ISSN 1302-0072

# The Medical Bulletin of Haseki

2022
Volume 60
Issue
November 5

www.hasekidergisi.com

# The Medical Bulletin of Haseki

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**Publisher Certificate Number:** 14521

**Online Publishing Date:** November 2022

**ISSN:** 1302-0072 **E-ISSN:** 2147-2688
International scientific journal published quarterly.

# The Medical Bulletin of Haseki

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

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# The Medical Bulletin of Haseki

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# The Medical Bulletin of Haseki

Contents


## Original Articles



## Case Report

Original Article

DOI: 10.4274/haseki.galenos.2022.8467
Med Bull Haseki 2022;60:398-405

# Comparison of the Effects of Kinesio Taping Versus Dry Needling on Pain Intensity, Shoulder range of Motion, and upper Limb Function in Patients with Myofascial Pain Syndrome in the Trapezius Muscle: A Randomized Controlled Trial

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## Abstract

**Aim:** We hypothesized that both dry needling (DN) and Kinesio taping (KT) combined with exercise training would have short-term therapeutic effects. In this context, we aimed to compare the efficacy of DN versus KT combined with exercise training on pain intensity, shoulder range of motion (ROM), and upper limb function in patients with myofascial pain syndrome of the trapezius muscle.

**Methods:** Fifty participants with myofascial pain syndrome of the trapezius muscle were randomly assigned to three groups; KT combined with exercise training (KTG, n=17), DN combined with exercise training (DNG, n=16), and only exercise training (ExG, n=17). The training duration was for 3 weeks. The Visual Analogue Scale (VAS), universal goniometer, and the Disability of the Arm, Shoulder, and Hand (DASH) questionnaire were used at baseline and after training.

**Results:** Compared to DNG, VAS-activity (p=0.03; p=0.02) and DASH (p=0.01; p=0.03) scores were significantly decreased in favor of KTG and ExG. Shoulder flexion ROM increased significantly in KTG compared with DNG (p=0.008) and ExG (p=0.008).

**Conclusion:** Compared to DN, the adjunct of KT to exercise training and exercise training alone have significant effects on reducing pain intensity and improving shoulder ROM and upper extremity functionality in patients with myofascial pain syndrome of the trapezius muscle.

**Keywords:** Myofascial pain syndrome, range of motion, dry needling, trapezius, visual analog scale

## Introduction

Pain in the shoulder area is the third most common reason for musculoskeletal evaluations worldwide (1). Signs and symptoms are usually seen in the shoulder and scapular regions and are characterized by shoulder stiffness and limited range of motion (ROM), often causing limitations in activities of daily living (2). Myofascial trigger points (MTrPs) are defined as hypersensitive points in a taut band of muscle and are characterized by referred pain and motor dysfunction in a taut band or fascia of the muscles (3). It has been shown that patients with pain in the shoulder area have a high number of active and latent MTrPs in their muscles (4). The active MTrP causes clinical complaints of pain, whereas the latent MTrP may have a taut band that increases muscle tension and limits ROM (3).

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**Received:** 09.05.2022 **Accepted:** 13.09.2022

Manual techniques (such as trigger point compression or other methods), trigger point stretching, and dry needling (DN) can inactivate MTrPs. However, MTrP inactivation can be combined with exercise training (5). DN and Kinesio taping (KT) are the two most common methods used recently for treating acute illnesses and musculoskeletal problems (6,7). KT is a fairly new technique that has been widely used for therapeutic purposes in various rehabilitation settings (8). It supports muscles, fascia, joints and improves blood circulation and lymphatic drainage by increasing the gap between the skin and soft tissue. As a result, KT increases muscle strength, tone, and ROM and reduces oedema and inflammation. It can also act with proprioceptive and nociceptive stimulations via cutaneous mechanoreceptors. However, DN is recognized as an effective intervention to directly inactivate MTrPs (9) and plays an important role in the treatment of muscle pain caused by MTrPs (10) by targeting trigger and non-trigger point structures (11). It has been shown that DN reduces pain by increasing pressure-pain threshold and increasing ROM, whereas no superiority to placebo was demonstrated in others (12). Choosing the most effective modality among the available treatment options will benefit the patients and shorten the treatment time. The effectiveness of KT and DN methods in MTrP has been investigated in many studies, but which one is superior to the others is still controversial (3,6,7). Given the high prevalence of MTrPs and the lack of consensus on the optimal treatment, we hypothesized that both DN and KT combined with exercise training would have short-term therapeutic effects. However, the expected benefit from DN combined with exercise training may be significantly higher.

Therefore, the current study compared the effects of KT or DN combined with exercise training on pain intensity, shoulder ROM, and upper limb function in patients with myofascial pain syndrome of the trapezius muscle.

## Materials and Methods

### Compliance with Ethical Standards

The 3-arm randomized controlled trials were conducted at Istanbul University, Department of Sports Medicine, between May 2016 and November 2017. The study was approved by the Clinical Ethics Committee of the University of Health Sciences Turkey, Bakirkoy Dr. Sadi Konuk Training and Research Hospital (decision no: 2014/17/06, date: 15.12.2014) and the study protocol was registered prospectively. Written informed consent was obtained from all participants, and the study was conducted in accordance with the Declaration of Helsinki.

### Sample Size

The study sample size was calculated based on the reported effect size of the Disability of the Arm, Shoulder, and Hand (DASH) questionnaire. The GPower software (G*Power version 3.1, Düsseldorf, Germany) was used to determine the sample size (13). Based on a priori power analysis, a power of 0.95, a 5% level of significance (a=0.05), and an effect size of 1.13 (14), a minimum of 14 patients per group were required to achieve significance. A total of 57 participants, by considering patient drop-out during follow-up, were enrolled in the current study.

### Participants

Consecutive patients with trapezius myofascial pain syndrome were screened for the inclusion criteria. The inclusion criteria of the study are as follows: a) 18 years or above, b) pain in the shoulder area for at least two months, and c) presence of an active trigger point or area of mechanical hypersensitivity in at least one muscle (upper trapezius, middle trapezius, and supraspinatus) in the shoulder region. Patients who experienced problems such as previous surgery on the shoulder area, shoulder bone fractures, frozen shoulder, shoulder impingement syndrome, and those currently receiving other physiotherapy treatments for shoulder region pain were excluded.

According to the inclusion criteria, 68 patients were screened for the study. Of these, 11 participants didn't meet the study inclusion criteria. The remaining 57 patients were randomly divided into 3 groups, with 19 patients in each group. One patient left the study due to personal reasons, and one patient left due to an allergic reaction to the tape in KTG (n=17). In DNG, one patient was excluded due to needle phobia, and two for not completing the treatment due to personal reasons (DNG, n=16). Two patients in ExG were excluded from the study for not completing the treatment due to personal reasons (ExG, n=17) (Figure 1).

### Randomization

Fifty-seven participants were randomly divided into one of three groups (1:1:1) using a validated web-based "Research Randomizer" (https://www.randomizer.org/): KT application combined with exercise (KTG, n=19), DN combined with exercise (DNG, n=19) and the exercise group received only exercise (ExG, n=19) (Figure 1).

## Intervention Programs

### Exercise Training Group

The exercise training program consisted of Codman exercises, stretching, and strengthening exercises (15). Stretching exercises were applied to the upper trapezius, supraspinatus, and pectoralis muscles for at least ten

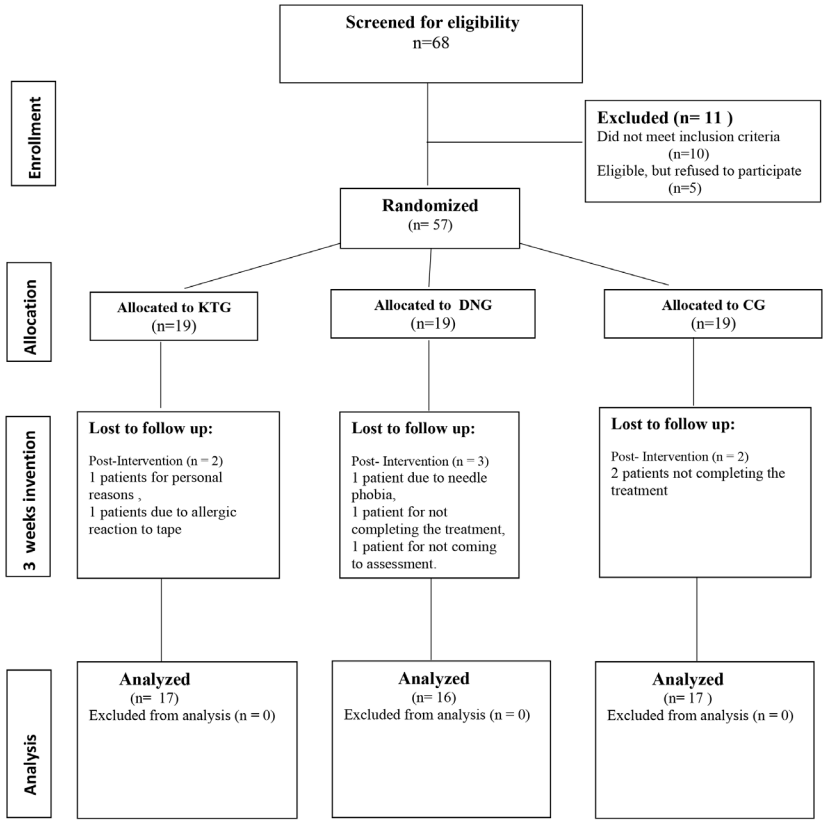


**Figure 1.** Design of the study.

seconds in a sitting position. Isometric strengthening exercises for the trapezius, supraspinatus, and serratus anterior muscles were applied. The exercise protocol consisted of 3 sets of each exercise, and each set consisted of 10 repetitions performed under the supervision of a physiotherapist. This program was applied to all groups for 45 minutes a day, 5 times a week for 3 weeks.

### Kinesio Taping Application Combined with Exercise Training

In addition to the abovementioned exercise program, KT (Ares Tape®) was applied to the upper trapezius, middle trapezius, and supraspinatus in this group. Taping was done by a professional physiotherapist who had received KT training. KT was applied to myofascial pain points in the supraspinatus muscle of 2 patients; the middle trapezius muscle of 3 patients; the supraspinatus and upper trapezius muscles of 8 patients; and the upper trapezius and supraspinatus muscles of 5 patients in the KT combined with the exercise training group (KTG). Before the application of KT, the patient's skin was shaved, wiped with alcohol, and dried. For trapezius muscle MTrPs, star-shaped KT was performed. As shown in Figure 2, four I-strips were cut and applied. Four stripes were fixed to the trapezius muscle, while MTrP was centered at the intersection of these strips. The inhibition technique was applied according to the Kenzo Kase method (stretching it 15-25% of the original length). KT treatment was applied twice a week for 3 weeks (Figure 2).

### Dry Needling Combined with Exercise Training

The DN procedure used in this study was applied as specified by Hong (16). In this study, the physiotherapist applied DN to each MTrP in at least two muscles (upper trapezius, middle trapezius, and supraspinatus) in patients with shoulder pain (2,4). Seirin® B type needles with a length of 25-40 mm and a diameter of 0.25 mm were used. Each needle was used once or twice. The DN was applied to myofascial pain points in the supraspinatus muscle of 3 patients; the middle trapezius muscle of 2 patients, the supraspinatus and upper trapezius muscles of 7 patients, and the upper trapezius and supraspinatus muscles of 4 patients in the DN combined with exercise (DNG). The application of DN to each MTrP region took approximately 1-2 minutes (17). In this group, patients received DN in addition to the above-mentioned exercise program for 3 weeks (twice a week periodically).

