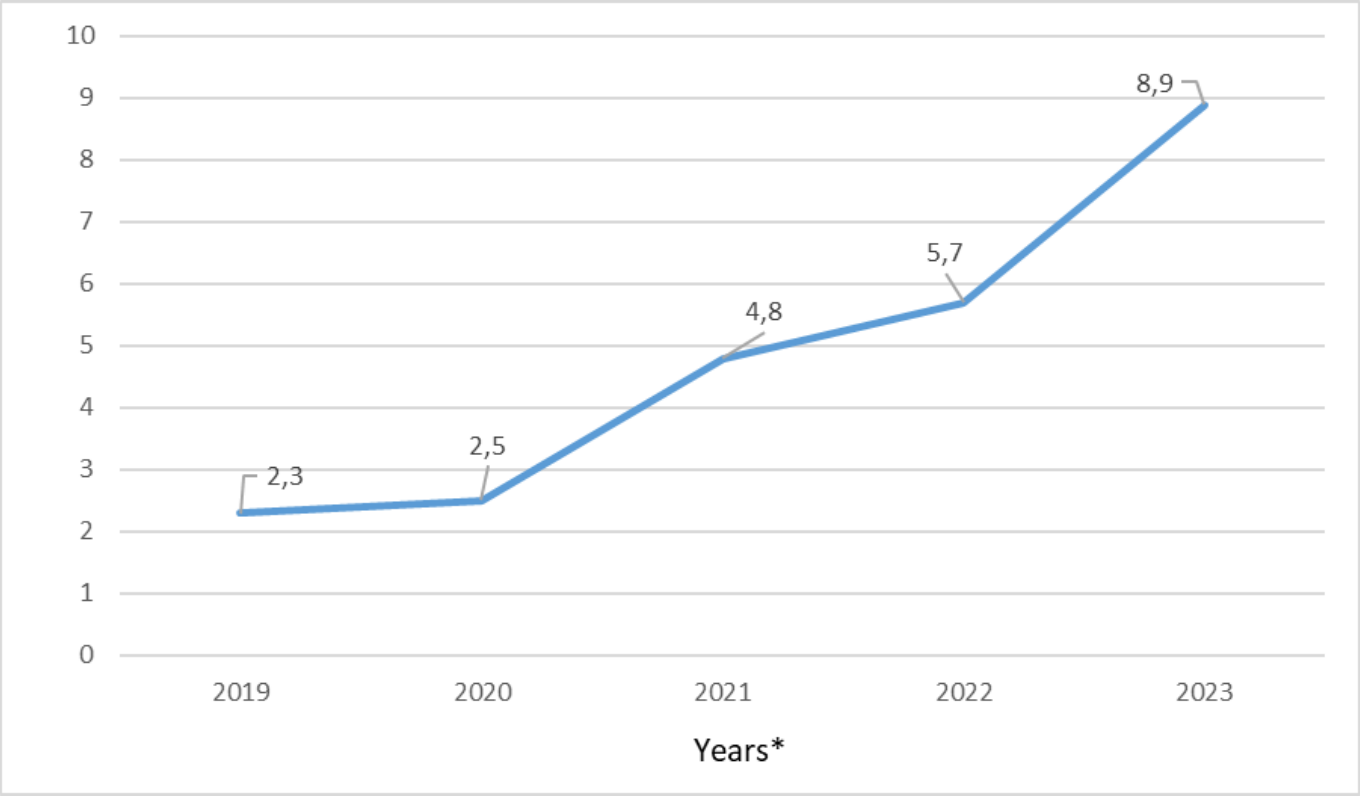
The number of infants/children who had not received at least one vaccine due to family refusal was 98 in 2019, and this number increased each year, reaching 99, 184, 213, and 317 in the subsequent years. These children including 431 girls (47,3%) and 480 boys (52.7%). According to the live birth data and Birth Notification System information released for Giresun province, the rate of vaccine hesitancy/refusal calculated was 2.3% in 2019 and increased each year to 2.5%, 4.8%, 5.7%, and 8.9% for the years 2020, 2021, 2022 and 2023, respectively (Figure 1).

When the reasons for vaccine refusal were examined, the most common reason was identified as 'I think the vaccine could be harmful' (26.9%), followed by 'I don't believe in the benefits of the vaccine' (26.6%), 'I am afraid of the side effects of all vaccines' (23.5%), and 'I don't think my child needs vaccination' (15.5%) (Table 1).

When the education levels of the parents engaging in vaccine refusal behaviors were examined, it was noteworthy that 43.9% of the mothers and 51.7% of the fathers were university graduates (Table 2).

The occupational distributions of parents engaging in vaccine refusal behavior are presented in Table 3. According to this, the majority of mothers engaging in vaccine refusal behavior were housewives (70.8%), followed by teachers (9.0%). Among fathers, 37.9% were industrial workers, 13.2% were religious officials, 13.2% were self-employed, and 9.9% were teachers.

**Figure 1.** Frequency of Vaccine Hesitancy/Refusal in Giresun, 2019-2023.




* The number of live births used in calculating vaccine refusal rates for the years 2019, 2020, 2021, and 2022 was obtained from the TSI. The data for the number of live births in the year 2023 is based on the Birth Notification System since this has not yet been disclosed by the TSI.

**Table 1**. Reasons for Vaccine Hesitancy/Refusal in Giresun, 2019-2023.

| Reasons (N=911) | n | % |
|---|---|---|
| I think the vaccine could be harmful. | 245 | 26.9 |
| I don't believe in the benefits of the vaccine. | 242 | 26.6 |
| I am afraid of the side effects of all vaccines. | 214 | 23.5 |
| I don't think my child needs vaccination. | 141 | 15.5 |
| Due to the health of my child. | 81 | 8.9 |
| There is no specific reason. | 63 | 6.9 |
| I do not trust the contents of vaccines. | 57 | 6.3 |
| There are negative opinions about this vaccine in the media. | 53 | 5.8 |
| I don't think my child will contract the disease that this vaccine is designed to prevent. | 49 | 5.4 |
| I do not approve of the vaccination due to my beliefs. | 48 | 5.3 |
| My child had a problem with this vaccine before. | 37 | 4.1 |
| I experienced problem after the vaccination. | 26 | 2.9 |
| I don't trust it because it's a foreign vaccine; if it were a domestic one, I would get it. | 23 | 2.5 |
| I have a phobia of any kind of needles. | 21 | 2.3 |
| A relative of mine experienced a problem after this vaccine. | 20 | 2.2 |
| Community leaders/my immediate family/my other relatives did not want me to. | 9 | 1.0 |

**Table 2.** Education Levels of Parents Engaging in Vaccine Hesitancy/Refusal Behavior in Giresun, 2019-2023.

| Education Level | n | % |
|---|---|---|
| Mother (n=757) | | |
| Literate | 7 | 0.9 |
| Elementary school graduate | 65 | 8.6 |
| Middle school graduate | 99 | 13.1 |
| High school graduate | 254 | 33.6 |
| University graduate | 332 | 43.9 |
| Father (n=748) | | |
| Literate | 3 | 0.4 |
| Elementary school graduate | 37 | 4.9 |
| Middle school graduate | 65 | 8.7 |
| High school graduate | 256 | 34.2 |
| University graduate | 387 | 51.7 |

**Table 3.** Distribution of Occupations of Parents Engaging in Vaccine Hesitancy/Refusal Behavior in Giresun, 2019-2023.

| Occupation | n | % |
|---|---|---|
| Mother's (n=742) | | |
| Housewife | 525 | 70.8 |
| Teacher | 67 | 9.0 |
| Healthcare professional | 38 | 5.1 |
| Industrial worker | 31 | 4.2 |
| Religious official | 19 | 2.6 |
| Other civil servant | 18 | 2.4 |
| Self-employed | 14 | 1.9 |
| Engineer | 8 | 1.1 |
| Security guard | 4 | 0.5 |
| Other | 18 | 2.4 |
| Father's (n=737) | | |
| Industrial worker | 279 | 37.9 |
| Religious official | 97 | 13.2 |
| Self-employed | 97 | 13.2 |
| Teacher | 73 | 9.9 |
| Other civil servant | 67 | 9.1 |
| Security guard | 27 | 3.7 |
| Police officer | 25 | 3.4 |
| Farmer | 12 | 1.6 |
| Engineer | 11 | 1.5 |
| Healthcare professional | 9 | 1.2 |
| Retired | 5 | 0.7 |
| Lawyer | 4 | 0.5 |
| Unemployed | 10 | 1.4 |
| Other | 21 | 2.8 |

## Discussion

This research covers the years 2019-2023, during which the frequency of vaccine hesitancy/refusal, which was identified as 2.3% in 2019, increased every subsequent year, reaching 8.9% in 2023. In a study conducted in Giresun province in 2018, the rate was noted as 1.2% [7]. The data clearly indicates an increasing frequency of vaccine hesitancy/refusal behavior in recent years in Giresun province. In a nationwide study conducted in Türkiye in 2020 and 2021, the frequency of vaccine hesitancy/refusal was found to be 11.2%, highlighting that this issue is a serious concern across the country [8]. According to the TDHS 2018 data, the proportion of children who have never been vaccinated did not show a significant change between 1993 and 2018 [9]. The data for the last five years, which will be revealed in the TDHS 2023 data, is eagerly awaited, as it will reflect the increasing prominence of vaccine hesitancy and refusal.

Examining the reasons for vaccine hesitancy/refusal in our research, the most frequently cited statements were 'I think the vaccine could be harmful,' 'I don't believe in the benefits of the vaccine,' 'I am afraid of the side effects of all vaccines,' and 'I don't think my child needs vaccination.' Evaluating the statements 'I think the vaccine could be harmful' and 'I am afraid of the side effects of all vaccines' together, they made up 50.4% of responses. Similarly, assessing 'I don't believe in the benefits of the vaccine' and 'I don't think my child needs vaccination' together, the percentage was 42.1%. In other words, families often exhibited vaccine hesitancy/refusal due to the belief that the vaccine could be harmful and/or the vaccine had no benefits. In a study conducted by Kurt et al., it was found that 99% of families exhibiting vaccine hesitancy/refusal behavior believed that vaccines were not safe, and 71.7% believed that vaccines were not necessary [10]. Similar reasons have been highlighted in many studies conducted in our country [11-13]. In an international study involving a total of 16 countries, including Türkiye, the percentage of families expressing concerns about the potential harm of chemicals in vaccines and the possibility of vaccine side effects was determined to be 69.4%. Views regarding the possibility of side effects and the perception that vaccines are unnecessary have also been found to be prominent in different societies [14-16].

As observed, similar reasons for vaccine hesitancy/refusal have been identified in different regions of our country and in various other countries and societies worldwide. The beliefs that vaccines are harmful and unnecessary seem to be prevalent. Therefore, in addition to ensuring that accurate information is disseminated to the public, it is particularly crucial to prevent misinformation from becoming widespread. In this regard, as highlighted in a study conducted in Sweden, families exhibiting vaccine refusal behavior tend to use social media and internet searches more frequently as sources of information than other groups [15]. To effectively disseminate information, social media and internet channels should specifically be utilized, and policies should be formulated to counteract misinformation propagated through these platforms.