**Table 1. The demographic variables of participants**

| | KTG (n=17) | DNG (n=16) | ExG (n=17) | p-value |
|---|---|---|---|---|
| | Mean ± SD or n | Mean ± SD or n | Mean ± SD or n | |
| **Age (years)** | 47.4±4.1 | 46.9±4.4 | 47.3±3.8 | 0.624[a] |
| **Sex (female/male)** | 15/3 | 14/2 | 16/2 | 0.121[b] |
| **Height (cm)** | 167.9±8.1 | 166.3±8.6 | 168.1±9.4 | 0.329[a] |
| **Weight (kg)** | 75.8±8.9 | 76.4±9.2 | 75.3±9.1 | 0.423[a] |
| **BMI (kg/m²)** | 25.5±4.2 | 26.1±3.7 | 25.9±5.1 | 0.256[a] |

[a]One-Way ANOVA; significance level set at <0.05.
[b]Chi-squared test; significance level set at <0.05.
KTG: Kinesio taping application combined with exercise, DNG: Dry needling combined with exercise, ExG: Only exercise, SD: Standard deviation, BMI: Body mass index

**Table 2. Comparison of pain intensity and functionality intra and intergroup**

| | KTG (n=17) | | DNG (n=16) | | ExG (n=17) | | Intergroup | |
|---|---|---|---|---|---|---|---|---|
| | Mean ± SD | | Mean ± SD | | Mean ± SD | | p-value | |
| | Baseline | End of the intervention | Baseline | End of the intervention | Baseline | End of the intervention | Baseline | End of the intervention |
| VAS-rest | 4.5±2.1 | 2.9±2.2[a] | 4.4±2.8 | 3.1±1.2[c] | 4.8±2.3 | 3.0±2.4[e] | 0.762 | 0.146 |
| VAS-activity | 6.9±2.3 | 3.2±2.1[a] | 6.6±3.1 | 4.9±1.8[d] | 6.5±3.3 | 3.1±2.2[e] | 0.391 | 0.034[*] |
| VAS-night | 5.1±3.2 | 3.9±2.1[a] | 4.9±2.7 | 3.7±2.4[c] | 4.9±3.6 | 3.8±2.5[e] | 0.740 | 0.189 |
| DASH | 80.4±22.33 | 61.9±18.1[b] | 82.2±19.3 | 72.3±13.2[d] | 80.5±19.5 | 63.5±16.9[e] | 0.868 | 0.008[**] |

[a,b]Paired-sample t-test; (p<0.05, p<0.01) indicating the difference between VAS and DASH scores before and after the treatment in KTG.
[c,d]Paired-sample t-test; (p<0.05, p<0.01) indicating the difference between VAS and DASH scores before and after the treatment in DNG.
[e]Paired-sample t-test; (p<0.01) indicating the difference between VAS and DASH scores before and after the treatment in ExG.
[*]One-Way ANOVA test, Bonferroni correction; indicating that after intervention pain during activity significantly decreased in KTG (p=0.007) and ExG (p=0.011) compared with DNG.
[**]One-Way ANOVA test, Bonferroni correction; indicating that after intervention DASH scores significantly decreased in KTG (p=0.004) and ExG (p=0.013) compared with DNG.
KT: Kinesio taping application combined with exercise, DN: Dry needling combined with exercise, ExG: Only exercise, VAS: Visual analog scale, DASH: Disabilities of the arm, shoulder and hand, SD: Standard deviation

**Table 3. Comparison of shoulder range of motion**

| | KTG (n=17) | | DNG (n=16) | | ExG (n=17) | | Intergroup | |
|---|---|---|---|---|---|---|---|---|
| | Mean ± SD | | Mean ± SD | | Mean ± SD | | p-value | |
| | Baseline | End of the intervention | Baseline | End of the intervention | Baseline | End of the intervention | Baseline | End of the intervention |
| **Shoulder Flex ROM** | 154.1±24.8 | 162.2±23.1[a] | 159.5±22.3 | 165.5±23.1[b] | 155.6±23.3 | 164.6±23.7[c] | 0.662 | **0.043[d]** |
| **Shoulder Ext ROM** | 30.3±15.2 | 31.5±16.3 | 29.6±12.5 | 30.5±16.4 | 30.6±13.7 | 32.1±12.3 | 0.391 | 0.567 |
| **Shoulder Abd ROM** | 119.6±40.3 | 143.5±36.1[a] | 123.4±37.6 | 131.3±35.1 | 122.5±32.1 | 141.8±30.3 | 0.340 | **0.023[e]** |
| **Shoulder Add ROM** | 45.7±10.1 | 47.4±13.4 | 43.4±13.9 | 44.3±13.5 | 44.8±11.1 | 45.9±12.9 | 0.879 | 0.567 |
| **Shoulder IR ROM** | 76.5±14.3 | 77.1±13.2 | 73.4±17.5 | 73.9±15.4 | 74.8±13.5 | 76.9±14.6 | 0.521 | 0.325 |
| **Shoulder ER ROMs** | 75.3±18.5 | 83.2±16.4[a] | 75.2±22.1 | 77.1±21.5 | 74.2±19.8 | 81.4±21.1[c] | 0.868 | 0.012[f] |

[a]Paired-Sample t-test; (p<0.05) indicating the difference between before and after the treatment in KTG.
[b]Paired-Sample t-test; (p<0.05) indicating the difference between before and after the treatment in DNG.
[c]Paired-Sample t-test; (p<0.05) indicating the difference between before and after the treatment in ExG.
[d]One-Way ANOVA test, Bonferroni correction; indicating that after intervention, shoulder Flex ROM significantly increased in KTG compared with DNG (p=0.008) and ExG (p=0.008).
[e]One-Way ANOVA test, Bonferroni correction; indicating that after intervention, shoulder Abd ROM significantly increased in KTG (p=0.003) and ExG (p=0.007) compared with DNG.
[f]One-Way ANOVA test, Bonferroni correction; indicating that after intervention, shoulder ER ROM significantly increased in KTG (p=0.008) and ExG (p=0.012) compared with DNG.
KT: Kinesio taping application combined with exercise, DN: Dry needling combined with exercise, ExG: Only exercise, ROM: Range of motion, Flex: Flexion, Ext: Extension, Abd: Abduction, Add: Adduction, IR: Internal rotation, ER: External rotation, SD: Standard deviaiton

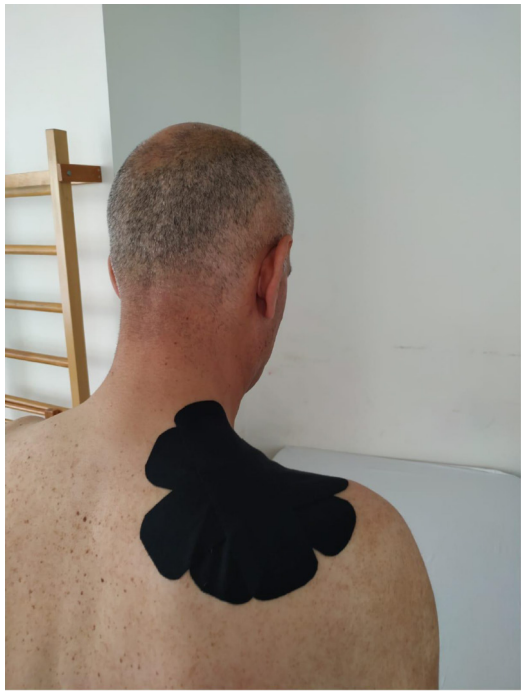

**Figure 2.** Kinesio Tape application

### Outcome Measure

#### Pain Intensity

Patient's pain was evaluated using a visual analog scale (VAS). The patient was asked to describe the pain she/he felt at rest, at activity, and at night. According to VAS, motion, pain and 10-were rated the worst pain (18).

#### Range of Motion

Active ROM of the patient's shoulder was assessed by a goniometer (Saehan®) in a supine position as described by Clarkson and Gilwich. Measurements were repeated three times in all directions of the shoulder and the average value was recorded (19,20).

#### Upper Limb Functions

The DASH questionnaire is used to evaluate upper limb functions. The questionnaire consists of 30 items on the disability/symptom scale related to the patient's health status last week. All items have five responses, ranging from "no problem or no symptoms" (1 point score) to "severe symptoms" (5 point score) (21). The Turkish version of the DASH questionnaire was used in the study (22).

#### Statistical Analysis

The analysis of the study data was performed using SPSS version 24.0. Data are presented as mean ± standard deviation, and frequencies. One-Way ANOVA and chi-square tests were used for intergroup comparisons of demographic and baseline clinical variables. A paired-sample t-test was used to determine the improvement within the groups, whereas a One-Way ANOVA was applied to compare the improvements between the groups. Pairwise post-hoc comparisons were made using Bonferroni's test and the level of significance was determined to be $p<0.017$ (23).

### Results

Participants were similar in baseline demographic and clinical variables (Table 1). After the 3-week intervention, patients' VAS and DASH scores significantly reduced within all three groups. The VAS-activity pain score was significantly decreased in favor of KTG ($p=0.007$) and ExG ($p=0.011$) compared with DNG (Table 2). The DASH scores significantly decreased in KTG ($p=0.004$) and ExG ($p=0.013$) compared with DNG (Table 2).

After the 3-weeks of intervention, shoulder flexion ($p=0.02$), shoulder abduction ($p=0.02$), and shoulder external rotation ROM ($p=0.04$) were significantly improved in the KTG, whereas DNG showed improvement in shoulder flexion ROM only ($p=0.02$), and ExG showed improvement in shoulder flexion ($p=0.03$), and shoulder external rotation ROM ($p=0.04$) compared to baseline. The inter-group comparison revealed that shoulder flexion ROM increased significantly in KTG compared with DNG ($p=0.008$) and ExG ($p=0.008$). Whereas shoulder abduction and shoulder external rotation ROM significantly increased in both KTG (shoulder abduction: $p=0.003$; shoulder external rotation: $p=0.008$) and ExG (shoulder abduction: $p=0.007$; shoulder external rotation: $p=0.012$) compared with DNG (Table 3).

### Discussion

The findings of the current study demonstrated that after 3 weeks of intervention, pain intensity and DASH scores decreased significantly in all patients. However, pain intensity during activity and DASH scores were significantly decreased in favor of KTG and ExG compared with DNG. Considering ROM, KTG showed significant improvement in shoulder flexion, external rotation, and abduction ROM, whereas the DNG group showed improvement in shoulder flexion ROM only, and ExG showed improvement in shoulder flexion and external rotation ROM. The shoulder flexion ROM increased significantly in KTG compared to other groups, and shoulder external rotation and abduction ROM significantly increased in KTG and ExG compared to DNG.

Previous studies reported different and sometimes conflicting results due to differences in interventions used (taping technique, target muscle, etc.) and/or methodological differences in study designs. In this study, KT combined with exercise training resulted in an important decrease in pain intensity during activity compared to

DN application, which is consistent with the findings of Shakeri et al. (24). They demonstrated that KT application immediately reduced pain during physical activity and night pain intensity in participants with impingement syndrome compared with placebo KT application. Similarly, Öztürk et al. (25) reported that KT application to the trapezius muscle provided an important progression in pain intensity levels after KT. Delkhoush (26) reported that the use of the DN or inhibitory KT method in subjects with MTrPs of the upper trapezius muscle provided an immediate improvement in pain intensity and functional disability. Similarly, Doğan et al. (27) reported significant progress in resting and cervical motion pain intensity, tenderness pain threshold, cervical ROM, and function in both KT and DN groups, with no relative superiority. The authors suggested that KT could be an option for trigger point inactivation in patients who are afraid of injections or have contraindications for treatments other than KT. In another study, they reported that KT and DN combined with posture and stretching exercises were efficient in improving both VAS pain and tenderness thresholds at the end of the intervention, and the improvements were sustained even two months after the intervention (28). There are several theories that can explain the effect of KT on pain reduction. The most accepted theory is the Gate Control Theory. KT is believed to stimulate the neuromuscular pathway by increasing afferent feedback. Increasing afferent stimulation of large-diameter nerve fibers can reduce the effect of small-diameter nerve fibers that transmit pain (29). The applied KT reduces pain by stimulating the pain relief mechanism descending from the upper centers of the brain (30). One of the other proposed mechanisms is based on the reduction of the pressure on the subcutaneous nociceptors because of the lifting of the skin with KT application (31).

Additionally, applications of DN to shoulder girdle muscles have been increasing recently. Currently, little is known about the mechanism of action of DN. Stimulating the MTrP with a needle can result in increased blood flow and a decrease in nociceptive substances. DN can also stimulate ad fibers and activate inhibitory pain systems (32). De Meulemeester et al. (33) compared the short and long-term therapeutic effects of DN and manual pressure techniques and reported that both DN and manual pressure techniques resulted in similar short- and long-term treatment effects. The possible reason for this might be that all the muscles treated were superficial muscles, and they may not be suitable for either technique. Similar to this study, the DN application was not as effective as KT in our study. The possible reason is that we also applied DN superficial muscles only. Besides, recent studies conducted by Calvo-Lobo et al. (34) showed that the effects of DN on shoulder pain and function differ. We think that the difference in pain and function score results of our study from the similar outcome measurements of these studies is because our patients were relatively young, the number of DN sessions applied in the studies, and the difference in the muscles applied. However, differences between studies may be due to differences in study design, such as taking activated or latent trigger points, and differences in the KT technique. Therefore, KT needs to be performed more frequently compared with DN, which might increase the work load of clinicians. However, it is safer and not as time-consuming as DN.