When the educational backgrounds of the families exhibiting vaccine hesitancy/refusal behavior were examined, it was determined that 43.9% of the participating mothers and 51.7% of the fathers in our study were university graduates. Reviewing the literature, varying percentages, ranging from 40% to 70%, can be observed with regard to the educational status of families with vaccine hesitancy/refusal in which the parents have undergraduate degrees or higher [7, 8, 10, 11, 13, 14]. However, in a study conducted by Hasar et al., no difference in terms of education level was found between the group exhibiting vaccine hesitancy/refusal behavior and the control group [13]. Similarly, in a study conducted by Byström et al., no difference was observed in this regard [15]. A nationwide cross-sectional study conducted in France says that more highly educated parents were delayers or refusers more often than those with less education [17]. On the other hand, according to a study conducted in Italy, lower education among the parents, both mother and father, was significantly associated with vaccine refusal [18]. It can be said that the effect of education level on vaccine hesitancy/refusal varies across different populations. In this context, when designing information campaigns, how to reach an audience with low and high level of education should be considered, and the content should be designed accordingly, providing satisfactory explanation and answers to any questions people may have and also easy to understand.

When the occupational statuses of the families exhibiting vaccine hesitancy/rejection behavior were examined, it was noteworthy that 70.8% of the mothers in our study were housewives, followed by 9.0% who were teachers, and 5.1% who were healthcare workers. In fathers, the most common occupation was industrial worker, accounting for 37.9%, followed by 13.2% who were religious officials, another 13.2% who were self-employed, and 9.9% who were teachers. In a previous study conducted in Giresun, 14.8% of mothers were identified as teachers, and 11.1% as healthcare workers. In the same study, 25.9% of the fathers were teachers and 20.4% were religious officials [7]. In a nationwide study conducted by Tekin et al., it was determined that occupational status did not have a statistically significant impact on vaccine hesitancy/refusal [8]. However, when looking at occupational status, similar to the educational background, the finding that individuals in socially valued professions,

such as teachers, religious officials, and healthcare workers also engaged in vaccine hesitancy/refusal, provides insight into the magnitude and complexity of the issue. In particular, the fact that this group included healthcare workers poses a serious question that needs to be thoroughly examined. When formulating policies and preparing information on the topic of vaccines, this aspect of the issue must also be taken into consideration.

### Limitations

Due to a considerable proportion of the participants (51.5%) did not disclose their income, and also significant fluctuations in inflation over the years, income information was not included in the analysis on the grounds that a reliable assessment could not be made.

Since the ages of the children were not queried in the survey form, it was not possible to analyze which vaccines each child had/had not received according to the vaccination schedule. Therefore, the frequencies of vaccine refusal and vaccine hesitancy could not be presented separately. Based on this feedback, the survey form will be revised.

### Conclusion

Vaccine hesitancy/refusal is emerging as a problem growing day by day, and remains significant regardless of the education level and occupation of those who engage in it. Policies that can prevent misinformation about contents of vaccines and potential harms should be developed and implemented swiftly. Accurate information should be disseminated to the public in a clear and unambiguous manner, leaving no room for doubt, especially through the use of internet and social media platforms, and with the cooperation of all sectors under the coordination of the government.

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**Ethical Declaration:** The permission for this study has been obtained from the Giresun Training and Research Hospital Ethics Committee with decision number 20.11.2023/23.

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CERASUS JOURNAL OF MEDICINE

ORIGINAL ARTICLE



# Survival-effective prognostic factors of rectal cancer patients receiving neoadjuvant chemoradiotherapy

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**Abstract**

**Objective:** Our aim in this study is to investigate the survival-effective prognostic factors of rectal cancer patients receiving neoadjuvant chemoradiotherapy.

**Methods:** A total Data from 102 patients who underwent surgery due to rectal cancer at the Gastroenterology Surgery Clinic of Koşuyolu High Specialization Training and Research Hospital, Health Sciences University, between January 2013 and October 2019 were retrospectively reviewed. Two patients who underwent total proctocolectomy, nine patients with distant organ metastasis, and seven patients who did not receive neoadjuvant therapy and had fewer than 12 lymph nodes removed were excluded from the study. A total of 84 patients, including 54 who received neoadjuvant CRT and 30 who did not, were included in the study. The study end date was set as July 30, 2020.

**Results:** 84 patients were included in our study. Of these patients, 40 were male(47%) and 44 were female(53%). The patients were followed for an average of 44 months. Neoadjuvant chemoradiotherapy treatment was applied to 64.3% of the 84 patients who underwent surgery for rectal cancer. According to Kaplein Meier long rank test analysis, no statistical difference was found in the survival Deciency between the two groups (p=0.115). It was found that the presence of positive lymph nodes within the excised lymph nodes serves as a prognostic factor in patients receiving neoadjuvant chemotherapy (p=0.005).

**Conclusion:** The incidence of rectal cancer is still high today. Neoadjuvant CRT at the local advanced stage is a standard treatment approach. In our study, the most important prognostic factor effective survival after neoadjuvant CRT was found to be the presence of lymph node metastasis after surgery.

**Keywords:** Rectum cancer; neoadjuvant cemoradioterapy; lymph node

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## Introduction

Although the diagnosis and treatment of rectal cancer have improved dramatically over the past decade, its incidence has also been steadily increasing. The universal acceptance of the total mesorectal excision (TME) technique and improved imaging with magnetic resonance imaging (MRI) have provided better selection of high-risk patient groups, and neoadjuvant chemoradiotherapy (CRT) treatment before surgery has become a standard treatment method in these patient groups[1]. The benefits of preoperative CRT for rectal cancer are well known in terms of reduction to pathological complete response, increased sphincter-protective surgery, and a significant reduction in local relapses[2]. The use of neoadjuvant chemoradiotherapy with clinical stage T3 or T4 based on transrectal endoscopic ultrasound (EUS) or MRI is recommended for all patients with newly diagnosed rectal adenocarcinoma. Neoadjuvant therapy, radiotherapy can be alone or in combination with chemotherapy[3].

Low anterior resection(LAR) or abdominoperineal resection(APR) combined with total mesorectal excision is the standard surgical treatment for rectal cancer surgical treatment, and these methods have significant disadvantages, including a 2% risk of perioperative mortality, an 11% risk of anastomosis leakage, a 5% risk of re-surgery for complications, and a risk of sexual and urinary dysfunction[4]. It is important to note that not every patient responds positively to radiation therapy, and there may be toxicity related to treatment, which may negatively affect the overall and health-related quality of life of patients. Moreover, neoadjuvant radiotherapy can cause excessive tissue payoff, which can lead to the loss of surgical plans, which can pose an increased surgical difficulty, especially in the narrow male pelvis[5].

Our aim in this study will be to investigate the survival-effective prognostic factors of rectal cancer patients receiving neoadjuvant CRT.

## Material and Method

A total Data from 102 patients who underwent surgery due to rectal cancer at the Gastroenterology Surgery Clinic of Koşuyolu High Specialization Training and Research Hospital, Health Sciences University, between January 2013 and October 2019 were retrospectively reviewed. Two patients who underwent total proctocolectomy, nine patients with distant organ metastasis, and seven patients who did not receive neoadjuvant therapy and had fewer than 12 lymph nodes removed were excluded from the study. A total of 84 patients, including 54 who received neoadjuvant CRT and 30 who did not, were included in the study. The study end date was set as July 30, 2020. Patients were divided into two groups, those who received neoadjuvant CRT and those who did not, and their clinicopathological features and overall survival were compared. Additionally, prognostic factors affecting survival in patients receiving neoadjuvant CRT were examined.

Statıstıcs Analysıs: Evaluation between patients receiving and not receiving neoadjuvant CRT was evaluated using Student T test, Mann Whitney U test, Fisher Exact test and Chi square test. Survival analysis between the two groups was checked with the Kaplan-Meier test and whether there was a difference was evaluated with the longrank test. Prognostic factors affecting survival of patients receiving neoadjuvant CRT were evaluated with Cox regression analysis.

## Results

84 patients were included in this study. 40 of these patients were male (47%) and 44 were female (53%). Patients were followed for an average of 44 (+/-12 months) months. Neoadjuvant chemoradiotherapy treatment was applied to 64.3% of 84 patients who underwent surgery for rectal cancer. Patients were divided into two groups according to neoadjuvant chemoradiotherapy status: those who did not receive treatment and those who received it. In the clinicopathological evaluation of the two groups, there was no statistically significant difference between

the treatment response rates of men and women (p = 0.434). This suggests that gender is not a determining factor on response to treatment. There is no significant relationship between pre-treatment T stage and surgery type after neoadjuvant chemoradiation (p=0.681). Lymph node positivity can be considered as a factor affecting response to treatment. However, there is no statistically significant relationship between lymph node positivity and surgical outcomes after neoadjuvant chemoradiation (p=0.712). There is no statistically significant relationship between the cancer stage before treatment and the type of surgery after neoadjuvant chemoradiotherapy (p = 0.322). This suggests that cancer stage is not a direct determinant in surgical planning. There is a significant relationship between the type of surgery (LAR or APR) and protective ileostomy (p<0.001). This demonstrates the nature of the surgical procedure and its impact on overall survival. The effect of lymphovascular and perineural invasion on treatment outcomes was examined. However, neither showed a statistically significant association with surgical outcomes (p=0.173 and p=0.230, respectively). The incidence of anastomotic leakage after surgery is low and does not show that neoadjuvant chemoradiotherapy has a significant effect on this complication (p = 0.875). There is no statistically significant difference in surgical outcomes between patients' ages and body mass indexes (BMI) (p=0.128 and p=0.374, respectively). The total number of lymph nodes removed after neoadjuvant chemoradiation is associated with the type of surgery and lymph node positivity (p<0.001). This highlights the effect of neoadjuvant chemoradiotherapy on lymph node dissection. Surgery time is related to surgery type and complexity, but there is no statistically significant difference (p = 0.118) (Table 1).

According to Kaplein Meier long rank test analysis, no statistical difference was found in the survival comparison between the two groups (p = 0.115) (Figure 1). While the average life expectancy of patients who received neoadjuvant chemoradiotherapy was 66.713±4.833 months, it was 76.665±4.443 months in patients who did not receive neoadjuvant treatment .

Prognostic factors affecting survival in rectal cancer patients receiving neoadjuvant chemoradiotherapy were investigated by Cox regression analysis. It was found that age, gender, depth of tumor wall invasion, development of anastomotic leakage, presence of lymphovascular invasion and perineural invasion had no prognostic significance. Positive lymph node involvement within the lymph node removed after neoadjuvant chemoradiotherapy was found to be a poor prognostic factor on survival (p = 0.005) (Table 2).