Previous studies have examined the effect of KT use on outcome measures, and the findings of different studies are conflicting. Kaya et al. (35), reported that DASH scores were significantly lower in the KT group compared to the traditional physiotherapy group. Similarly, Thelen et al. (29) reported that there were no differences between KT and sham taping groups in terms of SPADI scores. According to Yasar et al. (36), KT and DN methods had more positive effects for treating MTrPs in terms of pain and disability than the control group. In another study, KT and DN applied with conventional physical therapy improved VAS pain and daily living activity scores in as little as 4 weeks, providing health benefits to MTrP patients (37). In our study, comparing three different methods, we detected significant differences in DASH scores after all applications, although the difference between groups was significantly decreased in favor of KT and Ex compared to DN. In this regard, we conclude that both KT and Ex applications may provide beneficial effects on upper extremity functions. Unlike DN application, we think this result is due to the tape being available to assist muscles, fascia, and joints in addition to unrestricted ROM.

Previous studies in the literature have reported that KT increases ROM (29,38,39). Thelen et al. (29) reported that the KT group demonstrated progress in pain-free shoulder abduction. In terms of facilitating the movement of the shoulder throughout its ROM, the KT-induced stretching of the skin over the area guides the shoulder in an arc. Improving the movement of the shoulder joint will ease the KT effect. This will reduce mechanical irritation to the soft tissue surrounding the shoulder joint. Şimşek et al. (39) reported that pain during the night and activities was decreased, and shoulder external rotation and abduction ROM were increased after 12 days of KT application. They also emphasized that the KT application was more effective when combined with an exercise program than exercise alone. Another study documented that KT decreased different types of pain, increased ROM, and sense of proprioception more than placebo taping when applied to the quadriceps muscle for patients with knee osteoarthritis

(40). In our study, KT application improved shoulder flexion ROM compared with DN and Ex, and shoulder abduction and shoulder external rotation ROM importantly increased with KT and Ex application compared to DN. As understood from these results, KT combined with exercise is superior to only exercise training and DN application, in addition to exercise, in improving the shoulder ROM. Previous authors reported that a reduction in pain intensity with KT resulted in improvement in shoulder ROM (41).

### Study Limitations

The current study has some limitations. Firstly, researchers who performed KT and DN applications and performed measurements were not blind to treatment allocation. Secondly, the duration of treatment applied in our study was only 3 weeks, which was shorter than similar studies in the literature, and there were no long-term results. Another limitation is that no meaningful clinical difference was calculated in the shoulder ROM. The fact that the measurements were made by the same physiotherapist to avoid possible personal measurement differences can be considered the study's strength.

## Conclusion

In patients with myofascial pain syndrome of the trapezius muscle, the use of kinesio tape in addition to exercise training and exercise training alone had more effects on decreasing pain severity and improving shoulder ROM and upper extremity functionality compared to dry needling.

### Acknowledgments

The authors thank Ishtiaq Ahmed for English language editing support.

### Ethics

**Ethics Committee Approval:** The study was approved by the Clinical Ethics Committee of the University of Health Sciences Turkey, Bakirkoy Dr. Sadi Konuk Training and Research Hospital (decision no: 2014/17/06, date: 15.12.2014).

**Informed Consent:** Written informed consent was obtained from all participants, and the study was conducted in accordance with the Declaration of Helsinki.

**Peer-review:** Externally peer-reviewed.

### Authorship Contributions

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

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

**Financial Disclosure:** The authors declared that this study received no financial support.

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Original Article

DOI: 10.4274/haseki.galenos.2022.8728
Med Bull Haseki 2022;60:406-410

# The Effect of Listening to Music on Reducing Anxiety and Pain During Extracorporeal Shock Wave Lithotripsy; A Randomized Controlled Study

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## Abstract

**Aim:** Many patients experience anxiety during their first shock wave lithotripsy (SWL) experience. We investigated the effect of music therapy on anxiety and pain during SWL.

**Methods:** This study was designed as a randomized controlled trial between June 2021 and December 2021. A total of 100 patients were evaluated prospectively. Fifty patients were assigned to each group using a simple randomization method. The study group was exposed to music therapy, while the control group was not exposed to it. Demographic data (age, gender, and body mass index), stone characteristics (size, location, and laterality), and SWL characteristics (SWL duration, energy, and number of shock waves) were recorded. The state-trait anxiety inventory (STAI) was used to assess anxiety, and the visual analog scale (VAS) was used to assess pain. After the SWL, general patient satisfaction and willingness to repeat the procedure were evaluated.

**Results:** Baseline STAI-state (STAI-S) and STAI-T values measured before SWL were similar between the groups (p=0.51 and p=0.46, respectively). STAI-S after SWL was statistically significantly lower in the music group (p=0.02). In the music group, satisfaction and willingness to repeat were higher, while the VAS was lower (p=0.04, p=0.03 and p=0.03, respectively).

**Conclusion:** Music therapy during SWL is an inexpensive and effective method to reduce patient anxiety and the patient's perception of pain.

**Keywords:** Music, lithotripsy, pain, anxiety

## Introduction

Shock wave lithotripsy (SWL) treatment for kidney and ureteral stones has recently become more popular due to advantages such as being less invasive than other surgical treatments, being performed without anesthesia, being relatively inexpensive, and having the option of outpatient treatment (1). The success rate of SWL is between 50 and 80%. In addition to factors such as stone location, size, and composition, skin-to-stone distance, and patient compliance, other factors also affect the success rate (2,3).

SWL is considered a stressful and painful procedure. Patient anxiety and pain are factors that affect patient compliance and procedure tolerability (4). While the pain reduces the effectiveness of SWL by defocusing attention due to excessive respiratory activity and undesirable movements, it also reduces the rate of continuation of the procedure (5). To reduce pain perception and anxiety during SWL, pharmacological treatments (non-steroidal anti-inflammatory drugs, opiate agents, and anxiolytics) and non-pharmacological distraction techniques such as aromatherapy, hypnosis, acupuncture, biofeedback, and reflexology have been suggested (6). Another non-pharmacological method is music therapy, which has been known for its relaxing effect since ancient times (7). It has been reported that music therapy has a positive effect on pain perception and anxiety in various non-urological

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**Received:** 19.08.2022 **Accepted:** 25.11.2022

procedures (8). Therefore, we investigated the effect of music therapy on anxiety and pain during SWL.

## Materials and Methods

### Compliance with Ethical Standards

This study was designed as a randomized controlled trial between June 2021 and December 2021 in University of Health Sciences Turkey, Basaksehir Cam and Sakura City Hospital in patients with kidney and upper ureteral stones who were planned for SWL, after the approval of the University of Health Sciences Turkey, Basaksehir Cam and Sakura City Hospital Local Ethics Committee (approval number: 2021.04.64, date: 28.04.2021).

### Study Design

Patients aged <18 years with solitary kidneys, kidney anomalies, hearing problems, illiteracy, non-opaque stones, previous SWL history, the presence of a ureteral stent, anxiolytic drug use, or an anxiety disorder were excluded from the study. All patients included in the study were selected from patients who received the first session of SWL.

Demographic data such as age, gender, body mass index (BMI), stone size, stone location, and SWL process data (during, energy, and number of shock waves) were collected from medical records. The patients were asked to fill out the forms [state-trait anxiety inventory (STAI), visual analog scale (VAS), willingness to repeat the procedure, and patient satisfaction]. Informed consent was obtained from all patients, both for the SWL procedure and for participation in the study. All patients received SWL treatment from an experienced technician who was unaware of the study. An electromagnetic SWL (Multimed EM, Elmed Medical Systems, Turkey) was used for the SWL procedure for all patients.

A simple randomization method was applied to avoid intervention contamination. Randomization was decided by tossing a coin at the beginning of each day. While the patients who applied were given music therapy (the music group) for one day in accordance with the randomization, the other group was not given music therapy (the control group). The patients in the music group were given a playlist where they could find the type of music they wanted during SWL, and they were given the freedom to choose the type of music they preferred. It is also possible to change the volume of the music.

STAI-trait (STAI-T) and STAI-state (STAI-S) questionnaires were completed in all patients before the procedure, and STAI-S, VAS (0=no pain, 10=maximum possible pain), overall patient satisfaction (0=extremely dissatisfied, 4=extremely satisfied), and willingness to repeat the procedure (0 never, 4=willing) questionnaires were completed after the procedure. Anxiety levels were measured using STAI. The STAI-S scale measures anxiety at a given time, whereas the trait anxiety (STAI-T) scale measures long-term anxiety levels. STAI-S and STAI-T involve 20 items. It involves a four-point Likert type scale where the items can be scored between 1 and 4. The reverse statements' total weighted score is subtracted from the direct statements' total weighted score. Then, a constant value is added to this number. The values are 50 and 35 for STAI-S and STAI-T, respectively. The scale's maximum possible score is 80, while its minimum possible score is 20 (9).

### Statistical Analysis

Statistical analysis was performed using the IBM SPSS Statistics 22 (SPSS Inc., Chicago, IL, USA) software. A normal distribution of the quantitative data was checked using the Kolmogorov-Smirnov test. Descriptive statistics for continuous variables were expressed as mean ± standard deviation. The number of cases and percentages were used as categorical data. For intergroup comparisons, the chi-square test was used for categorical variables, and the Student's t-test was used for continuous variables. A p-value less than 0.05 was considered statistically significant.

## Results

A total of 100 patients were prospectively evaluated by assigning 50 patients to each group. Demographic data (age, gender, and BMI), stone characteristics (size, location, and laterality), and SWL characteristics (SWL duration, energy, and number of shock waves) were similar in both groups (Table 1).

There was no statistically significant relationship between the groups between the baseline STAI-S (43.89±7.63 and 42.5±4.77, respectively) and STAI-T (38.1±3.37 and 37.06±4.97, respectively) values measured before SWL (p=0.51 and p=0.46, respectively). STAI-S after SWL (42.89±9.24 and 35.42±4.52, respectively) was statistically significantly lower in the music therapy group (p=0.02) (Figure 1). While VAS (6.66±2.19 and 5.19±2.23, respectively) was statistically significantly lower in the music group (p=0.03), satisfaction (1.55±0.69 and 2.06±0.93, respectively) and willingness to repeat (1.52±0.78 and 2.19±0.98, respectively) scores were statistically significantly higher in the Music group (p=0.04 and p=0.03, respectively) (Table 2).

## Discussion

There are various factors that can cause patients' perceptions of pain to increase and cause high anxiety during SWL. Patients may feel pain from the direct effect of shock waves on cutaneous pain receptors, muscles, and skeletal structures such as the ribs, as well as from the

| Table 1. Demographic data, stone, and SWL characteristics | | | |
|---|---|---|---|
| | **Control group (n=50)** | **Music group (n=50)** | **p-value** |
| Age (years) (Mean ± SD) | 43.24±10.61 | 41.78±11.23 | 0.56[a] |
| **Gender n (%)** | | | 0.8[b] |
| Male | 29 (58%) | 31 (62%) | |
| Female | 21 (42%) | 19 (38%) | |
| BMI (kg/m$^2$) (Mean ± SD) | 26.63±3.16 | 26.4±2.48 | 0.83[a] |
| Stone size (mm) (Mean + SD) | 10.53±3.37 | 10.19±3.84 | 0.69[a] |
| **Stone location n (%)** | | | 0.68[b] |
| Renal pelvis | 30 (60%) | 33 (66%) | |
| Upper ureteral | 20 (40%) | 17 (34%) | |
| **Stone laterality n (%)** | | | 0.52[b] |
| Right | 14 (28%) | 18 (36%) | |
| Left | 36 (72%) | 32 (64%) | |
| SWL duration (min.) (Mean ± SD) | 30.64±3.40 | 31±2.39 | 0.69[a] |
| SWL energy (kV) (Mean ± SD) | 18.77±3.73 | 17.73±3.29 | 0.41[a] |
| Number of shockwaves (Mean ± SD) | 2707.4±303.73 | 2662.5±368.74 | 0.71[a] |

[a]: Student's t-test, [b]: Chi-squared
BMI: Body mass index, SWL: Shock wave lithotripsy, SD: Standard deviation

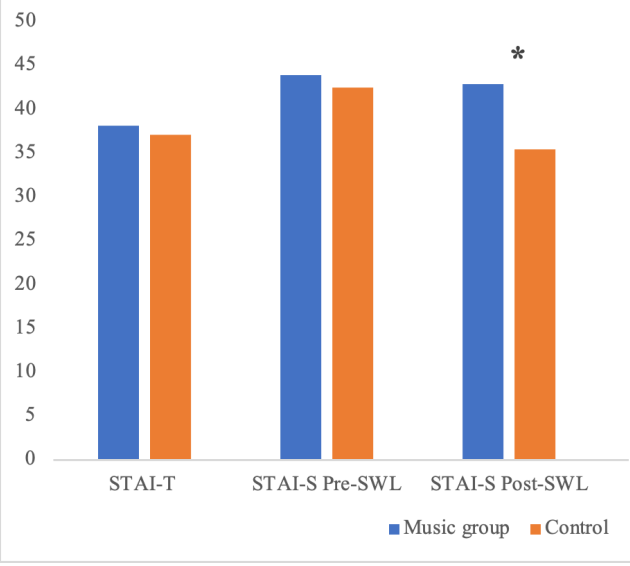


**Figure 1.** Comparison between groups; STAI-T, STAI-S pre-SWL and STAI-S post-SWL scores. *: Statistically significant difference between groups (p<0.05)
*SWL: Shock wave lithotripsy, STAI-S: State-trait anxiety inventory-state, STAI-T: State-trait anxiety inventory-trait*

formation of tension in the kidney capsule (10). Patients may feel anxious and stressed as the procedure is held alive by the SWL device (11). High anxiety may cause irregular breathing, which may be difficult to focus on the stone and prevent the maximum energy transmission, while pain may affect patient tolerability and patient comfort (5). Patients with high anxiety tend to have higher pain scores, and they affect each other indirectly (12). Many

| Table 2. Comparison between groups; Pre-SWL STAI-T, STAI-S scores and post-SWL VAS, satisfaction, willingness to repeat, and STAI-S scores | | | |
|---|---|---|---|
| | **Control group (n=50)** | **Music group (n=50)** | **p-value** |
| STAI-T (Mean ± SD) | 38.1±3.37 | 37.06±4.97 | 0.46[a] |
| STAI-S Pre-SWL (Mean ± SD) | 43.89±7.63 | 42.5±4.77 | 0.51[a] |
| STAI-S Post-SWL (Mean ± SD) | 42.89±9.24 | 35.42±4.52 | 0.02*[a] |
| VAS-Pain (0-10) (Mean ± SD) | 6.66±2.19 | 5.19±2.23 | 0.03*[a] |
| Patient satisfaction (0-4) (Mean ± SD) | 1.55±0.69 | 2.06±0.93 | 0.04*[a] |
| Willingness to repeat (0-4) (Mean ± SD) | 1.52±0.78 | 2.19±0.98 | 0.03*[a] |

*Statistically significant, [a]: Student's t-test
SWL: Shock wave lithotripsy, SD: Standard deviation, STAI-S: State-trait anxiety inventory-state, STAI-T: State-trait anxiety inventory-trait, VAS: Visual analog scale

studies have shown a positive effect of music therapy on pain, anxiety, and hemodynamic parameters in various procedures (13-16). We found that music therapy during SWL reduced anxiety and pain scores. We also found that patient satisfaction and willingness to repeat the procedure increased with music therapy.

We think that besides the relaxing and stress-reducing effects of music therapy, it reduces anxiety levels by masking the disturbing sounds of the device. Music therapy has previously been shown to reduce pain perception by activating the cingulofrontal cortex, and this pathophysiology explains the relationship between pain and music therapy (17,18). We can also say that

distracting has a positive effect. Pharmacological and non-pharmacological interventions were applied to increase patient compliance by reducing pain and anxiety levels that affect patient compliance. Although pharmacological methods such as anesthesia, sedative agents, opioids, and analgesics are effective, they have limitations such as cost, side-effect profiles, and addiction potential (19,20). Non-pharmacological methods have been found interesting because they have fewer side effects and because many studies have been conducted (6,21,22). We also examined the effect of music therapy, which can be an alternative to pharmacological methods. The lack of side effects and cost are the biggest advantages of this method. Additionally, while pharmacological pain-reducing methods only reduce pain, they do not have a direct effect on the patient's anxiety. However, we think that music has a direct effect on both anxiety and pain.

In one of the first studies to examine the effect of music therapy on SWL, it was shown to help significantly reduce the need for analgesia (alfentanil) (23). Yilmaz et al. (12) compared intravenous 2 mg midazolam with music therapy and reported the anxiolytic effect of music. Çift and Benlioglu (24) reported that STAI and VAS scores were significantly lower compared to the control group in their study, in which they had patients listen to different types of music with headphones. Karalar et al. (25) had the patients listen to Turkish classical music with and without noise-cancelling headphones during SWL, and they found a significant decrease in VAS and STAI scores in the groups that listened to music compared to the control group. They claimed that listening to music with headphones was more effective than listening to music without headphones. Dogan and Ceylan (26) reported that the application of music therapy before or during the procedure had a similar effect.

In most of these studies, music was played through a headset, and the type of music was generally determined by the researchers. However, listening to music with headphones changes according to people's listening habits. The weakness of these studies may be that the patients' music listening habits were not questioned. We think the headset itself can be an uncomfortable factor for some people. Another weakness was that researchers usually determined the type of music that patients would listen to. Music type preferences may vary from person to person, and many reasons, such as mood changes and socio-cultural level, may affect this preference. In our study, we did not use headphones to listen to music, as we thought that it might disturb the comfort of the patients. We left the type of music to be listened to and the adjustment of the music volume to the patients' preference. We believe that this way, the patients are more comfortable and their anxiety regresses more easily. Additionally, we believe that it should not be forgotten that it is not always possible to provide ideal standardization since the scales used to be measured in such studies are subjective criteria such as pain and anxiety.

### Study Limitations

Firstly, we did not evaluate the relationship between music types. Secondly, we did not examine the effect of music therapy on stone-free rates. Third, although we found that patients' pain scores decreased with music therapy, we did measure their pain medication needs. Despite these limitations, our strength is that we selected all patients from those who received the first SWL session and formed a more homogeneous group.

## Conclusion

Music therapy during SWL is an inexpensive and effective method to reduce patient anxiety and the patient's perception of pain. We think that adding this practical and effective method to the SWL procedure will increase the patient's compliance with the treatment.

### Ethics

**Ethics Committee Approval:** The ethical permission for the research was obtained from the University of Health Sciences Turkey, Basaksehir Cam and Sakura City Hospital Local Ethics Committee (approval number: 2021.04.64, date: 28.04.2021).

**Informed Consent:** Informed consent was obtained from all patients.

**Peer-review:** Externally and internally peer-reviewed.

### Authorship Contributions

Concept: M.B., Design: M.B., E.K., Data Collection and/or Processing: M.E., E.D., Analysis and/or Interpretation: M.B., O.C., H.L.C., Literature Research: M.B., O.C., Writing: M.B.

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

**Financial Disclosure:** The authors declared that this study received no financial support.

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Original Article

DOI: 10.4274/haseki.galenos.2022.8419
Med Bull Haseki 2022;60:411-418

# Evaluation of the Relationship Between Quality of Life, Serum 25 (OH) Vitamin D Levels, and Anxiety and Depression in Patients with Irritable Bowel Syndrome: A Case-Control Study

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**Abstract**

**Aim:** Recent data have highlighted the association between serum vitamin D deficiency and gastrointestinal system diseases and the effect of vitamin D on intestinal functions. Our study assesses the relationship between IBS disease and quality of life, depression, anxiety, and serum vitamin D levels.

**Methods:** The study was conducted between January 1st, 2020, and April 30th, 2020. The study data were collected from patient files and the hospital's digital file system. A total of 142 patients with IBS and 142 patients from non-IBS control groups were enrolled in this study. ROMA IV criteria were used to diagnose IBS. Accordingly, the SF-36 quality of life scale score, serum vitamin D levels, the Hamilton depression rating scale (HDRS), the Beck anxiety inventory (BAI), and the participants' scores were evaluated.

**Results:** The univariate analysis showed that marital status, body mass index, smoking status, glomerular filtration rate, serum albumin, alanine aminotransferase and aspartate aminotransferase levels were not associated with disease risk. A higher level of education, a low serum vitamin D level, a decrease in physical component scale and mental component scale scores, and increasing BAI and HDRS scores increased the disease risk ($p=0.003$, $p<0.001$, $p<0.001$, $p<0.001$, $p=0.008$, $p<0.001$ and $p<0.001$ respectively).

**Conclusion:** We propose that a high education level, low serum vitamin D, and an increase in BAI and HDRS scores may be independent risk factors for IBS.

**Keywords:** Vitamin D, irritable bowel syndrome, quality of life, anxiety, depression

## Introduction

Irritable bowel syndrome (IBS) is a chronic gastrointestinal system disease that causes abdominal bloating, pain, and changes in bowel habits (1). Although its etiopathogenesis is not well known, many factors have been implicated as causative factors, including genetics, the endocrine system, emotional stress, and axial disease between the brain and the intestinal microbiota. Furthermore, the global prevalence of IBS currently stands between 10 and 20% (2,3). The associations between IBS and diseases such as chronic fatigue syndrome, depression, anxiety disorder, fibromyalgia, headache, and sexual dysfunction have also been observed (4). Furthermore, IBS also increases emotional stress with changes in bowel habits, such as chronic abdominal pain, persistent diarrhea, or constipation, resulting in a person's quality of life being negatively affected. Recurrent symptoms worsen a person's mental and social health (5,6). In IBS patients, the presence of symptoms, the frequencies and durations of these symptoms, the treatment modalities used, and IBS-related changes in diet and psychological state affect the quality of life. The presence of extra-intestinal symptoms and the severity of the symptoms also affect the quality of life of patients with IBS in a negative direction. Additionally, it was found that low educational and sociocultural levels render coping with IBS and its

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**Received:** 22.04.2022 **Accepted:** 30.10.2022

symptoms difficult, thus negatively affecting the quality of life of IBS patients (7,8).

When compared with normal individuals in the community, the psychological status and recurrent gastrointestinal symptoms of patients with IBS reduce their quality of life (9). Furthermore, patients' quality of life is also affected by the duration of the illness, the frequency of symptoms, their adaptation to the illness, and the training they receive about the illness. Moreover, factors such as receiving an IBS diagnosis, having fears and worries about the disease, lacking information on diagnosis and treatment, and being unable to cope with problems can negatively impact the patient's quality of life (10).

Gastrointestinal disease can lead to the malabsorption of certain compounds, such as vitamin D, thereby causing a deficiency in this vitamin. Globally, the prevalence of hypovitaminosis D is between 30 and 50% (11). The primary role of vitamin D is in calcium metabolism. Additionally, more than 200 genes have been implicated in the proliferation, apoptosis, and differentiation of vitamin D during the cell cycle. The vitamin D receptor can be found in the central nervous system, immune system, and intestines (12,13). The relationship between vitamin D and IBS disease is vague. Recently, high-dose vitamin D treatment has been deemed beneficial for patients with diarrhea-predominant IBS. Nonetheless, the effect of vitamin D in such instances remains unclear. It is unclear whether vitamin D helps reduce the symptoms of IBS or whether it lessens the symptoms of anxiety and depression, which are commonly observed in patients with IBS (14,15). Notably, there is a significant relationship between vitamin D deficiency and anxiety and depression, yet the effect of vitamin D deficiency on patients' quality of life remains unclear (16).

In our study, we sought to examine the complex and unclear association between IBS disease, quality of life, depression, anxiety, and vitamin D by comparing patients with IBS with healthy individuals and by evaluating potential associations in this network of relationships.

## Materials and Methods

### Compliance with Ethical Standards

Written informed consent was obtained from all participants, and the study protocol was approved by the University of Health Sciences Turkey, Erzurum Regional Training and Research Hospital Clinical Research Ethics Committee (2020/01-07). The authors report no conflicts of interest and no grant support. This research did not receive any specific grant from funding agencies from within the public, commercial, or not-for-profit sectors.

### Study Design

The study involved 242 patients with IBS who were diagnosed based on the Rome IV criteria. An additional 258 healthy, non-IBS patients also took part in the study. All participants were admitted to the internal medicine outpatient clinic between January 1, 2020, and April 30, 2020. Moreover, study participants were aged between 26 and 50 years.

Of the 242 individuals initially selected to be included in the control group, 100 were excluded from the study because of viral hepatitis, liver diseases, intestinal malabsorption, and other intestinal diseases. Of the 254 patients with IBS initially selected to be included in the patient group, 56 patients were excluded from the study due to a history of active infection and drug use, and 48 patients were excluded from the study due to meeting one or more of the criteria listed in the study exclusion criteria (Figure 1).

### The Inclusion Criteria

To be diagnosed with IBS according to the ROMA IV criteria in the age range of 26-50 years.

### The Exclusion Criteria

Hepatitis B and C disease, hepatosteatosis, and other liver diseases; bile duct pathologies; malabsorption (including celiac disease); diabetes mellitus; any malignancy; pregnancy; lactation; active infection; history of alcohol use; dyspepsia; peptic ulcer; inflammatory bowel disease; gastroesophageal reflux disease; individuals taking active vitamin D, vitamin C, and fish oil; individuals taking active vitamin D.