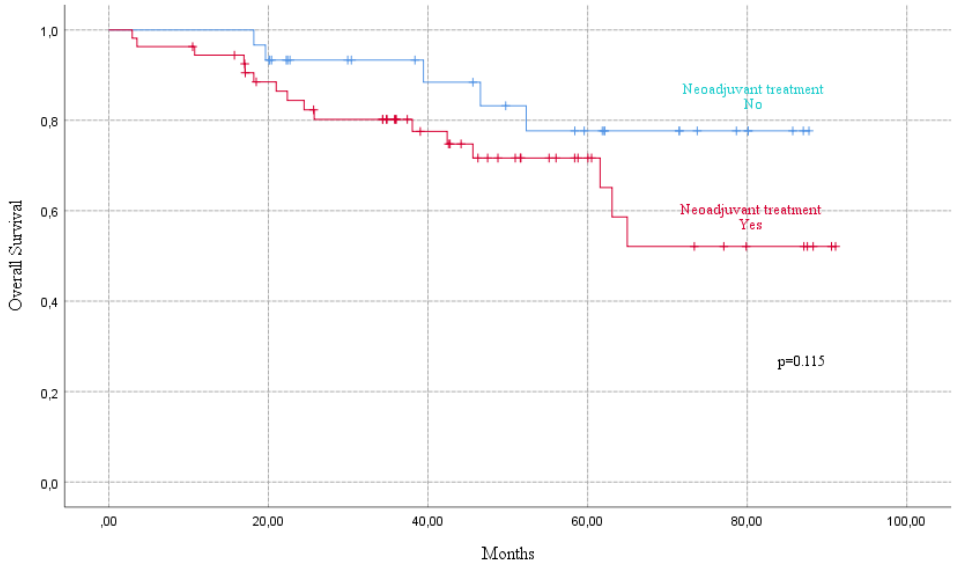


**Figure 1**: Comparison of Patient Survival According to Neoadjuvant Treatment Status

**Table 1.** Clinical and Histopathological Features of Rectal Tumors with and without Neoadjuvant Chemoradiotherapy

| Neoadjuvant Chemoradiotherapy Status | | | | | | |
|---|---|---|---|---|---|---|
| | | No | | Yes | | |
| | | n | % | n | % | p |
| **Sex** | Male | 16 | 53,3% | 24 | 44,4% | 0.434 |
| | Female | 14 | 46,7% | 30 | 55,6% | |
| **T** | T1 | 3 | 10,0% | 2 | 4,1% | 0.681[a] |
| | T2 | 6 | 20,0% | 13 | 26,5% | |
| | T3 | 17 | 56,7% | 29 | 59,2% | |
| | T4 | 4 | 13,3% | 5 | 10,2% | |
| **Lymph Node** | Negative | 23 | 76,7% | 35 | 72,9% | 0.712 |
| | Positive | 7 | 23,3% | 13 | 27,1% | |
| **Stage** | Stage I | 8 | 26,7% | 7 | 17,9% | 0.322 |
| | Stage II | 12 | 40,0% | 12 | 30,8% | |
| | Stage III | 10 | 33,3% | 20 | 51,3% | |
| **Operation Type** | LAR | 29 | 96,7% | 41 | 75,9% | 0.015* |
| | APR | 1 | 3,3% | 13 | 24,1% | |
| **Loop İleostomy** | No | 20 | 66,7% | 3 | 5,6% | p<0.001** |
| | Yes | 9 | 33,3% | 37 | 94,4% | |
| **Lymphovascular Invasion** | Negative | 22 | 73,3% | 42 | 85,7% | 0.173 |
| | Positive | 8 | 26,7% | 7 | 14,3% | |
| **Perineural Invasion** | Negative | 25 | 83,3% | 35 | 71,4% | 0.230 |
| | Pozitive | 5 | 16,7% | 14 | 28,6% | |
| **Anastomotic Leak** | No | 27 | 90,0% | 48 | 88,9% | 0.875 |
| | Yes | 3 | 10,0% | 6 | 11,1% | |
| | | Median | (IQR) | Median | (IQR) | |
| **Age** | | 64 | 58-70 | 61 | 48-68 | 0.128 |
| **BMI** | | 27,95 | 25,30-31,30 | 29,25 | 25,50-32,90 | 0.374[b] |
| **Total Number of Lymph Nodes Removed** | | 18 | 15-33 | 12 | 9-19 | p<0.001** |
| **Operation Time** | | 238 | 180-280 | 248 | 230-300 | 0.118 |

*[a] Likelihood Ratio, [b]Student T test, Ki Kare test, Mann Witney U test, *p<0.05, **p<0.001*

*LAR:Low Anterior Rezection APR:Abdominoperineal Rezection BMI;Body-Mass Index*

**Table 2:** Multivariate Cox Regression Analysis of Prognostic Factors Affecting Survival in Rectal Cancer Patients Receiving Neoadjuvant Chemoradiotherapy

| | OR | 95,0% CI | | p |
|---|---|---|---|---|
| **Gender** | 1,710 | ,425 | 6,880 | 0.450 |
| **Age** | ,964 | ,915 | 1,016 | 0.174 |
| **T stage** | | | | 0.963 |
| **T1** | ,957 | ,077 | 11,863 | 0.973 |
| **T2** | ,927 | ,075 | 11,399 | 0.953 |
| **T3** | ,539 | ,018 | 16,575 | 0.723 |
| **T4** | | | | |
| **Lymph Node Involvemen** | 15,520 | 2,272 | 106,024 | 0.005* |
| **Lymphovascular Invasion** | ,278 | ,041 | 1,901 | 0.192 |
| **Perineural Invasion** | ,483 | ,126 | 1,848 | 0.288 |
| **Anastomotic Leak** | 3,300 | ,471 | 23,121 | 0.229 |

## Discussion

Neoadjuvant chemoradiotherapy is increasingly used in the treatment of rectal cancer, and much research is being conducted on the clinical effectiveness of this treatment regimen. This study aimed to evaluate the effects of neoadjuvant chemoradiotherapy on surgical outcomes and survival in rectal cancer patients. Our findings have helped us better understand the effects of neoadjuvant chemoradiation on specific clinical and pathological factors.

Fan and colleagues showed that female gender and younger age are associated with better prognosis[6]. However, when the patients were examined in terms of their response to neoadjuvant chemoradiotherapy in our study, no statistically significant difference was found. This result shows that gender is not a determining factor on response to treatment in rectal cancer treatment.

It has been shown that T stage has a significant impact on the long-term survival of rectal cancer patients[7]. It is known that stage T3 patients have lower long-term survival and recovery probabilities compared to patients in T1[8]. Many studies have reported that T stage plays an important role in determining survival and that the recurrence rate is higher in T3 tumors than in T1 tumors [9]. In our study, no significant relationship was found between tumor stage and survival after neoadjuvant chemoradiotherapy. This suggests that the stage of cancer is not a determinant.

One study, the largest of its kind to date, examined patients undergoing LAR and APR and found that LAR produced higher overall survival rates compared to APR, but disease-free survival rates were similar[10]. We found significant differences between surgical procedures depending on whether patients received neoadjuvant chemoradiation. In particular, in the comparison between low anterior resection (LAR) and abdominoperineal resection (APR), a significant relationship was observed between the type of surgery and protective ileostomy. This highlights the nature of the surgical procedure and its implications for the risk of complications.

Caricato et al. [11] analyzed the effect of preoperative CRT on lymph node (LN) status in 28 patients who underwent surgical treatment. Complete response was seen in the LNs of 18 patients (51%), while the others showed variable or no response. Due to the low number of cases, no prognostic evaluation was made. Lindebjerg et al.[12] examined a cohort of 135 patients who responded to CRT (major + complete response = 66%). They found a significantly lower survival rate in patients with post-treatment LN metastases than in LN-negative patients. However, in our own study, no statistically significant relationship was found between lymph node positivity and surgical outcomes after neoadjuvant chemoradiotherapy. However, an important finding showing the effect of neoadjuvant chemoradiotherapy on lymph node dissection is that the total number of lymph nodes removed after neoadjuvant chemoradiotherapy is associated with the type of surgery and lymph node positivity. Additionally, a lower incidence of anastomotic leak was observed in patients receiving neoadjuvant chemoradiation, although this was not statistically significant.

Data from randomized trials have demonstrated better tumor control and reduced toxicity with preoperative (versus postoperative) chemo-radiotherapy, leading to widespread acceptance of the preoperative approach as the preferred treatment sequence[13]. Preoperative concurrent chemo-radiotherapy has also been associated with tumor regression and resulted in an improvement in pathological tumor stage[14]. Since the number of cases was high in the sample group in both studies, a statistically significant difference was detected between patients who received neoadjuvant CRT and those who did not. On the other hand, since the number of patients in this study was smaller, it shows that no statistically significant difference was found between patients who received neoadjuvant chemoradiotherapy and those who did not. However, it has been determined that the average life expectancy of patients receiving neoadjuvant chemoradiotherapy is lower compared to those who do not receive neoadjuvant treatment. Evaluation of prognostic factors by Cox regression analysis revealed that positive lymph node involvement within the lymph node removed after neoadjuvant chemoradiation was a poor prognostic factor.

There were some limitations in this study. The limitations of our study are that it was conducted with a small sample group, was retrospective, and was planned as a single center.

**Conclusion**

In conclusion, this study examined the effects of neoadjuvant chemoradiotherapy on clinical and pathological factors in rectal cancer patients. Our findings highlight the effect of neoadjuvant chemoradiotherapy on lymph node dissection and show that positive lymph node involvement is a poor prognostic factor. However, the prognostic significance of other clinical and pathological factors should be further investigated, and the effects of this treatment regimen on surgical outcomes and survival should be evaluated more comprehensively.

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**Conflict of Interest:** None of the authors have a conflict of interest.

**Ethical Approval:** The study was approved by the Clinical Research Ethics Committee Koşuyolu Yuksek Ihtisas Research and Training Hospital, and adhered to the ethical standards expected for medical research involving human participants.

**Authors' contribution:** Surgical and Medical Practices: O.U, E.P, M.D, S.G, Concept: O.U, E.P, M.D, S.G, Design: O.U, E.P, M.D, S.G, Data Collection or Processing: O.U, E.P, M.D, S.G, Analysis or Interpretation: O.U, E.P, M.D, S.G, Literature Search: M.T, S.S, D.O, M.D, Writing: M.T, S.S, D.O, M.D.

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CERASUS JOURNAL OF MEDICINE

ORIGINAL ARTICLE



# Early clinical outcomes of congenital encephalocele and mortality risk factors: A tertiary center experience

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**Abstract**

**Objective:** To investigate the early clinical outcomes and prognostic factors of infants with congenital encephalocele.

**Methods:** We investigated newborns diagnosed with congenital encephalocele and treated in our hospital. We recorded data of the patients regarding the delivery history, anthropometric features, and clinical outcomes regarding mortality, shunt need, and hydrocephalus. We used conventional statistical methods (student's t test, Mann-Whitney u test) assuming a p significance at <0.05 and Bayesian models (Bayesian Kendall's tau test).

**Results:** We included 18 patients (%61.1 female, 38.9% male) in the study. The median birth week was 38 (36.3-39) weeks, and the mean birth weight was 2837+/-816 grams. 83.3% of the patients had undergone an operation with a median of 5 days. The defect diameter was more than 5 cm in 61.1% of the patients, and brain parenchyma was positive in the sac in half of the patients. 22.2% of the patients needed ventriculoperitoneal shunt insertion. The overall survival resulted in 61.1% in all patients and 73.3% in operated. There were statistically significant differences in terms of birth weight (p<0.001, 3150 v.s 2470 grams) and birth week (38.6 v.s 34.6 weeks, p=0.021), as deceased patients had lower birth weight and birth week.

In Bayesian Kendall's tau calculations, Neural tissue involvement, defect diameter more than 5 cm, birth weight (very strong evidence), operation within three days of life and birth week (strong evidence), and shunt need and seizures (moderate evidence) had an impact on mortality. There was no significant risk factor for hydrocephalus development, but there was a correlation between hydrocephalus and shunt need. Also, Dandy walker deformity correlated with shunt need (moderate evidence), but the birth week and neural tissue involvement were independent of shunt need (moderate evidence).

**Conclusion:** The poor prognostic factors for mortality were defect diameter larger than 5 cm, neural tissue involvement in the sac, lower birth week, lower birth weight, and seizures, and the good prognostic factor was operation before postnatal three days of life.

**Keywords:** Congenital encephalocele; infant; newborn; ventriculoperitoneal shunt; hydrocephalus

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## Introduction

Congenital encephalocele is a type of bone defect on the calvarium resulting in protrusion of meningeal or brain tissue [1]. The terminology encephalocele refers to brain tissue herniation to the bone defect, and meningocele refers to the herniation that includes solely cerebrospinal fluid [2]. Congenital encephalocele is a variation of neural tube defect, like anencephaly and myelomeningocele [1]. This type is not a common neural tube defect variation, but it consists of 15-20% of all neural tube defects [3, 4], and congenital encephalocele prevalence is predicted as 0.8-5 in 10000 live births [5, 6].