### Participants and Recruitment

One hundred and forty-two IBS and 142 control groups, who were matched for age and gender, were included in the study. Thus, this served to eliminate the age and gender factors from the cases remaining after the application of the exclusion criteria. Information on the participants' marital status and education levels was also collated. For all patients with IBS, the symptoms' frequency and the duration of the illness were recorded. Following 12 h of fasting, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and albumin tests were assessed in the participants. Moreover, the glomerular filtration rate (GFR) and the participant's body mass index (BMI) were calculated.

### Vitamin D

The participants' blood samples were collected in ethylene diamine tetraacetic acid tubes. The blood was centrifuged and collected in microcentrifuge tubes. Serum 25-hydroxyvitamin $D_2$/D3 levels were determined using an ARCHITECT 5P02 enzyme immunoassay kit and an Abbott ARCHITECT analyzer. Vitamin D levels were measured in

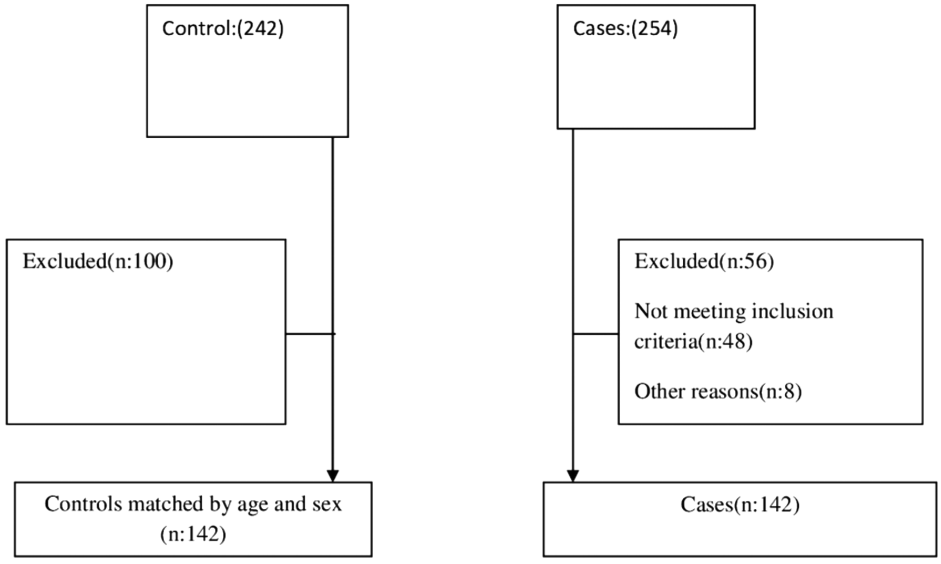


**Figure 1.** Flow diagram of the study

January. Participants were considered deficient if their serum 25(OH) vitamin D3 levels were less than 30 nmol/L. Serum 25(OH)D3 deficiency was determined if levels were between 30 and 50 nmol/L. Serum 25(OH)D3 vitamin levels in participants were considered adequate if they were greater than 50 nmol/l.

Participants' quality of life levels, anxiety levels, and depression levels were evaluated using the SF-36 Quality of Life Scale, the Beck anxiety inventory (BAI), and the Hamilton depression scale, respectively.

### SF-36 Quality of Life Questionnaire

The SF-36 questionnaire encompasses both physical and mental health components and consists of two subscales and eight scales (17). The sections of the subscale are A. Physical health Group: 1. physical function; 2. role limitations due to physical problems; 3. pain; and 4. the general perception of health. B. Mental health Group: 5. energy/vitality, 6. social function, 7. role limitations because of emotional problems, and 8. mental health. In summary, the higher the scale score, the higher the level of quality of life.

### Beck Anxiety Inventory

BAI was developed in 1961 by Beck et al. (18). It is a Likert-type self-reporting scale consisting of 21 items, where a score of 0-3 can be assigned to each item. The higher the total score, the higher the anxiety level experienced by the individual. Specifically, for this study, participants with a score of eight points and above were identified as experiencing anxiety.

### Hamilton Depression Scale

Hamilton (19) developed this scale to measure depression levels. The upper limit of the scale stands at 53 points, and patients scoring less than eight points are considered normal. 8- Scores of 8-16 were accepted as mild-moderate depression and scores of 17 and above as severe depression. Once again, for this study, a score of 8 or above was considered to signify depression.

### Statistical Analysis

The collated data were recorded in a spreadsheet, and statistical analyses were performed using SPSS Version 22 (IBM Corp. in Armonk, NY). The Shapiro-Wilk test was used to evaluate the distribution of the data. Descriptive data were presented as the median with an interquartile range (IQR) for non-normally distributed numerical data. Categorical data were presented using the frequency (n) and percentage (%). Pearson's chi-square test was used to compare categorical variables, and the Mann-Whitney U test was used to compare numerical variables among IBS and non-IBS groups. The disease risk was determined by univariate and multivariate binary logistic regression analyses. Demographics, clinical characteristics, health-related quality of life status, anxiety, and depression scores were included in the multivariate logistic regression model. Disease risk was assessed using odds ratios with 95% confidence intervals. A p-value where $p<0.05$ was considered statistically significant.

## Results

Patients with IBS had a statistically significant higher education level, lower serum vitamin D level, and higher albumin level compared with non-IBS patients ($p<0.001$, $p<0.001$, and $p=0.012$, respectively). In contrast, all the serum albumin levels were within the reference range (3.5 to 5.5 g/dL). Of the patients with IBS, 39 reported a daily

symptom frequency, and more than 65% suffered from disease symptoms at least one day a week. Nearly one-third of patients with IBS have had the disease for one to five years (Table 1).

Table 2 lists the health-related quality of life status, anxiety, and depression scores of the patients. All subdomain, physical component scale (PCS) and mental component scale (MCS) scores were significantly higher in non-IBS patients, thus indicating that patients with IBS had a lower health-related quality of life than non-IBS patients. Furthermore, anxiety and depression scores were significantly higher in patients with IBS compared to non-IBS patients (p=0.004 and p<0.001, respectively) (Table 2).

The univariate analysis showed that marital status, BMI, smoking status, GFR, serum albumin, ALT, and AST levels were not associated with disease risk. A higher level

**Table 1.** Demographics and clinical characteristics

| **Variables** | **IBS (n=142)** | **Non-IBS (n=142)** | **p-value** |
|---|---|---|---|
| Age (years), Median (IQR) | 38.0 (26.0-50.0) | 38.0 (26.0-50.0) | - |
| Female, n (%) | 80 (56.3) | 80 (56.3) | - |
| Marital status, n (%) | | | |
| Single | 45 (31.7) | 51 (35.9) | 0.452* |
| Married | 97 (68.3) | 91 (64.1) | |
| Education level, n (%) | | | |
| Primary | 31 (21.8) | 64 (45.1) | <0.001* |
| Secondary | 78 (54.9) | 71 (50.0) | |
| Higher | 33 (23.2) | 7 (4.9) | |
| Current smoking status, n (%) | | | |
| Smoker | 57 (40.1) | 61 (43.0) | 0.630* |
| Non-smoker | 85 (59.9) | 81 (57.0) | |
| BMI (kg/m$^2$), Median (IQR) | 27.1 (25.1-28.2) | 26.8 (25.3-27.9) | 0.636** |
| Normal weight, n (%) | 31 (21.8) | 27 (19.0) | 0.140* |
| Overweight, n (%) | 92 (64.8) | 105 (73.9) | |
| Obese, n (%) | 19 (13.4) | 10 (7.1) | |
| 25(OH) vitD (nmol/L), Median (IQR) | 13.0 (9.4-16.7) | 16.1 (14.3-18.8) | <0.001** |
| Insufficiency, n (%) | 6 (4.2) | 9 (6.3) | 0.426* |
| Deficiency, n (%) | 136 (95.8) | 133 (93.7) | |
| GFR (mL/min/1.73 m$^2$), Median (IQR) | 99.7 (94.6-109.6) | 101.8 (92.4-111.8) | 0.454** |
| Albumin (g/dL), Median (IQR) | 4.5 (4.3-4.6) | 4.3 (4.2-4.6) | 0.012** |
| ALT (U/L) | 17.0 (13.0-27.0) | 17.5 (15.0-22.0) | 0.487** |
| AST (U/L) | 18.0 (15.0-22.0) | 18.0 (16.0-22.0) | 0.181** |
| Symptom frequency, n (%) | | | |
| Everyday | 39 (27.5) | | |
| 4 to 6 days per week | 37 (26.1) | | |
| 2 to 3 days per week | 8 (5.6) | | |
| 1 day per week | 7 (4.9) | | |
| 2 to 3 days per month | 17 (12.0) | | |
| 1 day per month | 34 (23.9) | | |
| Disease duration, n (%) | | | |
| 1-5 years | 46 (32.4) | | |
| 6-10 years | 33 (23.2) | | |
| 11-15 years | 24 (16.9) | | |
| 16-20 years | 14 (9.9) | | |
| More than 20 years | 25 (17.6) | | |

Note: Mean vitamin D level of the IBS group was statistically significantly lower than that of the control group.
*Pearson chi-square test was used. **Mann-Whitney U test was used.
IBS: Irritable bowel syndrome, IQR: Interquartile range, BMI: Body mass index, GFR: Glomerular filtration rate, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase

of education, a low serum vitamin D level, a decrease in PCS and MCS scores, and increasing BAI and Hamilton depression rating scale (HDRS) scores increased the disease risk (p=0.003, p<0.001, p<0.001, p<0.001, p=0.008, p<0.001 and p<0.001 respectively). Additionally, two multivariate regression analysis models were also performed. In the first model, the education level, serum vitamin D level, BAI, and HDRS scores were similar, but the significance was lost between PCS, MCS, and disease risk. In the second model, all variables included in the analysis had a significant association with disease risk (Figure 2). Consequently, a higher education level, decreasing serum vitamin D levels, and increases in the BAI and HDRS scores were independent risk factors for IBS (Table 3).

## Discussion

Evaluation of the quality of life scores between the IBS group and the healthy groups in this study using the SF-36 questionnaire established lower quality of life scores in the IBS group compared to the healthy group. Moreover, the difference between the results was deemed statistically significant. These findings agree with the study by Buono et al. (20), which examined 1102 patients with IBS and a healthy control group using the SF-36 quality of life questionnaire. The scores generated were also lower in patients with IBS, and the difference was found to be statistically significant. Furthermore, a study by Addante et al. (21) involving 290 patients with IBS and a healthy group also reported a lower quality of life for the IBS group compared to the control group. Thus, the findings of this study were concordant with the literature, as they established that the quality of life of the IBS group was lower in all parameters compared with the control group. Thus, we propose that the prolonged disease duration and the high frequency of symptoms in the patients with IBS contributed to reducing the patients' quality of life.

We also found a significant association between the participants' education levels and IBS disease. While the rate was higher in patients with IBS who had a primary or secondary education level, we found that the rate of IBS

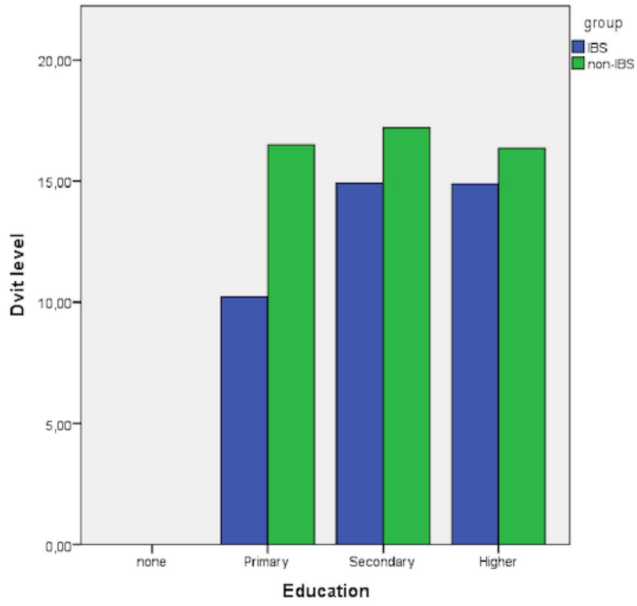


**Figure 2.** IBS and control group of vitamin D levels according to education in levels

*IBS: Irritable bowel syndrome*

**Table 2. Health-related quality of life and mental health status**

| Variables | IBS (n=142) | Non-IBS (n=142) | p-value |
|---|---|---|---|
| SF-36, Median (IQR) | | | |
| PF | 49.0 (40.0-61.0) | 53.0 (45.0-66.0) | 0.001* |
| RP | 47.5 (41.0-58.0) | 52.0 (45.0-62.3) | 0.001* |
| BP | 49.0 (42.0-58.3) | 53.0 (47.0-65.3) | <0.001* |
| GH | 49.0 (41.0-62.0) | 54.0 (46.0-64.3) | 0.008* |
| VT | 49.0 (39.0-63.0) | 53.0 (46.0-66.0) | 0.007* |
| SF | 49.0 (40.0-61.0) | 53.0 (45.0-66.0) | 0.001* |
| RE | 48.5 (40.0-61.3) | 52.5 (44.0-64.0) | 0.011* |
| MH | 48.0 (41.0-61.0) | 52.0 (45.0-63.5) | 0.005* |
| PCS | 38.8 (35.6-42.8) | 40.3 (37.5-45.1) | <0.001* |
| MCS | 38.9 (35.6-45.3) | 40.9 (37.4-47.0) | 0.004* |
| BAI, Median (IQR) | 5.0 (3.8-10.3) | 4.0 (2.0-6.0) | <0.001* |
| HDRS, Median (IQR) | 4.0 (3.0-6.0) | 3.0 (3.0-5.0) | <0.001* |

Note: Quality of life scale parameters were found to be statistically significantly lower in the IBS group than in the control group. On the other hand, anxiety and depression questionnaire scores were higher in the IBS group.
IBS: Irritable bowel syndrome, SF-36: 36-Item short form survey, IQR: Interquartile range, PF: Physical functioning, RP: Role limitation due to physical problems, BP: Bodily pain, GH: General perception of health, VT: Energy and vitality, SF: Social functioning, RE: Role limitation due to emotional problems, MH: Mental health, PCS: Physical component scale, MCS: Mental component scale, BAI: Beck anxiety inventory, HDRS: Hamilton depression rating scale

was lower in those with a higher education level. Thus, we conclude that education is an independent risk factor for IBS. Choghakhori et al. (22) found no difference in education levels in a study conducted between 90 patients with IBS and a control group. In a study by Chatila et al. (23) with 553 participants, no significant relationships were identified between the participants' education level and IBS, although they reported higher rates of IBS in individuals with university education. In this study, although the ratio was higher in individuals who secured education at the primary and secondary education levels, the risk of IBS was found to be statistically significant in individuals with medium and higher education levels, following a two-tailed analysis of the data. We propose that the discrepancies in the findings compared to the literature may be due to socioeconomic differences in societies.

Changes in the gut microbiota, inflammation, and the release of proinflammatory cytokines may cause changes in the gut-brain axis. Consequently, this process may negatively affect the hypothalamic-pituitary-adrenal gland axis, which contributes to stress in the body. Excessive cortisol release caused by the hypothalamus-pituitary-adrenal axis secondary to inflammation contributes to emotional stress. Excessive cortisol release has also been associated with anxiety and depression. Despite the complex relationships in the brain-gut axis, it contributes biologically, socially, and psychologically to pathophysiology (24,25). The findings of this study demonstrated higher anxiety and depression scores for patients with IBS compared to the control group. In the study by Zamani et al. (26), the rate of anxiety in patients with IBS was 39.1%, which was 3.1 times higher than that in healthy individuals. Similarly, depression was observed at a rate of 28.8%, which equates to being 3.08 times more common in patients with IBS compared to the healthy population. Despite a similar finding in this study, the data do not fully reveal whether depression causes IBS or whether IBS symptoms that worsen lead to depression. Thus, we propose that depression and anxiety disorders are independent risk factors for IBS. However, the findings are unclear, and further studies on intestinal microbiota with larger participant groups are needed.

The findings of our study indicated that patients with IBS had lower vitamin D levels compared with the control group and that 95.8% of patients with IBS had a vitamin D deficiency. These findings agree with some recent studies. Khayyat and Attar (14) concluded that 82% of patients with IBS had a vitamin D deficiency, and Abbasnezhad et al. (11) found this rate to be 85%. We attribute the higher rate noted in this study to the environmental conditions and the measurement of vitamin D levels in

**Table 3. Univariate and multivariate regression analysis of the patient characteristics for disease risk**

| Characteristics | | Univariate | | Multivariate model 1 | | Multivariate model 2 | |
|---|---|---|---|---|---|---|---|
| | | OR (95% CI) | p-value | OR (95% CI) | p-value | OR (95% CI) | p-value |
| Marital status | Single | Ref | | | | | |
| | Married | 1.21 | 0.452 | | | | |
| Education level | Primary | Ref | | Ref | | Ref | |
| | Secondary | 2.27 (1.33-3.88) | **0.003** | 3.77 (1.94-7.32) | **<0.001** | 3.98 (2.07-7.63) | **0.003** |
| | Higher | 9.73 (3.87-24.46) | **<0.001** | 13.30 (4.58-38.60) | **<0.001** | 14.80 (5.23-41.88) | **<0.001** |
| BMI | | 1.05 (0.98-1.13) | 0.176 | | | | |
| Smoking status | Non-smoker | Ref | | | | | |
| | Smoker | 0.89 (0.56-1.43) | 0.630 | | | | |
| 25(OH) Vit D level | | 0.90 (0.85-0.94) | **<0.001** | 0.88 (0.83-0.94) | **<0.001** | 0.88 (0.83-0.93) | **<0.001** |
| GFR | | 0.99 (0.97-1.02) | 0.498 | | | | |
| Albumin | | 2.01 (0.87-4.67) | 0.103 | | | | |
| ALT | | 1.01 (0.99-1.03) | 0.321 | | | | |
| AST | | 1.01 (0.98-1.03) | 0.519 | | | | |
| PCS | | 0.90 (0.85-0.95) | **<0.001** | 0.91 (0.77-1.09) | 0.302 | | |
| MCS | | 0.94 (0.90-0.98) | **0.008** | 1.10 (0.97-1.25) | 0.123 | | |
| BAI | | 1.24 (1.15-1.35) | **<0.001** | 1.18 (1.05-1.33) | **0.007** | 1.15 (1.05-1.27) | **<0.001** |
| HDRS | | 1.29 (1.13-1.47) | **<0.001** | 1.24 (1.06-1.44) | **0.007** | 1.20 (1.05-1.38) | **<0.001** |

Note: The univariate analysis showed that marital status, BMI, smoking status, GFR, serum albumin, ALT, and AST levels were not associated with disease risk. A higher level of education, low serum vitamin D level, decrease in PCS and MCS scores, and increasing BAI and HDRS scores increased the disease risk.
*Pearson chi-square test was used, **Mann-Whitney U test was used.
OR: Odds ratio, CI: Confidence interval, Ref: Reference category, BMI: Body mass index, GFR: Glomerular filtration rate, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, PCS: Physical component scale, MCS: Mental component scale, BAI: Beck anxiety inventory, HDRS: Hamilton depression rating scale

the winter months. Vitamin D is central to the regulation of calcium and phosphorous metabolism. Furthermore, it has immune-modulatory and anti-inflammatory properties. The intestine is rich in microflora. Thus, the intestine is an important region in terms of inflammatory events that can be activated by T helper type 1 cells. One study reported that inflammation in the intestine affects vitamin D regulation (27). The 1-alpha hydroxylase enzyme found in the kidneys converts calcitriol into 1.25-dihydroxyvitamin D. This enzyme is also involved in the regulation of the epithelial barrier and inflammation. Notably, increased inflammation in the intestines can impair the functions of this enzyme, thereby impairing IBS symptoms and intestinal function (28). Currently, the findings in the literature do not clarify whether a vitamin D deficiency or insufficiency is a predisposing factor to IBS disease or whether the vitamin D level worsens the prevailing symptoms of existing IBS disease. The findings of our study did not indicate a statistically significant relationship between vitamin D deficiency or insufficiency and IBS. Nonetheless, the data did indicate that patients with low vitamin D levels had a higher risk of IBS than the normal group.

### Study Limitations

The study limitations included the investigation of a single center, a small number of participants, and disregarding the patients' dietary habits. Apart from these limitations, comparing patients with IBS with a control group of matching age and gender characteristics and evaluating the quality of life along with psychological factors such as anxiety and depression can be cited among the study's strengths.

## Conclusion

Our study sought to contribute to the literature on the relationship between IBS disease, psychological factors, and vitamin D, which are considered current research topics. We propose that education, anxiety, depression, and vitamin D status are all independent risk factors for IBS. However, the findings on this subject are unclear. Accordingly, we recommend that prospective studies with larger participant numbers and the examination of other factors further investigate IBS.

### Ethics

Ethics Committee Approval: The study was approved by the University of Health Sciences Turkey, Erzurum Regional Training and Research Hospital Clinical Research Ethics Committee (2020/01-07).

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

**Peer-review:** Externally peer-reviewed.

**Authorship Contributions**

Concept: M.B., K.C., Design: M.B., K.C., Data Collection, or Processing: M.B., K.C., Analysis, or Interpretation: M.B., K.C., Literature Search: M.B., K.C., Writing: M.B., K.C.

**Conflict of Interest:** The authors report no conflicts of interest and no grant support. The authors alone are responsible for the content and writing of the paper.

**Financial Disclosure:** This research did not receive any specific grant from funding agencies from within the public, commercial, or not-for-profit sectors.

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Original Article

DOI: 10.4274/haseki.galenos.2022.8326
Med Bull Haseki 2022;60:419-424

# The Effect of Weekday Preference on Length of Stay in Unilateral Bicompartmental Total Knee Arthroplasty

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**Presented in:** The manuscript was presented at "9. Ortopedi ve Travmatoloji Istanbul Bulusmasi" (PS-26) in 02.04.2022.

## Abstract

**Aim:** There are few studies in the literature evaluating the effect of the day of surgery on length of hospital stay. This study evaluates the effect of the day of surgery on the duration of hospitalization in unilateral primary total knee arthroplasty (TKA) in a group of hospitals providing wide-ranging health services and clarifies the implications for reducing economic burdens.

**Methods:** Between March 2020 and January 2022, patients treated by TKA with the code P612420 according to the Health Practice Communique were retrospectively scanned in a group of hospitals with different levels. Patients who underwent bilateral TKA on the same day or during hospitalization, underwent any secondary surgical procedures, or developed early complications were excluded from the evaluation.

**Results:** The data of 743 patients who underwent unilateral TKA were evaluated. The mean hospital stay was 3.32 (2-14) days. It was seen that the shortest hospitalization periods were in the surgeries performed on Saturday (3.15 days), while the longest ones were on Friday (3.62 days). It was found that the patients who underwent surgery on Saturday had significantly shorter hospital stays than on Friday (p=0.006).

**Conclusion:** While planning TKA, the choice of surgery day is a factor that should be addressed to reduce hospital stays and, therefore, costs.

**Keywords:** Arthroplasty, replacement, knee, length of stay, financial stress

## Introduction

Total knee arthroplasty (TKA) is a widely used surgical procedure for end-stage knee arthrosis. This surgical procedure is cost-effective, but efforts to reduce costs are still ongoing. The length of hospital stay (LOS) is the factor that creates the most financial burden after TKA (1). Recently, LOS has been reduced with the help of clinical guidelines for (2-4). Therefore, a decrease in LOS reduces the economic burden of TKA.

In addition to the cost impact, LOS is associated with the quality of patient care (5). Some studies show higher patient satisfaction with rapid discharge regimens. The effect of patient- and surgery-related factors such as age, gender, comorbidities, type of anesthesia, and blood transfusions on LOS has been the subject of many studies. Still, there are few studies in the literature evaluating the effect of the day of surgery on LOS (6-8). Although studies and results have been reported in multicenter heterogeneous groups in which hip and knee joint replacements were evaluated, studies on patients in a homogeneous group who underwent only unilateral TKA are limited.

This study evaluates the effect of the day of surgery on LOS in unilateral primary TKA in a group of hospitals that provide wide-ranging health services and proposes inferences to reduce economic burdens.

## Materials and Methods

### Compliance with Ethical Standards

The ethics committee approved the study and the processing of the data to be analyzed before the study

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**Received:** 11.03.2022 **Accepted:** 23.11.2022

was started. Generalized informed consent was obtained from all patients according to the law on the processing of personal data, but there was no specific informed consent obtained due to the study's data analysis. Since the data used in the study were obtained from the hospital registration system, an individual informed consent form was not required. The study was approved by the Istinye University Clinical Research Ethic Committee (approval no: 2017-KAEK-120, decision no: 3/2022.K-32).