The underlying pathology is a fusion defect in cranial neuropore closure at 24-26th days of embryogenesis [1,7]. The genetic and environmental factors also have an impact on congenital encephalocele development [8]. Approximately 60% of Congenital encephalocele-diagnosed patients have additional malformation or chromosomal defects [9, 10], 20% have microcephalus, Arnold-Chiari malformations type 2 or 3, craniosynostosis, and syringomyelia [11]. Also, associations are reported with congenital infections of toxoplasmosis, rubella, cytomegalovirus, and herpes simplex virus, as well as maternal history of children with neural tube defect and consanguineous marriages [12]. In general, neural tube defect recurrence in the following siblings is reported as 3.8%; however, this ratio is at an 8.9% rate for congenital encephalocele [13]. However, if the congenital encephalocele occurs as a part of an autosomal recessive syndrome like Meckel-Gruber, the recurrence rate will increase to 25% [14].

The differential diagnosis includes congenital cranial cysts, vascular malformations, and inflammatory lesions, which can mimic congenital encephalocele [15]. The prognosis is dependent on the mass of the herniated neural tube and the additional anomalies of the infant [15]. This study investigated the prognostic factors regarding mortality and the associated factors with complications in congenital encephalocele-diagnosed infants in this study who were treated in our 3rd-stage neonatal intensive care unit. The study aimed to help clinicians inform the families regarding prognosis and perform interventions in a timely fashion.

## Materials and Methods

We included all patients diagnosed with encephalocele in Gungoren Hospital Neonatal Intensive Care Unit (NICU) between 2017-2023. We retrospectively recorded the perinatal history, anthropometric measurements at birth, birth week, and postnatal operation time. We also recorded the ventriculoperitoneal shunt need, hydrocephalus status, co-morbid diseases, and survival status. We investigated the mortality risk factors as well as the need for shunt and development of hydrocephalus. In addition, we assessed factors that are not correlated (in other words independent from) with mortality, shunt need, and hydrocephalus. We included all patients who underwent treatment in our NICU with congenital encephalocele and only excluded patients with concomitant anencephaly.

We obtained the study permission from Biruni University Ethical Committee with file number:2024-86-61.

In statistical calculations, we assessed the data distribution with the Kolmogorov-Smirnov test, skewness, kurtosis, and Q-Q plots. We used the student's t-test and Mann-Whitney test with normal and non-normal distributed data, respectively. We presented the data as mean+/-standard deviation, median (interquartile range), and % (n).

Also, we built H1 (correlation) and H0 (non-correlation, independence) hypotheses and assessed correlation coefficients with Bayesian Kendall's tau b test (stretched beta prior width was set at 1) and presented Bayes factors (BF). Bayes factors (BF10)>30 represent very-strong evidence, 10-30 strong, 3-10 moderate, and 1.1-3 anecdotal evidence, where <0.03 represent very-strong evidence for null (H0) hypothesis, 0.1-0.03 strong, 0.3-0.1 moderate, 0.3-09 anecdotal evidence. We

set alpha error rate significance at p<0.05. We used the Jamovi 2.3.18 package program with the jsq extension.

**Results**

We included 18 patients (61.1% (n=11) female) in the study. The median birth week at birth was 38 weeks (36.3-39), and the mean birth weight was 2837+/-816 grams. The perinatal features and anthropometric measurements are presented in Table 1.

All the congenital encephalocele cases were referred from surrounding cities and hospitals for delivery or after birth.

As we assessed prognostic factors regarding mortality, birth weight was 3150+/-516 in survivors, whereas it was 2470+/-760 in deceased patients (student's t-test, p=0.002). Also, the mean birth week was 38.6+/-1.3 in survivors, whereas it was 34.6+/-5.0 in deceased patients (student's t-test, p=0.021). The postnatal operation day was a median of 7 days in survivors, whereas it was 11 days in deceased patients (Mann-Whitney u test, p=0.072). None of the patients had a maternal folate replacement history or family history.

One patient had aortic coarctation, another patient had Meckel-Grubel syndrome, and one patient had both

**Table 1.** Descriptive features of the patient group

| | |
|---|---|
| Birth week at delivery | 38 weeks (36.3-39) |
| Gender | 61.1% (n=11) Female<br>38.9% (n=7) Male |
| Delivery | 72.2% (n=13) Cesarean Section<br>27.8% (n=5) Normal Spontaneous Delivery |
| Birth weight | 2837+/-816 grams |
| Operated | 83.3% (n=15) |
| Operation time | 5 days (3-10) |
| Ventriculoperitoneal Shunt | 22.2% (n=4) |
| Defect diameter >5 cm | 61.1% (n=11) |
| Chiari type 3 malformation | 5.6 % (n=1) |
| Operated within 3 days | 27.8 (n=5) |
| Antenatal hydrocephalus | 27.8% (n=5) |
| All hydrocephalus | 33.3% (n=6) |
| Brain tissue involvement | 50% (n=9) |
| Seizures | 61.1% (n=11) |
| Operated | 83.3% (n=15) |
| Survival | 61.1% (n=11) in all patients<br>73.3% (n=11) in operated patients |
| Mortality causes | 1 patient: Concomitant trakeoeosefageal fistula and anal atresia |
| | 1 patient: Meckel Grubel syndrome+prematurity |
| | 4 patients: Defect diameter >15 cm |
| | 1 patient: Prematurity |

anal atresia and trakeo-özefageal atresia. Two patients were born with prematurity, and four patients had big congenital encephalocele defects (more than 15 cm in diameter).

As we investigated factors that have an impact on survival were birth weight, neural tissue involvement, defect diameter >5 cm (very strong evidence), birth week and operation within 3 days of life (strong evidence), postnatal operation day, seizure, and shunt need (moderate evidence). We did not find any significant risk factor for hydrocephalus development except the correlation between hydrocephalus and shunt need. Delivery type was independent from survival and birth week, and Neural tissue involvement was independent from shunt need (moderate evidence), where Dandy Walker deformity was correlated with shunt need (moderate evidence). The results are presented in Table 2.

**Discussion**

Encephalocele has a female tendency in our patient group with 61.1%, whereas this ratio is reported as 48.7% [16], 49% [17], 58% [18], 58.8% [19], 69% [20], and up to 78.9% [21], and these results indicate

| | Survival | | Hydrocephalus | | Shunt need | |
|---|---|---|---|---|---|---|
| | Kendall's tau | $BF_{10}$ | Kendall's tau | $BF_{10}$ | Kendall's tau | $BF_{10}$ |
| Hydrocephalus | 0.3223 | 1.538 A | — | | | |
| Shunt need | 0.4264 | 5.21 M | 0.4725 | 9.939 M | — | |
| Gender | 0.0649 | 0.321 | 0.1612 | 0.452 AI | 0.3959 | 3.522 M |
| Defect diameter >5 cm | -0.6364 | 165.4 | -0.1612 | 0.452 AI | -0.1218 | 0.379 AI |
| Neural tissue involvement | -0.5698 | 48.0 VS | 0 | 0.3 MI | 0 | 0.3 MI |
| Antenatal hydrocephalus | 0.2403 | 0.745 | 0.8771 | >1000 VS | 0.5635 | 43.0 VS |
| Dandy Walker deformity | 0.1846 | 0.508 | 0.3385 | 1.649 A | 0.4507 | 5.984 M |
| Seizures | -0.4545 | 5.176 | -0.0348 | 0.322 MI | 0.3892 | 2.466 A |
| Birth week | 0.5187 | 20.3 S | 0.0293 | 0.304 MI | -0.0442 | 0.309 MI |
| Birth weight | 0.6008 | 84.104 | 0.1529 | 0.434 AI | 0.2601 | 0.871 AI |
| Delivery type | -0.0141 | 0.301 | -0.1754 | 0.487 AI | -0.3315 | 1.69 A |
| Postnatal operation day | -0.4401 | 3.637 | -0.0737 | 0.35 AI | -0.2043 | 0.551 AI |
| Operation within 3 days | 0.4947 | 13.9 S | 0.0877 | 0.339 AI | -0.0331 | 0.305 AI |

AI: Anecdotal evidence for independence hypothesis, MI: Moderate evidence for independence hypothesis, A: Anecdotal evidence for correlation hypothesis M: Moderate evidence for correlation hypothesis, S: Strong evidence for correlation hypothesis, VS: Very strong evidence for correlation hypothesis

that the female gender has a tendency for congenital encephalocele.

The median postnatal operation day in our study was 5 days, similar to a study reporting this duration as 8 days [18]. We could not find a study regarding mortality association with the operation time, but our results indicated that operation within 3 days was associated with lower mortality with strong evidence; however, this result should be proved with larger numbers of studies conducted with more patients.

Antenatal hydrocephalus was present in 27.8% of the patients, and a total of 33.3% of patients had hydrocephalus during the treatment in our study group. A study reported that 23.5 patients had hydrocephalus before surgery, 41.2% developed hydrocephalus after surgery, and 64.7% of patients suffered from antenatal or postnatal hydrocephalus [19], whereas other studies reported the total hydrocephalus ratio as 32.4% (ventriculomegaly) [17], 50% [18], and 73.5% [22].

Shunt operation was needed in 22.2% of the patients, but we did not include a patient who died due to prematurity to this ratio. Another study from our country reported this ratio as 26.3% [21], and other studies as 29.4% [17], 48% [18]. Another aspect is that two Chiari III needed shunt in the same study [18]. A patient with Chiari III malformation needed a shunt operation in our study. Shunt need is not rare in congenital encephalocele patients but clinicians should also be aware of Chiari III malformation.

Brain parenchymal involvement in the sac occurs in half of the patients in our patient group. A study reported that 47.4% of the patients had parenchyma inside the sac [21]. Also another study reported that 42.2% [17] and 58.8% [19] of patients had neural tissue in sac. Parenchymal involvement is a poor prognostic factor in congenital encephalocele diagnosed patients [17, 19], and according to the literature and our results roughly half of the patients suffer from neural defects in congenital encephalocele cases. Neural tissue involvement was associated with mortality in our study group with very strong evidence, where it did not affect shunt need with moderate evidence.

Encephalocele might occur in various regions, but is mostly seen in the occipital region at approximately 90% rate [23]. All of our encephalocele-diagnosed patients had occipital defects. Defect size is also another concern for clinicians as a study reported that 15.3% of the cases had a larger than 5 cm defect [16]. This rate was 61.1% in our study group. We think this high rate is higher than the literature as most of our cases were referred to our hospital from surrounding cities.

Seizure is also another concern for clinicians as a study reported a seizure rate of 25.5 rate [24] where 61.1% of our patients had seizures during hospitalization.

Mortality occurred in 38.9% of all patients and 26.7% in operated ones in our study, but other causes like prematurity or major congenital anomalies play significant roles. Studies reported mortality rates as 8%. [18], 28.2% [16], 29%. [23], and 32.1% (of the operated) [22], but these rates dropped from the 57% [20] rate, which was reported in the 80's. Trakeoeosefageal fistula, anal atresia, Meckel-Grubel syndrome, prematurity, and giant encephalocele sac were the causes of death in our study group. The prognostic factors for mortality resulted in defect diameter >5 cm, neural tissue involvement, birth weight, birth week, operation before 3 days (strong and very strong evidence), and seizures (moderate evidence) in our study group. Hydrocephalus did not affect mortality significantly (anecdotal evidence). A study reported that the presence of brain tissue in the sac and size were the main prognostic factors, but hydrocephalus was not [16], similar to our findings. Another study reported that cerebral tissue in the sac was a bad prognostic feature [20]. However, we still need more studies for prognostic features of congenital encephalocele.