### Study Design

Between March 2020 and January 2022, patients treated by TKA in a group of hospitals with different levels inside, according to the Health Practice Communique, were scanned retrospectively through the Hospital Information Management System (WisdomEra). Patients who underwent bilateral TKA on the same day or during hospitalization, who underwent any secondary surgical procedures such as trigger finger, carpal tunnel syndrome, toe arthrodesis, or interventional arthroscopy in the same session with TKA, or who developed early complications, were excluded from the evaluation. Groups were divided by the day of the surgery, and comparisons were performed by evaluating the patients' age, gender, and LOS.

### Data Analysis

WisdomEra's statistics tool, Wanalyzer v1.4.53, is a data analytics platform that uses the SciPy v1.2.3 library (https://www.scipy.org/). SciPy is a Python-based ecosystem of open-source software for mathematics, science, and engineering.

### Statistical Analysis

The Statistical Package for the Social Sciences software (version 24 for macOS) (SPSS Inc., Chicago, IL, USA, 2008) was used for the statistical analysis. Qualitative data were represented as numbers and percentages for categorical variables and calculated by computing each variable's mean and standard deviation. The one-sample Kolmogorov-Smirnov test was used to determine normality. Comparisons of numerical variables between the groups were evaluated with the One-Way ANOVA test. The post hoc comparisons were assessed with the Tukey HSD test. Differences were considered statistically significant when the p-value <0.05.

## Results

The data of 743 patients who underwent unilateral TKA were evaluated. The mean age of the 648 (87.1%) female and 95 (12.9%) male patients was 67.17 (43-92) years. The mean hospital stay was 3.32 (2-14) days (Figure 1). It was seen that 37.4% of the patients underwent surgical treatment in the winter, followed by summer (23.9%), autumn (20.4%), and spring (18.3%) (Figure 2). The autumn TKAs have a statistically significant higher LOS (p<0.001). In the analysis made according to the days of the week, it was seen that the shortest hospitalization periods were in the surgeries performed on Saturday (3.15 days) and Tuesday (3.18 days), while the longest ones were on Friday (3.62 days) and Wednesday (3.47 days) (Table 1 and Figure 3). In

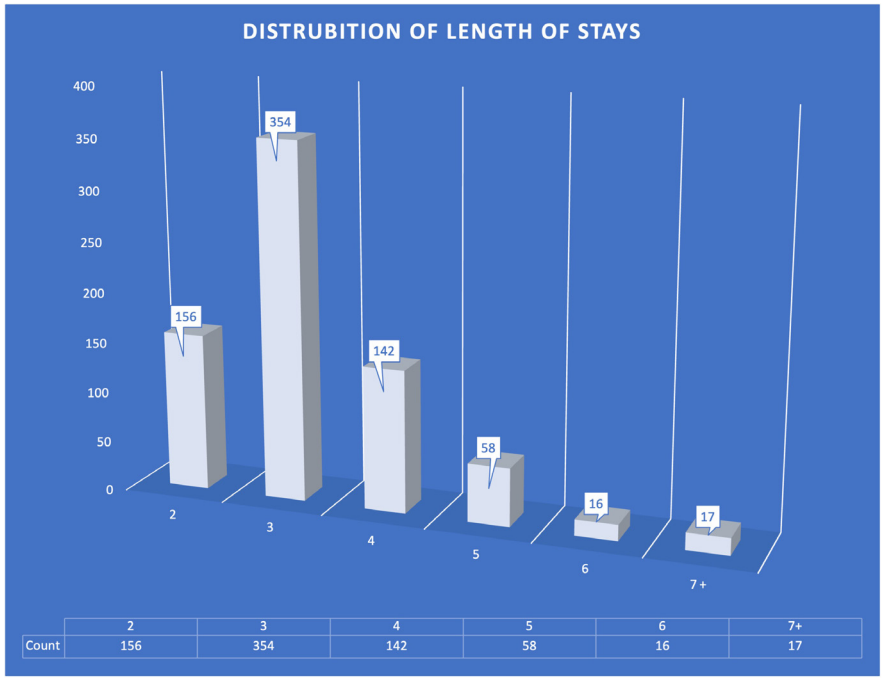


**Figure 1.** Length of stay chart

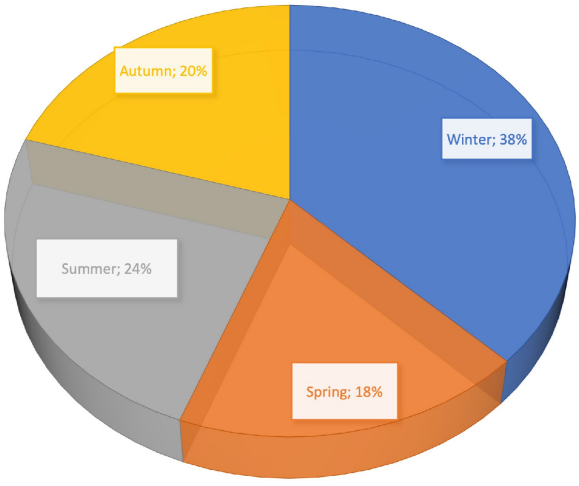


**Figure 2.** Surgery distribution by seasons

the statistical evaluation, the post hoc analysis between the groups determined that the patients who underwent surgery on Saturday had significantly shorter hospital stays than on Friday (p=0.006) (Table 2). Concurrently, the relationship between age and LOS was statistically significant (p<0.01). There was no association between the daytime of the surgery, gender, and LOS (p=0.320 and p=0.356, respectively).

## Discussion

Nowadays, the rising demand for TKA necessitates a reduction in the factors that may cause cost increases (9-11). The most crucial factor in this context is the length of the hospital stay (12,13). Although many studies have evaluated patient- and surgical procedure-related factors influencing LOS (7,14-16), relatively few studies exist on the effect (17,18). In these studies, hip, and knee arthroplasty were evaluated together, and there is no study assessing patients who only underwent unilateral knee arthroplasty. Therefore, we retrospectively determined the effect of the day of surgery on the mean LOS in patients who underwent unilateral, primary, and elective TKA.

**Table 1. The mean LOS table by weekdays**

| Day | | N | Subset for alpha=0.05 | |
|---|---|---|---|---|
| | | | 1 | 2 |
| Tukey HSD[a] | Saturday | 127 | 3.0709 | |
| | Tuesday | 176 | 3.1818 | |
| | Thursday | 110 | 3.2364 | 3.2364 |
| | Monday | 106 | 3.4151 | 3.4151 |
| | Wednesday | 118 | 3.4746 | 3.4746 |
| | Friday | 106 | | 3.6226 |
| | Sig. | | 0.090 | 0.119 |

[a]The statistical analysis was performed by the correlation analysis, Tukey HSD test
LOS: Length of hospital stay

In this study, TKA applications performed on Saturday were significantly shorter than those performed on Friday. Muppavarapu et al. (17) retrospectively analyzed 547 patients who underwent total joint replacement and showed that patients who underwent surgery on Monday or Tuesday had significantly less LOS than those on Thursday or Friday. Similarly, Chen (19) reported that patients who underwent TKA on Monday had 9.5% and 6.4% shorter LOS than those treated on Thursday and Friday, respectively. Reversely, Mathijssen et al. (18) showed an increased LOS for surgeries performed on Thursday. They attribute this situation to the small number of personnel, although discharges can be made on the weekends. Although the study by Newman et al. (8) on

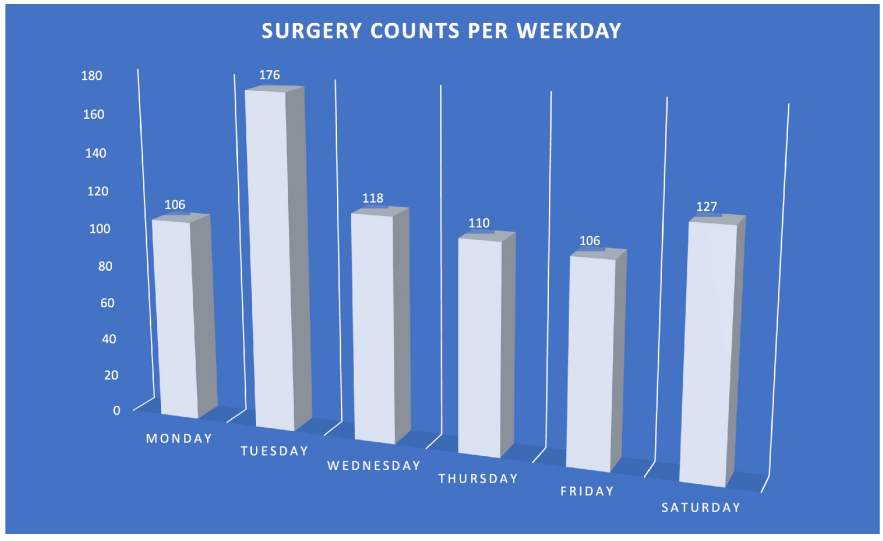


**Figure 3.** Weekday distribution of the surgeries

| Table 2. Tukey comparison of the LOS by weekdays | | | | | | |
|---|---|---|---|---|---|---|
| (I) Day | | Mean difference (I-J) | Std. Error | Sig. | 95% confidence interval | |
| | | | | | Lower bound | Upper bound |
| Monday | Tuesday | 0.23 | 0.15 | 0.599 | -0.183 | 0.650 |
| | Wednesday | -0.06 | 0.16 | 0.999 | -0.513 | 0.394 |
| | Thursday | 0.18 | 0.16 | 0.878 | -0.282 | 0.640 |
| | Friday | -0.21 | 0.16 | 0.799 | -0.673 | 0.258 |
| | Saturday | 0.34 | 0.16 | 0.236 | -0.102 | 0.790 |
| Tuesday | Monday | -0.23 | 0.15 | 0.599 | -0.650 | 0.183 |
| | Wednesday | -0.29 | 0.14 | 0.302 | -0.696 | 0.110 |
| | Thursday | -0.05 | 0.14 | 0.999 | -0.466 | 0.357 |
| | Friday | -0.44 | 0.15 | **0.031** | -0.857 | -0.024 |
| | Saturday | 0.11 | 0.14 | 0.967 | -0.284 | 0.505 |
| Wednesday | Monday | 0.06 | 0.16 | 0.999 | -0.394 | 0.513 |
| | Tuesday | 0.29 | 0.14 | 0.302 | -0.110 | 0.696 |
| | Thursday | 0.24 | 0.16 | 0.654 | -0.211 | 0.687 |
| | Friday | -0.15 | 0.16 | 0.938 | -0.602 | 0.305 |
| | Saturday | 0.40 | 0.15 | 0.084 | -0.030 | 0.837 |
| Thursday | Monday | -0.18 | 0.16 | 0.878 | -0.640 | 0.282 |
| | Tuesday | 0.05 | 0.14 | 0.999 | -0.357 | 0.466 |
| | Wednesday | -0.24 | 0.16 | 0.654 | -0.687 | 0.211 |
| | Friday | -0.39 | 0.16 | 0.160 | -0.847 | 0.075 |
| | Saturday | 0.17 | 0.15 | 0.893 | -0.276 | 0.607 |
| Friday | Monday | 0.21 | 0.16 | 0.799 | -0.258 | 0.673 |
| | Tuesday | 0.44 | 0.15 | **0.031** | 0.024 | 0.857 |
| | Wednesday | 0.15 | 0.16 | 0.938 | -0.305 | 0.602 |
| | Thursday | 0.39 | 0.16 | 0.160 | -0.075 | 0.847 |
| | Saturday | 0.55 | 0.16 | **0.006** | 0.106 | 0.998 |
| Saturday | Monday | -0.34 | 0.16 | 0.236 | -0.790 | 0.102 |
| | Tuesday | -0.11 | 0.14 | 0.967 | -0.505 | 0.284 |
| | Wednesday | -0.40 | 0.15 | 0.084 | -0.837 | 0.030 |
| | Thursday | -0.17 | 0.15 | 0.893 | -0.607 | 0.276 |
| | Friday | -0.55 | 0.16 | **0.006** | -0.998 | -0.106 |

LOS: Length of hospital stay

a large patient series showed that surgeries performed in the second half of the week were associated with an increase in costs and LOS compared to those performed in the first half, our results did not support this conclusion. When the week was evaluated as having two or three parts, no statistically significant difference was found between the subdivisions. The reason for our study result may be that active service continues on Saturdays, and only Sundays are holidays in the group of hospitals whose data was analyzed. The average discharge day of patients who were operated on Friday, which coincided with a Sunday, the day before the planned discharge, may cause a delay in their discharge. Performing joint replacement surgeries early or late in the week in hospitals that provide active service on Saturday does not affect the duration of hospitalization.