Folic acid intake is a preventive factor for neural tube defects, and a study reported that 10.5% of the mothers used folic acid supplementation but was not effective [21]. None of the mothers used folic acid intake in our patient group. The daily adult folic acid need is 400 mcg [25], whereas the World Health Organization recommends 400 to 800 mcg doses to prevent neural tube defects [26].

## Conclusion

The female gender has a tendency to encephalocele. Operation within postnatal 3 days of life was associated with lower mortality. Shunt operation need is not rare in congenital encephalocele patients, but clinicians should also be aware of Chiari III malformation. Neural tissue involvement was associated with mortality, where it did not affect shunt need. Seizures are not rare. The prognostic factors for mortality were defect diameter >5 cm, neural tissue involvement in the sac, birth week, birth weight, operation before 3 days, and seizures. Hydrocephalus did not affect mortality significantly.

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CERASUS JOURNAL OF MEDICINE

ORIGINAL ARTICLE



# Radiant defense: Harnessing boron-based gel for shielding against radiation-induced dermatitis in rat models

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**Abstract**

**Objective:** Radiation therapy commonly induces dermatitis as a side effect. This study aims to assess the efficacy of a boron-based gel in alleviating radiation-induced dermatitis and explore its potential molecular mechanisms.

**Methods:** Thirty-two rats were divided into four equal groups: control, boron alone, irradiation alone, and irradiation with boron groups. The boron-based gel was applied to the skin area receiving 30 Gy of irradiation, 30 minutes before exposure. The evaluation of radiation-induced dermatitis was conducted using a skin scoring system, alongside the analysis of tissue expression levels of Bax, Bcl-2, and Bcl-xl proteins.

**Results:** In the irradiation with boron group, both the skin scores for radiation-induced dermatitis and the levels of Bax protein were significantly lower compared to the radiotherapy-only group ($p<0.001$, $p<0.05$ respectively). Bcl-2 expression was reduced in both the irradiation alone and irradiation with boron groups compared to the control group ($p<0.05$). Additionally, Bcl-xl expression was lower in the irradiation with boron group compared to the other groups ($p<0.05$).

**Conclusion:** The application of boron-based gel demonstrates a preferential impact on Bax rather than Bcl-2. Moreover, the use of boron-based gel on the skin effectively reduces radiation-induced dermatitis in rats through a Bax-dependent mechanism.

**Keywords:** Apoptosis; bax; radiation; rats

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## Introduction

Radiation-induced dermatitis (RID) commonly follows radiation therapy (RT). Literature suggests that approximately 85% of patients experience dermatitis, with up to 95% developing moderate to severe skin reactions [1]. Radiation-induced skin reactions manifest as acute (within 90 days of treatment) or late effects (months to years after RT). More common in head and neck, breast, or skin cancer patients due to higher skin radiation doses, risk factors include dose parameters, anatomical sensitivity, breast size/reconstruction, and lifestyle habits like obesity and smoking [2,3]. Skin microbiome, especially Staphylococcus aureus colonization, may exacerbate reactions [4]. Genetic disorders impairing DNA repair and concurrent chemotherapy, or targeted therapy increase susceptibility to severe reactions [5]. The energetic radiation emitted in radiotherapy induces both direct and indirect ionization, leading to cellular macromolecule impairment, mainly through radiation-triggered DNA damage. This DNA-damaging process affects nearly all cellular elements of the skin, with a notable impact on epidermal keratinocytes, encompassing their stem and progenitor cells [6].

Initial treatment typically involves non-pharmacological approaches such as moisturizers and gentle bath therapies like neutral soaps and emollients. For moderate to severe cases, pharmaceutical interventions become necessary [7]. However, cosmetics can play a supportive role in subsequent therapeutic stages by aiding moisturization and alleviating irritation and itching [8]. But a definitive solution has not been found yet.

Boron is a very stable element. The physiological and metabolic mechanisms of boron's action in organisms are not yet fully understood, despite its wide-ranging effects. Boron influences cell-membrane functions, affecting responses to hormonal actions, trans-membrane signaling, and the movement of regulatory ions [9]. Additionally, boron serves as a metabolic regulator in various enzymatic systems [10]. Oxygen free radicals are highly reactive and can cause cellular and tissue damage by interacting with cell membranes and organelles. Boron helps limit oxidative damage by boosting the body's glutathione reserves and its derivatives, or by inducing other agents that neutralize reactive oxygen species [11-13].

While the wound-healing effects of boron compounds have been demonstrated in previous in vivo and in vitro studies using various wound models [14-17], its effects on radiation therapy-induced skin damage have not been evaluated before. In this study, we investigated the effects of a boron-based compound on an in vivo model of radiation-induced dermatitis.

## Methods

This study was performed after the approval of the local Animals Ethics Committee. All protocols were in accordance with the regulations governing the care and use of laboratory animals in the Declaration of Helsinki. Before the research protocol started boron-based gel was prepared described as below.

Thirty-two male Sprague-Dawley rats (mean weight 275g; mean age 4 months) were randomly divided into four equal groups. There was no intervention to the control group. RT group rats were anesthetized under aseptic conditions with intramuscular injection of ketamine-xylazine mixture (ketamine, 90mg/kg; xylazine, 10 mg/kg) and the back regions were shaved before RT procedure. Rats received a single dose of 25 Gy to the lower left side of back using bolus and 4x4 cm standard blocking accessories by 6MV photons to the body surface area (SSD 100) in 28 days. RT applications were generated with the Eclipse (Varian, Palo Alto, CA) and Varian Clinac® DHX 2100 (2.2011, USA).

In boron group 1 g/day boron-based gel were applied

lower left side of the back of the rats in 28 days. In boron+ RT group RT procedure applied described as RT group but before 30 minutes of per RT applications procedure 1g/day boron-based gel was applied to the same area.

RID was evaluated daily by a person blinded by the groups according to skin scoring system (table 1) which is adapted from Randall and Coggle's study [18]. All rats were sacrificed on the 28th day. RT areas were excised for Bax, Bcl-2 and Bcl-xl protein analyses with Western blot technique.

**Gel Preparation**

Sodium pentaborate pentahydrate was kindly provided by National Boron Research Institute-BOREN (Ankara, Turkey). Pluronic F68 and F127 were purchased from BASF® Corporation (Badische Anilin und Soda-Fabrik, Ludwigshafen-am-Rhein, Germany). Hydrogel formulations were prepared by dispersing 1%(w/v) carbopol polymer (Carbopol Ultrez-21, Lubrizol, USA) in distilled water. The neutralization buffer (1.6g of 1M sodium hydroxide solution for 1L polymer-water suspension) was used for the gelation of the polymer. Sodium pentaborate pentahydrate (3% w/v), F68 (2% w/v) and F127 (2% w/v) were mixed into the blank hydrogel and stored at 4 °C until it completely dissolved (approximately 24 h). pH of the hydrogel formulation was set to 6.5-7.0 using 1M sodium hydroxide.

**Western blot analysis**

Skin tissue was harvested from the lower right back of the rats, immediately frozen in liquid nitrogen, and stored at −80°C. The frozen samples were pulverized into powder, homogenized, and lysed with lysis buffer (1 M Tris-HCl, 5 M NaCl, Triton-X-100, 0,5 M EDTA, protease inhibitor coctail; #20-201, Millipore). Protein content was assessed using a protein assay kit, then quantified with a Qubit Fluorometer 2.0 after (#Q32866; Invitrogen) after staining with Qubit® kit (Q33211; Invitrogen). The lysate was mixed with LDS buffer and Reducing agent, heated, and applied to a Bis-Tris gel (#NP0321BOX; Invitrogen) for electrophoresis at 200 V for 60 min. Proteins were transferred to PVDF membranes (#IB4010-01: Invitrogen), blocked with skimmed milk powder (#sc-2325; ChemCruz), and probed with with polyclonal rabbit anti-Bax (#NB120-777; Novus), polyclonal rabbit anti-Bcl-2 (#2870S; Cell Signaling) and monoclonal rabbit anti-Bcl-XL (#2764; Cell Signaling) primary antibodies overnight at 4°C. After rinsing, membranes were incubated with secondary antibody, assayed with ECL detection solution (ECL prime western blot detection kit, # RPN2232; Amersham), and visualized with a Fusion FX7 (Vilber Lourmat) imaging system. Sample loading was confirmed by β-actin antibody (#sc47778; Santa Cruz) re-probing after stripping with strip buffer solution (10% SDS, 0,5 M Tris HCl, 100 mM β-mercaptoethanol) the blots.

**Results**

Before 14th day RID skin scores of all groups were 0. RID skin scores were started to elevate on the 14th day in RT group only. In the RT with boron group RID skin score started elevation in 20th day and total score was statistically significant lower compared to RT group ($p<0.001$, table 2, figure 1).

The concentration of Bax protein was statistically significant lower in boron+ RT group compared to other groups ($p<0.05$). Bax protein concentration was statistically significant lower in boron group compared to control group ($p<0.05$, figure 2).

Relative amounts of Bcl-2 protein in the skin were statistically significant lower in RT and boron+ RT groups compared to control group ($p<0.05$, figure 3). But when we evaluated to skin levels of Bcl-xl protein we revealed the boron+ RT group was significantly lower than the other groups ($p<0.05$, figure 4).

**Table 1:** The criterias for radiodermatitis in dermis

| Score | Definition |
|---|---|
| 1 | No reaction |
| 2 | Mild eryhthema |
| 3 | Depigmentation with 25% hair loss |
| 4 | Dry desquamation |
| 5 | Mild moist desquamation |
| 6 | Aggressive moist desquamation |
| 7 | Necrosis |

**Table 2:** Mean RID skin scores of the groups after 14th day

| Days | Control | RT | Boron | RT + Boron |
|---|---|---|---|---|
| 14 | 0 | 9 | 0 | 0 |
| 16 | 0 | 15 | 0 | 0 |
| 18 | 0 | 18 | 0 | 0 |
| 20 | 0 | 21 | 0 | 7 |
| 22 | 0 | 24 | 0 | 10 |
| 24 | 0 | 28 | 0 | 12 |
| 26 | 0 | 31 | 0 | 12 |
| 28 | 0 | 34 | 0 | 14 |
| Mean | 0 | 22,5 | 0 | 6,8 |

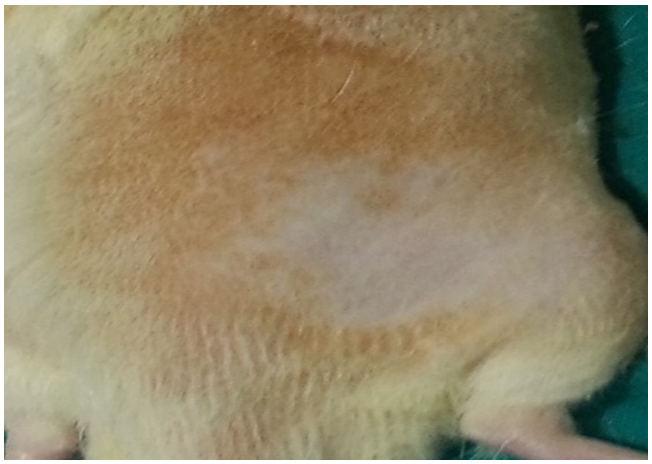

**Figure 1:** Grade four (moist desquamation) RID (sampling from RT group)

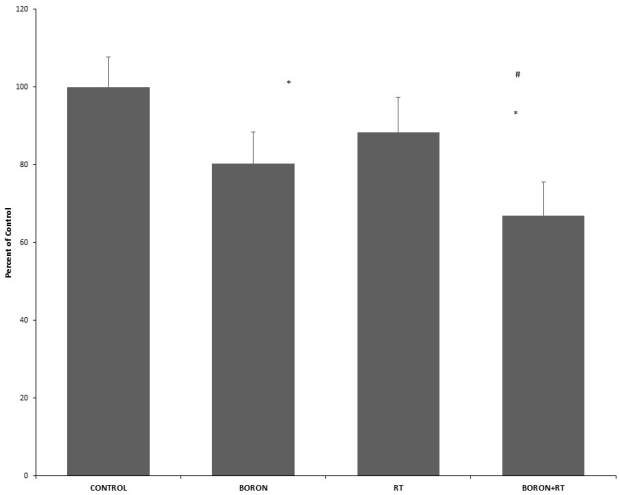


**Figure 2:** Results of relative amounts of Bax protein in the skin of rats with Western blotting test. (*Significant difference compared to control group, # significant difference compared to RT group)

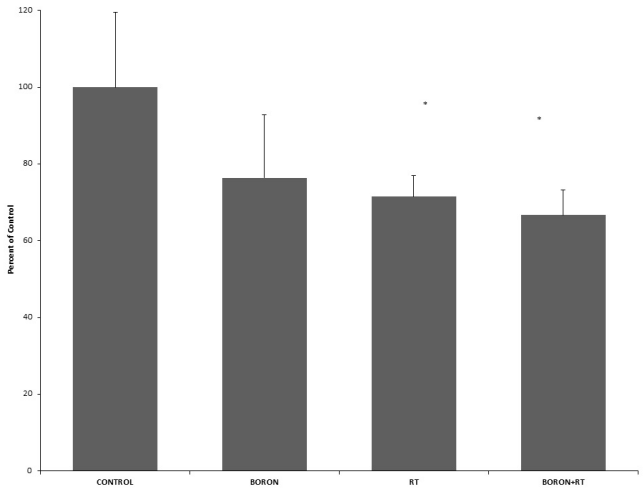


**Figure 3:** Results of relative amounts of Bcl-2 (compared with actin) in the skin of rats with Western blotting test. (*Significant difference compared to control group, # significant difference compared to RT group)

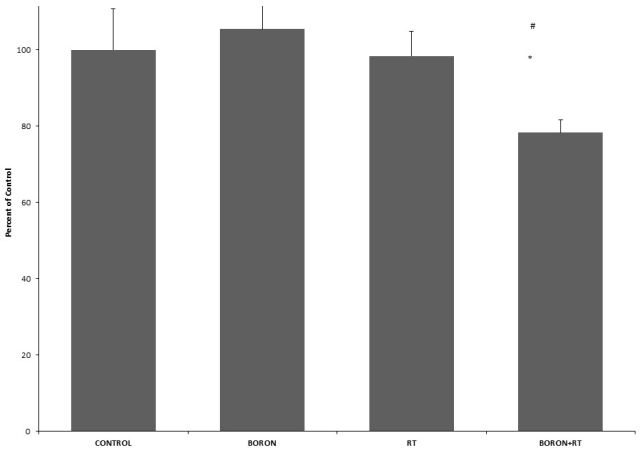


**Figure 4:** Results of relative amounts of Bcl-xl protein in the skin of rats with Western blotting test. (*Significant difference compared to control group, # significant difference compared to RT group)

## Discussion

Radiation exposure leads to tissue damage, resulting in various manifestations such as acute ulcer formation, muscle desquamation, erythema, and pigmentation changes. Additionally, it disrupts metabolic processes by reducing the expression levels of certain growth and survival factors and their receptors. Clinics offer numerous topical agents like corticosteroids, vitamins, minerals, antibiotics, and disinfectants for the protection or treatment of RID [19].

Boron is a bioactive mineral that has been linked to several metabolic processes, including the metabolism of calcium, potassium, vitamin D, insulin, estrogen, glucose, and reactive oxygen species [20]. The only study regarding the use of boron in RID in the literature was conducted by our group, and although the mechanism was not clearly determined in this study, it was found that boron gel reduced RDI compared to the control group [21]. To examine the molecular impact of boron-based gel on RID, we concentrated on the Bcl-2 family proteins. These proteins are crucial in apoptosis regulation due to their involvement in the cell cycle. The pro-apoptotic protein Bax plays a central role in the mitochondria-dependent apoptotic pathway. Conversely, Bcl-2 and Bcl-xl, which inhibit Bax, are anti-apoptotic and promote cell survival. They can be activated by signals that either support survival or inhibit cell death [22-24].

Our findings indicate that the application of boron-based gel reduces the levels of Bax protein, both when applied alone and in conjunction with RT. Boron appears to influence Bax protein levels even without the presence of any inducing agent. The pathogenesis of RID is closely linked to the intrinsic (mitochondria-dependent) apoptotic pathway. Previous reports have shown that irradiation elevates the levels of Bax, a pro-apoptotic Bcl-2 family protein that operates within the mitochondrial pathway [25].

According to the data obtained boron-based gel has a remarkable reductive action on Bax level even after the application of RT which is a triggering factor for Bax production. RT induces DNA damage and incorporates p53 into the process to initiate apoptosis pathway [26]. It was emphasized by variety of studies how p53 has a crucial action in the regulation of apoptosis which is stimulated by radiation [27]. Thus, Bax protein is

expected to increase with the promotion of RT.

The effect of boron-based gel on Bax protein may be associated with both tumor suppressor p53 and pro-survival NFκB transcription factor. NFκB pathway is one of the ways that tumor cells choose to maintain survival, proliferation, protection against apoptosis and metastasis. It is a transcription factor and involved in regulation of many processes such as immune and inflammatory responses, developmental events, cellular survival, and death. NFκB has an inhibitory role in apoptosis as it initiates transcription of anti-apoptotic protein Bcl-xl [28]. The p53 tumor suppressor protein becomes activated in response to various stressors such as excessive oncogenic activity or DNA damage [13]. Upon activation, p53 triggers the expression of numerous genes, including pro-apoptotic factors like Bax, Puma, and Noxa, while suppressing anti-apoptotic factors like Bcl-2 and Bcl-XL, through its sequence-specific transcriptional activity. p53 and NFκB often exert opposing roles in cellular fate determination, either directly or indirectly [29,30]. Considering this, we further investigated Bcl-2 and Bcl-XL, additional members of the Bcl-2 family of proteins involved in the apoptosis pathway as inhibitors. Bcl-2 directly interacts with Bax and plays a crucial role in determining cell survival or death during the cell cycle [22].

With respect to western blot results consistent with literature Bcl-2 protein falls after RT [31]. However, it is not clear to say how boron-based gel application affects Bcl-2 after RT. It is just seen Bcl-2 amount in the group applied with boron-based gel along with RT application is at the similar level with the solely RT applied group relative to the control group.

## Conclusion

Based on these results, we can conclude that boron-based gel acts on Bax rather than Bcl-2. This data may eliminate the option of NFκB directed activity of boron. For the further support we looked at the changes in another pro-survival protein Bcl-xl and observed that Bcl-xl amount declines either with the effect of RT or boron. We revealed that boron-based gel application on the skin ensure RID protection via Bax dependent activity.

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**Authors' contribution:** Surgical and Medical Practices: E.A, U.O.I, Concept: E.A, Design: E.A, Data Collection or Processing: E.A, U.O.I, F.S, Analysis or Interpretation: E.A, U.O.I, F.S, Literature Search: E.A, U.O.I, F.S, Writing: E.A, U.O.I, F.S.

**Ethical Declaration:** This study was performed after the approval of the local Animals Ethics Committee.

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CERASUS JOURNAL OF MEDICINE

CASE REPORT



# Ultrasound-guided aspiration of a large subacromial subdeltoid bursitis

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**Abstract**

Today, ultrasonography (US) is used for diagnosis in many areas of medicine (such as abdomen, cardiac, urological, gynecological, cerebrovascular and pediatric examinations). In the field of physical medicine and rehabilitation, it is the most important development in the diagnosis of muscle, joint, nerve, ligament and tendon lesions in recent years. At the same time, various injections (local anesthetic, corticosteroid, platelet-rich plasma and botulinum toxin, etc.), fluid aspiration and biopsy procedures (soft tissue, muscle, joint cavities, nerve sheath) are practiced with US.

In this medical case report, the importance of US in the diagnosis of subacromial subdeltoid bursitis and aspiration of this fluid will be discussed.

**Keywords:** Subacromial subdeltoid bursitis; ultrasound; shoulder

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## Introduction

Ultrasound (US) is a rapid, cost-effective, repeatable, practical imaging method that can be easily utilized by clinicians for musculoskeletal system visualization. Its ability to allow dynamic examination gives it an edge over other diagnostic modalities [1]. This non-invasive technique, devoid of radiation, does not require patient immobility, and enables patients to view the examined structure on the US screen, making it well-accepted. Competent interpretation necessitates practitioner training and experience [2, 3].

Ultrasound is not only a diagnostic tool but also a therapeutic modality, capable of concurrently displaying target structures and the needle during interventional procedures. Furthermore, during interventional procedures, visualization of the adjacent arteries, veins, tendons and nerves in the target area leads to a safer procedure. Under US guidance, various injections (local anesthetics, corticosteroids, platelet-rich plasma, botulinum toxin, etc.), fluid aspirations, and biopsies (soft tissue, muscle, joint spaces, nerve sheaths) are easily performed [4]. This case report discusses the significance of using US in the diagnosis and aspiration of subacromial subdeltoid (SASD) bursitis.

## Case Report

A 75-year-old female presented to outpatient clinic with a three-month history of left shoulder pain and restricted movement, worsening with overhead activities and recently disturbing her sleep. She had no history of trauma. Previously, she was advised to use non-steroidal anti-inflammatory drugs (NSAIDs) for two months by another physician, but experienced no relief. Her medical history included twenty years of hypertension, coronary heart disease, chronic obstructive pulmonary disease, and multiple medication use. Musculoskeletal examination revealed significant tenderness upon palpation, especially in the anterior and lateral aspects of the shoulder. Joint range of motion included: active left shoulder abduction 40°, flexion 60°, extension 40°, internal and external rotation 30°. Yergason, Speed, Neer, and Hawkins tests were positive. Her daily activities were severely affected, with a visual analog scale (VAS) pain score of 9. Laboratory results (including hemogram, erythrocyte sedimentation rate, C-reactive protein, and rheumatoid factor) were normal. Anteroposterior shoulder radiography was unremarkable. Subsequent US examination with a 7-12 MHz linear probe revealed a 4.5x2.3 cm SASD bursitis above the biceps tendon (**Image 1A**). Considering

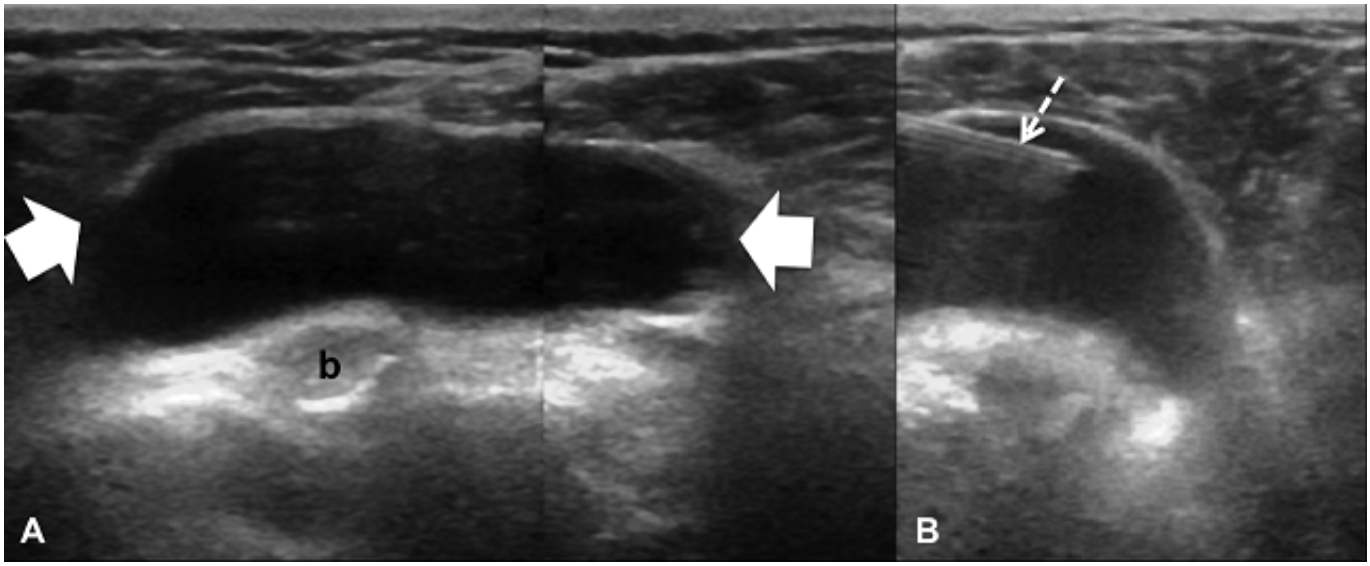


**Image 1 A-B:** *Ultrasonographic image of subacromial subdeltoid bursitis. Image A shows a 4.5x2.3 cm subacromial subdeltoid bursae(white arrows) situated above the biceps tendon (b) in an anteroposterior axial (split-screen image) ultrasonographic examination of the shoulder. Image B displays the needle (dashed arrow) during in-plane direct aspiration of the subacromial subdeltoid bursae fluid. Note: In image A, two images are merged and the fragmented part is marked with an asterisk.*

the ineffectiveness of previous NSAID treatment and severe pain, informed consent was obtained for US-guided fluid aspiration and intrabursal injection of 40 mg methylprednisolone acetate into the SASD bursae (**Image 1B**).

At the follow-up on day three, her pain was reduced to VAS pain score 1, with no restriction in shoulder movements. US examination showed complete regression of the SASD bursitis.

**Discussion**

Shoulder pain is a common musculoskeletal problem in the general population, with point prevalence and lifetime estimates as high as 26 and 67%, respectively. There are various causes of shoulder pain. The most common cause is soft tissue lesions involving structures such as bursa and tendons.These lesions are often associated with rotator cuff injuries and subacromial impingement syndrome [5-7].

Several bursae surround the shoulder joint, each located in different areas. The most important of these is the SASD bursae, situated between the rotator cuff tendons and the underside of the acromion. This bursae is a potential space and normally has a volume of 5-10 mL if there is no pathological condition like edema or adhesion. The SASD bursae facilitates movement by increasing lubrication between the rotator cuff, acromion, and acromioclavicular joint during shoulder movements. Normally, the SASD bursae has no relationship with the glenohumeral joint. Fluid accumulation in the bursae can occur due to reactive bursal inflammation associated with glenohumeral joint diseases such as rotator cuff tears, impingement, infection, arthritis, direct trauma, and calcific deposit disease. This leads to an abnormal relationship with the joint. After obtaining a detailed medical history to identify the etiological factors causing this abnormal relationship, specific tests for diseases should be performed along with a physical examination [7-9]. Various imaging methods are used to demonstrate fluid accumulation in the SASD bursae. Direct radiography is primarily used to assess bone structures, joints, degenerative changes, and the presence of calcification. US should be preferred first in evaluating fluid accumulation in the bursae [9, 10]. The reason for the preference of US in the first place is that it does not contain ionizing radiation, is portable, easily accessible and noninvasive. It can also be examined dynamically, can be easily repeated if necessary, and provides information about tissue blood supply with Doppler activity. It also guides interventional procedures like aspiration/biopsy. The most significant disadvantage is its dependence on the practitioner and its inability to provide information about the bone marrow due to strong back shadowing originating from the cortical bone [4, 10]. The diagnosis of SASD bursitis with US is made by the presence of hypoechoic fluid or effusion and a bursae thickness of >2mm. Thickening in the subacromial bursae is defined as the distance between the deep part of the deltoid muscle and the superficial part of the supraspinatus tendon being >2mm [11]. Since bursae thickening can be normal in certain life conditions and bursal thickness can vary with movement, it is recommended to compare with the asymptomatic side [12]. The incidence of SASD bursitis in patients with shoulder pain was found to be 40% in a study using US [13]. Magnetic resonance imaging (MRI) is often preferred in patients presenting with shoulder pain. While MRI has many advantages (high resolution, ability to image in various sequences, absence of radiation, non-invasiveness), its disadvantages should also be considered. These include the cost of MRI, the need for the patient to remain still during imaging, the presence of metallic and MRI-incompatible objects, claustrophobia, and operator-dependent interpretation. Evaluation can be suboptimal with MRI as it does not adequately signal some structures and tissues such as lung tissue, calcification, and cortical bone [14]. Magnetic resonance arthrogram is more valuable than MRI for detecting shoulder joint pathologies [8].

In the treatment of SASD bursitis, activity restriction, cold application, NSAIDs, exercise, and electrotherapy should be prioritized. Depending on the patient's condition and disease status, manual therapy, acupuncture, and subacromial steroid injections can be added to the treatment. If symptoms persist for more than three months despite these treatments, it is advised to seek a surgical evaluation [6]. In our case, considering both the previous two-month usage failure and the patient's age, comorbidities, and multiple drug use, oral NSAID usage might be risky and could exacerbate comorbidity. Therefore, aspiration of fluid in the SASD

bursa and local steroid injection are planned under US guidance. Studies have shown that patients receiving US-guided injections into the SASD bursae have better functional outcomes [15, 16]. It is a well-accepted fact in the literature that the success rate of interventional procedures performed under US guidance is higher compared to those done blindly [17-20]. Simultaneous imaging during US-guided interventional procedures ensures direct access to the target, increasing the success of the procedure. Additionally, it involves less risk of tissue damage as neighboring structures (vessels, nerves, tendons, ligaments, etc.) are easily visualized [17, 18].

In conclusion, solving the puzzle of treatment, as in our patient, when there is a specific goal for interventional procedures, in addition to diagnosing shoulder joint pathologies, is facilitated by US. Currently, there is no other diagnostic tool that provides simultaneous imaging capabilities during interventional procedures in daily clinical practice for physicians dealing with musculoskeletal system diseases. The safety and comfort it provides are beneficial for both the patient and the practitioner. In elderly patients like in this case, where polypharmacy is already increasing comorbidity, and the use of NSAIDs can further compound this, local treatments should be prioritized. Using systemic drugs with many side effects in such a patient is risky when safe aspiration can be performed under US guidance.

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CERASUS JOURNAL OF MEDICINE

CASE REPORT



# A rare cause of fever of unknown origin : Autoimmune hepatitis

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**Abstract**

Fever of unknown origin is difficult to diagnose, and it is seen in the course of infection, malignancy, inflammatory diseases and many other diseases. In this report, a case who presented with fever of unknown origin and was diagnosed with autoimmune hepatitis progressed to acute liver failure is presented. Our case showed a rapid and progressive clinical course, and liver biopsy performed in the early period was useful in the diagnosis. However, mortality developed on the fifteenth day of follow up.

**Keywords:** Biopsy; fever of unknown origin; autoimmune hepatitis

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## Introduction

Fever of unknown origin (FUO) is one of the challenging conditions in terms of diagnosis in infectious diseases practice. It was first defined by Petersdorf and Beeson, and various changes were made in the definition afterwards [1,2]. The classical definition of FUO includes cases with fever above 38.3°C with multiple measurements for more than three weeks and cases in which the diagnosis could not be made despite one week of hospitalization. The etiology of FUO is classified as infections, malignancies, non-infectious inflammatory diseases, miscelleneous diseases and undiagnosed cases.

Autoimmune hepatitis is a chronic liver disease that develops with immune mechanisms and is characterized by elevated transaminases, autoantibody positivity and interface hepatitis on histopathological examination of the liver [3]. Although the etiology of the disease is unknown, genetic and environmental factors are thought to play a role. It is more common in women. The incidence of the disease peaks in two periods, the first between the ages of 10-20 and the second between the ages of 45-70. The clinical course ranges from asymptomatic disease to cirrhosis and fulminant hepatitis.

In this report, a case who presented with FUO and was evaluated as autoimmune hepatitis after liver failure is presented.

## Case

A 61-year-old woman with no known disease presented with nausea and fever for two months. On admission, the temperature was 39°C and other vital signs were stable. System examination revealed no pathologic findings. Blood tests showed, white blood cell (WBC): 4050/mm$^3$, haemoglobin (Hgb): 7.2g/dL, platelets: 354000/mm$^3$, creatinine: 1.56mg/dL, aspartate transaminase (AST): 368u/L, alanine transaminase (ALT): 174u/L, total bilirubin: 0.66mg/dL, direct bilirubin: 0.45mg/dL, lactate dehydrogenaz (LDH): 429u/L, c reactive protein (CRP): 356mg/L, procalcitonin: 5.34ng/mL. Thoracic computed tomography(CT) was normal. Abdominal CT showed a 30 mm cystic lesion in the liver and increased wall thickness in the rectum. The patient was hospitalized with a preliminary of FUO. Blood and urine cultures were obtained. Empirical ceftriaxone treatment and supportive therapies were started. Transthoracic echocardiography showed no evidence of infective endocarditis. Anti nuclear antibody (ANA), anti mitochondrial antibody (AMA), anti double stranded DNA (dsDNA), anti liver kidney microsomal antibody (LKM), anti smooth muscle antibody (ASMA), c-anti-neutrophil cytoplasmic antibody (c-ANCA), p-anti-neutrophil cytoplasmic antibody (p-ANCA), anti Sm antibody, anti cyclic citrullinated peptide (anti-CCP), anti Jo-1, anti SSA, anti SSB, anti Scl-70 were negative. Tests for HBV, HCV, HAV, CMV, EBV, HSV, *Toxoplasma, Borrelia, Brucella*, Syphilis and Hydatid cyst were negative. Magnetic resonance imaging (MRI) of the abdomen showed heterogeneous signal in the liver, contour lobulation, simple cyst in segment 2, enlargement of periportal distances, complete diffusion restriction in the liver in diffusion-weighted series, and heterogeneous contrast enhancement in the arterial phase. The findings were interpreted as fulminant hepatitis secondary to infective or systemic disease. On the seventh day of follow-up, blood tests revealed WBC: 4070/mm$^3$, Hgb: 8.6g/dL, platelet: 83000/mm$^3$, creatinine: 0.45mg/dL, urea: 20mg/dL, AST: 308u/L, ALT: 79u/L, total bilirubin: 5.92mg/dL, direct bilirubin: 5.08mg/dL, albumin: 24.1g/dL, LDH: 503u/L, CRP: 251mg/L, international normalized ratio (INR): 1.58. Our case had a score of 14 according to the International Autoimmune Hepatitis Group (IAIHG) criteria and was in the probable case group (>15 definite cases). On the eighth day of hospitalization, liver biopsy was decided and the procedure was performed. Elective colonoscopy was decided after gastroenterology consultation for increased rectal wall thickness detected on imaging at admission, but this procedure could not be performed due to progressive deterioration of the patient. *Staphylococcus lugdunensis* was grown in

the blood culture, ceftriaxone was discontinued and piperacillin-tazobactam and vancomycin treatments were started. Echocardiography was planned for infective endocarditis. Echocardiography did not reveal any findings for endocarditis. AST, ALT and bilirubin levels continued to progressively increase. On the tenth day of follow-up, fever persisted, speech disorder and altered consciousness developed. Cranial imaging (CT and MRI) revealed no acute pathology. Bilirubins, INR and ammonia levels were elevated and platelet count was decreased. Acute liver failure and hepatic encephalopathy were considered in the patient, she was admitted to intensive care unit and planned to transfer to a center that can perform liver transplantation.The results of the tests related to liver function during the follow-up of the patient are shown in Table-1. On the 14th day of follow-up, the patient was intubated and had active bleeding. On the same day, the histopathology results of the liver biopsy, which had been previously examined, showed plasma cells in the immunohistochemical study with CD138, lymphoplasmacytic cell infiltration, interface hepatitis, biliary duct destruction and ductular reaction (Figure 1). These findings were interpreted in favor of autoimmune hepatitis by the pathology physician. On the 15th day of hospitalization, despite all interventions, patient died.

**Discussion**

While the frequency of infections has decreased in the etiology of FUO over the years, inflammatory diseases and various other causes have increased [4]. Despite advanced and up-to-date diagnostic methods, FUO still poses a challenging situation for clinicians in terms of diagnosis. It is a recommended approach to re-evaluate the patients every day with anamnesis, physical examination and from time to time by different doctors from different perspectives. There is no guideline for the diagnostic procedures that should be performed in patients with FUO. In the literature, studies on FUO mostly consist of case series. In a recently published case series including 214 FUO cases from Turkey, infections were reported 44.9%, malignancies 15.4%, inflammatory diseases 11.7%, other causes with a rate of 8.4% and the undiagnosed group with a rate of 19.6% [5].

Imaging techniques such as CT, MRI,scintigraphic imaging and positron emission tomography as well as invasive diagnostic tests such as liver biopsy, bone marrow biopsy, laparoscopy and laparotomy may be required for diagnosis. In the follow-up of patients, invasive procedures should be performed without delay when necessary while diagnostic procedures are being performed. It should be kept in mind that postponement of invasive procedures may result in delayed diagnosis and poor prognosis. In our case, liver biopsy was performed on the eighth day of hospitalization due to progressive liver failure and clinical deterioration.

There are studies reporting a 14-17% contribution of liver biopsy to the diagnosis in cases of fever of unknown cause [6,7]. Especially in autoimmune hepatitis with acute and fulminant course as in our case, autoantibodies can be found negative in 29-39% and immunoglobulin G level in 25-39% [8]. In another study, autoantibody negativity was found to be 29% in cases with fulminant course [9]. The importance of early diagnostic biopsy for the diagnosis of autoimmune hepatitis in cases with acute and fulminant course has been emphasised in the literatüre [10,11]. Our case had an acute and fulminant course. Considering that autoantibody and immunoglobulin G levels may be negative in cases with fulminant course, the importance of liver biopsy is obvious. Liver biopsy is generally a safe procedure and complications and procedure-related death are extremely rare. Considering the benefit provided by the examination, these minimal risks have been reported to be negligible [4]. In a study of 43 cases investigating the effect of liver biopsy on diagnosis in cases of FUO, patients were divided into three groups as group 1: liver biopsy was abnormal and helpful in diagnosis and treatment, group 2: liver biopsy was abnormal but not valuable for diagnosis and treatment, group 3: liver biopsy was normal.

6 (13.9%) patients in group 1, 11 (25.6%) patients in group 2 and 26 (60.5%) patients in group 3 were observed [6]. Hepatomegaly was statistically more common in group 1, which was the diagnostic group, and abnormal values in liver function tests were found more frequently in this group, emphasizing that liver biopsy may be diagnostic in a limited patient group [6].

Autoimmune hepatitis may present with various clinical forms ranging from asymptomatic to fulminant hepatitis. Autoimmune hepatitis patients present to the clinic with acute hepatitis with a rate of 10-25% [3]. It is difficult to differentiate this condition from acute hepatitis due to other causes. This acute clinical condition in the course of autoimmune hepatitis may be observed with two different mechanisms. The first is acute reactivation of undiagnosed subclinical autoimmune hepatitis and the second is acute hepatitis without chronic histologic changes [3]. Rarely, acute liver failure may occur in some of these cases as seen in our case. To prevent poor prognosis in this form of the disease, the diagnosis of autoimmune hepatitis should be kept in mind and necessary immunosuppressive treatment should be started after rapid diagnostic tests. In our case, although the necessary tests were performed for the diagnosis of the patient, mortality developed just before the initiation of treatment due to the acute and progressive course of the disease.

## Conclusion

Autoimmune hepatitis should be kept in mind as a rare cause in the etiology of FUO. Considering that the mortality rate increases with delay in diagnosis, it should be kept in mind that performing the necessary diagnostic tests without delay will contribute to the diagnosis and prognosis. As in our case, especially in FUO patients with liver failure, it is important to perform liver biopsy for diagnostic purposes in the early period without losing time, taking into account the cost-benefit ratio.

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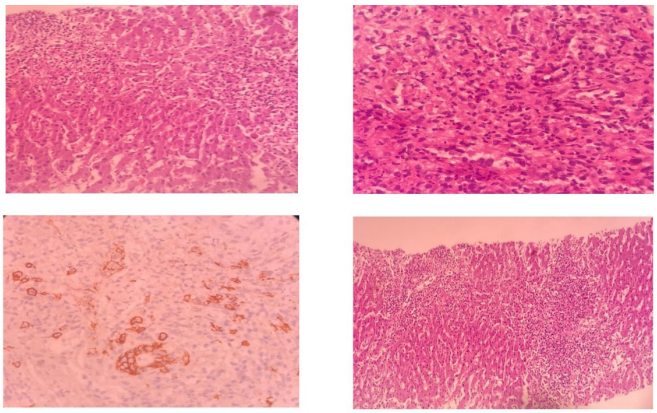

**Figure 1:** Plasma cells in the immunohistochemical study with CD138, lymphoplasmacytic cell infiltration, interface hepatitis, biliary duct destruction and ductular reaction

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CERASUS JOURNAL OF MEDICINE

LETTER TO THE EDITOR



# Papillary eccrine adenoma: A rare cutaneous appendage tumor

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Dear Editor,

An 11-year-old girl presented to our outpatient clinic with a papular lesion on the dorsal aspect of the left forearm for about 2 years. Throughout this period, there was no change in the dimensions of this lesion. In the dermatological examination, a skin-colored, papular lesion of approximately 0.5x0.5 cm in size, located on the dorsal distal 1/3 of the left forearm, with a centrally located hyperkeratotic plug-like structure, and of moderate hardness, was observed (Figure 1). There were no subjective symptoms such as itching or pain. Examination of the other skin areas, mucous membranes, hair, or nails was normal. The lesion was excised with a preliminary diagnosis of Spitz nevus, keratoacanthoma, molluscum contagiosum, squamous cell carcinoma, and benign and malignant skin appendage tumors. Histopathological examination revealed well-defined tumor islands consisting of numerous intradermal tubular structures with papillary projections (Figure 2). A diagnosis of papillary eccrine adenoma was established based on histopathological findings. No tumor was observed at the surgical margins. The patient, whose treatment was completed in the same session, was placed under follow-up.

Papillary eccrine adenoma is a rare cutaneous appendage tumor derived from sweat glands [1]. Papillary eccrine adenoma was first introduced to the literature by Rulon et al. in 1977, with a series of 14 cases [2]. Since its initial description, only a small number of cases have been reported. Although reported cases range from 9 to 78 years old, papillary eccrine adenoma is generally observed in adults [1,3]. The number of reported pediatric cases in the literature is less than 10 [4].

It typically presents as solitary dermal nodules on the extremities [1]. It can also be rarely observed on the face and trunk [4]. It can also rarely

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present as verrucous papules resembling cutaneous horn or viral wart [1].

Histopathologically, dilated ducts composed of two layers of tumor cells are most commonly observed. On the inner layers of the ducts characteristic intraluminal papillations are identified [4].

Although it is a benign lesion, clinically, it may resemble malignant skin tumors. In treatment, excision with clear surgical margins is usually sufficient [4]. Mohs surgery can also be applied to ensure complete removal of the lesion with clear surgical margins [5].

Due to its rarity, particularly in children, and the potential for confusion with malignant skin tumors, we found our case valuable to present.

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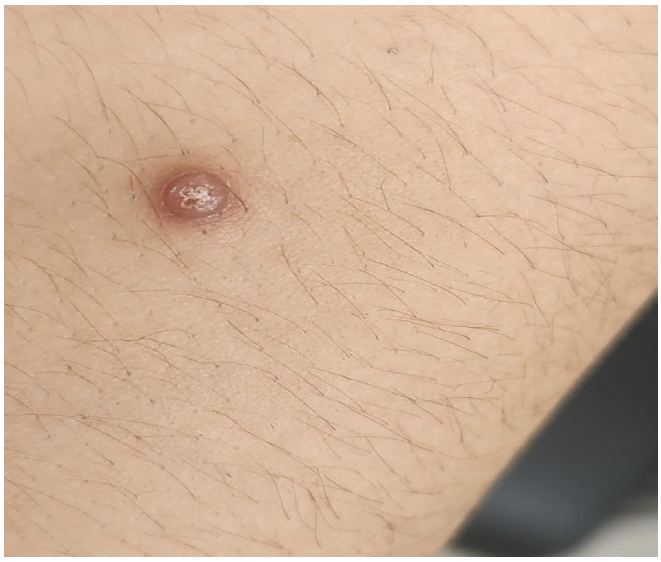

**Figure 1:** *Skin-colored umbilicated papular lesion on the left forearm*

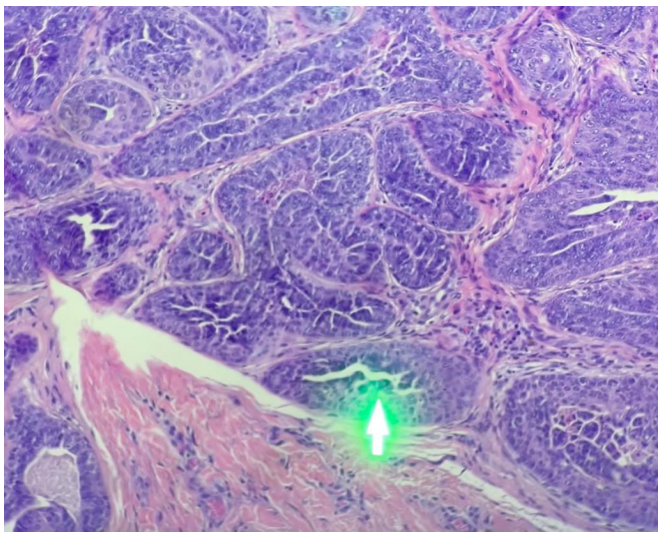

**Figure 2:** *Well-defined tumor islands and micro-papillae within tubules, Hematoxylin-eosin (H&E), 20x/0,40*

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