Our results also confirm the findings of other studies reporting that prolongation of LOS is associated with increasing age. The literature about age's effect on LOS is clear and well-known (20-22). But the effect of gender on LOS is unclear. Some studies have shown that female patients tend to have an increased LOS (7,23). Reversely, we did not find any correlation between LOS and gender, as Tan et al. (24) showed before.

### Study Limitations

Our study's first and most obvious limitation is that perioperative patient-specific data could not be evaluated, and the data were obtained retrospectively from the

database. Second, since there are different centers where the applications are made, there may be differences arising from the treatment approaches of different surgical teams. Another limitation is that our inferences may not be valid for hospitals where elective surgical treatment is not performed on Saturdays. The most substantial aspect of our study is our sample size in a relatively brief period, consisting of the hospitals of a single health group and the evaluation of isolated unilateral knee arthroplasty applications by excluding additional surgeries that may affect LOS. The fact that the health group consists of a large academic medical center and multiple satellite hospitals is considered a distinct advantage that will enable us to reflect on our findings in general.

## Conclusion

It is crucial to understand and analyze the factors associated with LOS after TKA. Planning unilateral primary TKA surgery on Saturdays or Tuesdays instead of Fridays may reduce costs by shortening hospitalization times. Also, age is an essential risk factor for increased LOS. It is helpful to consider planning before the operation, predicting that LOS may be prolonged in the older age group. Also, the development of programs to standardize the care of TKA and THA patients, including the supervision of discharge procedures, patient management on Sundays, and preoperative discharge planning, may shorten the prolonged LOS.

### Ethics

**Ethics Committee Approval:** The study was approved by the Istinye University Clinical Research Ethic Committee (approval no: 2017-KAEK-120, decision no: 3/2022.K-32).

**Informed Consent:** Since the data used in the study were obtained from the hospital registration system, an individual informed consent form was not required.

**Peer-review:** Externally peer-reviewed.

### Authorship Contributions

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

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

**Financial Disclosure:** The authors declared that this study received no financial support.

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Original Article

DOI: 10.4274/haseki.galenos.2022.8737
Med Bull Haseki 2022;60:425-432

# Evaluating the Information Content, Readability, and Reliability of Turkish Websites about Fibromyalgia

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**Presented in:** This study was presented as an oral presentation (summary text) at the 2nd Konya Rheumatology Symposium held on 7-9 October 2022.

## Abstract

**Aim:** Although fibromyalgia patients frequently use the internet to get information about their diseases, there is no comprehensive and strong study investigating the quality and reliability of websites offering online information in Turkish. The aim of this study was to examine the content, readability, and reliability levels of the information published on Turkish websites about fibromyalgia.

**Methods:** In May 2022, the words "fibromyalgia" and "muscle rheumatism" were scanned on a Google search, and the websites in the first 20 pages were investigated. The websites were divided into three groups according to the creator: Group 1= hospitals, associations, and official institutions; group 2= health professionals; and group 3= others (news sites, blogs, etc.). The readability level was evaluated according to the Ateşman and Bezirci-Yılmaz formula; the reliability was evaluated according to the Journal of the American Medical Association (JAMA) score; and the information content was evaluated by referring to the subject headings in the patient information booklet prepared by the Turkish Physical Medicine and Rehabilitation Association. The grouping of the websites and evaluation of the JAMA score were rated by two independent researchers.

**Results:** One hundred and seven websites were included in the study; 48 (44.8%) were in group 1, 28 (26.2%) were in group 2, and 31 (29.0%) were in group 3. The median Ateşman value of all websites was 47.3 [minimum (min.)=21.6, maximum (max.)=80.2]; the median Bezirci-Yılmaz value was 13.1 (min.=4.8, max.=22.7). The JAMA median score was 2.0 (min.=0, max.=4), and 102 (95.2%) websites were classified as low-reliable (JAMA score≤2). The information content of 12 (11.2%) websites was complete. There was no difference between the groups in terms of the JAMA score, Ateşman, and Bezirci-Yılmaz values (p=0.705, 0.801, and 0.697, respectively). Websites on the first two pages (n=16) had a slightly lower JAMA score than the next pages (p=0.011). Inter-rater consistency was excellent (Cohen's=0.89 and 0.823, respectively; p<0.001).

**Conclusion:** Turkish websites are far from providing sufficient and quality information on fibromyalgia. Physicians and patients should be aware of this situation; relevant institutions should develop the necessary health policies to solve the problem.

**Keywords:** Comprehension, fibromyalgia, information quality, search engine

## Introduction

Fibromyalgia is a polysymptomatic disease characterized by increased mechanical hyperalgesia and allodynia, accompanied by many symptoms such as chronic widespread pain, fatigue, morning stiffness, sleep disturbance, cognitive dysfunction, and depressed mood (1). The prevalence of fibromyalgia in the general population is 3%, and it is the third most common musculoskeletal disease (2). In cross-sectional studies conducted in Turkey, its prevalence was found to be between 3.6 and 8.8% (3). Fibromyalgia is a difficult disease whose etiopathogenesis is not yet known, which has no effective treatment and adversely affects the quality of life. Although there are different treatment options, the basis of high-evidence treatment is the combination of pharmacological (such as amitriptyline,

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**Received:** 13.09.2022 **Accepted:** 14.11.2022

duloxetine, and pregabalin) and non-pharmacological treatments (such as aerobics and relaxation exercises, patient education, cognitive behavioral therapy, and other alternative therapies) (4).

Due to developing technological opportunities, the use of the internet has become very common worldwide recently. Especially with the effect of the coronavirus disease-2019 (COVID-19) pandemic, people have started to spend more time at home and use the internet more. The Turkish Statistical Institute (TurkStat) reported that the rate of households with internet access in Turkey reach 92% in 2021, and the rate of those using the internet to seek health-related information reached 70% (5). This traumatic pandemic process, which developed quite suddenly, has revealed that health literacy is an important issue (6,7). In particular, fibromyalgia patients use the internet extensively to access information about their health status (8,9). However, in order for online information to be useful for a sensitive and exclusive population like those with fibromyalgia, it must contain enough information, be reliable, and be readable. Otherwise, this information will do more harm than good to the patient; it will cause additional difficulties in doctor-patient relations (10).

Readability is a quantitative technical concept in linguistics that refers to the situation where texts are easy or difficult to understand by readers. In studies examining online information about fibromyalgia in different languages, it was emphasized that the content, reliability, and readability levels were insufficient and worrying (11-13). Considering that readability is a technical assessment specific to language and society, and online information on the internet, where there is no control mechanism, can vary considerably from country to country, the online information content and quality are specific to each country and should be examined separately. However, there is no comprehensive and methodologically strong study in the literature examining Turkish websites about fibromyalgia in terms of information content, readability, and reliability.

The aim of this study was to examine the information content, readability, and reliability levels of Turkish websites containing information about fibromyalgia.

## Materials and Methods

### Compliance with Ethical Standards

This study was a cross-sectional study in which data were scanned on the internet. The study approval was obtained from the University of Health Sciences Turkey, Hamidiye Scientific Research Ethics Committee (date: 06.04.2022, and approval number: 9/13).

### Study Design and Data Collection

In May 2022, the keywords "fibromyalgia, muscle rheumatism" were written in Turkish on Google (https://www.google.com.tr), which is the most frequently used internet search engine in Turkey (85%) as it is worldwide (14). To prevent any possible impact on the study results, the browsing history and cookie settings in the computer's cache have been deleted, and the personal Google account has been logged out. In line with similar studies conducted on this subject, 200 websites in the first 20 pages were examined (15).

Websites that do not contain information about the disease, chat-forums, advertisements, magazines, for commercial purposes, contain only images or videos, have fewer than ten sentences, cannot reach the text in a maximum of three clicks and are repetitive were excluded from the study. According to the creator, the websites were divided into three categories: 1) prepared by a hospital, medical center, university, health-related associations, or other official institutions; 2) prepared by health professionals; 3) other (news sites, blogs, anonymous, unclassifiable). The grouping of websites was done by two independent researchers (RY and SK). In the event of an inconsistency among the researchers in the grouping, the third researcher (HHG) was also examined, and the final decision was made by consensus.

### Information Content

The information content on the websites was reviewed with reference to the topics in the online accessible information booklet prepared by the Turkish Physical Medicine and Rehabilitation Association (TPMRA) for fibromyalgia patients (16). The seven main headings in this booklet are: the definition of the disease, its frequency, cause, symptoms, how the diagnosis was made, its differential diagnosis, and whether information was given about the treatment of the disease were examined. The information content was recorded as "yes" or "absent" by a single researcher (RY), regardless of the length of the text, level of academic evidence, and general medical accuracy, depending on whether the above topics were mentioned.

### The Journal of the American Medical Association Benchmark Criteria

The Journal of the American Medical Association (JAMA) benchmark criteria is an international score used to evaluate the quality, reliability, reasonableness, and usefulness of medical information on the Internet (17). The evaluation examines four main elements: 1) Author information 2) attribution (reference, copyright information) 3) Transparency (advertising, sponsorship, and conflicts of interest) 4) currency. A score of 0 is given

for the absence of each criterion, and 1 for its presence. The total score can vary between 0 and 4. ≥3 points are considered "high reliability," and ≤2 points are considered "low reliability." The JAMA score was evaluated by two independent researchers (RY and SK). When there was inconsistency among the researchers in the scoring, it was also examined by a third independent researcher (HHG), and the final decision was made by consensus.

### Readability

To evaluate the readability level of the texts on the websites, the Ateşman and Bezirci-Yılmaz formulas, which were specially developed to determine the readability level of Turkish texts, were used. Readability calculations were made by copying the analyzed texts and transferring them to a special computer program.

### Ateşman Readability Formula

The Ateşman formula was developed by adapting the Flesch Ease of Reading formula, which evaluates English readability, into Turkish (18). It is a formula based on sentence length and the number of syllables in its words. The increase in sentence length and the number of syllables in words reduce the readability of the text. According to the Ateşman formula, if a text's score is between 90 and 100, it is "very easy," between 70 and 89, it is "easy," between 30 and 69, it is "medium," between 30 and 49, it is "difficult," and between 1 and 29 is considered "very difficult".

### Bezirci-Yılmaz Readability Formula

The Bezirci-Yılmaz formula was developed in 2010 based on the previously developed international readability scales and specific features of Turkish (19). Similar to the Ateşman formula, it considers the length of sentences and the number of syllables in words. This formula estimates how many years of training are needed to understand a text, similar to the Simple Measure of Gobbledygook score, which is commonly used to evaluate the readability of English texts. The numerical value obtained because of the calculation shows which class level it corresponds to according to the education system in Turkey. Accordingly, 1-8 refers to primary education, 9-12 refers to secondary (high school) education, 12-16 refers to university (undergraduate), and 16 refers to the academic level (19).

### Statistical Analysis

Statistical analyses were performed using IBM® SPSS Statistics 21 software (Armonk, NY, USA). The frequency and percentage [n (%)] of categorical data are given; numerical data are given as the median (min.-max.) or mean ± standard deviation (SD). Cohen's kappa coefficient (κ) was used to determine the inter-rater consistency of categorical and ordinal data. The Shapiro-Wilks test was used to determine whether the data were normally distributed or not. Mann-Whitney U test was used in the comparison of numerical (non-parametric) data between two independent groups that did not show a normal distribution, and the chi-square test was used in the comparison of categorical (dichotomous) variables. A student's t-test was used to compare two parametric and independent groups. The Kruskal-Wallis non-parametric test or the one-way ANOVA parametric test was used to compare more than two independent groups. The Spearman's rho test was used for correlating non-parametric data that did not have a normal distribution. All statistical analyses were performed in two directions: at the 5% significance limit and the 95% confidence interval.

## Results

Of the 200 websites examined, 107 were included in the study, as they were found to be suitable for the inclusion criteria. Of these sites, 48 (44.8%) were in group 1, 28 (26.2%) were in group 2, and 31 (29%) were in group 3 (Figure 1). The consistency among website-grouping raters was nearly perfect (Cohen's κ= 0.898, p<0.001).

We observed that the websites included an average of 5.0±1.23 (median=5, 1-7) of the seven main headings in the fibromyalgia information booklet of TPMRA. 104 (97.2%) of the web sites include the definition of the disease, 79 (73.8%) frequency, 87 (81.3%) causes, 105 (98.1%) symptoms, 38 (35.5%) how the diagnosis is made, 19 (17.8%) included information about differential diagnosis, and 103 (96.3%) information about treatment. The most common content was symptoms, and the least common content was differential diagnosis. Only 12 (11.2%) websites were complete in terms of content headlines. There was no difference between the groups in terms of the completeness of the topic information content (p=0.877) (Table 1).

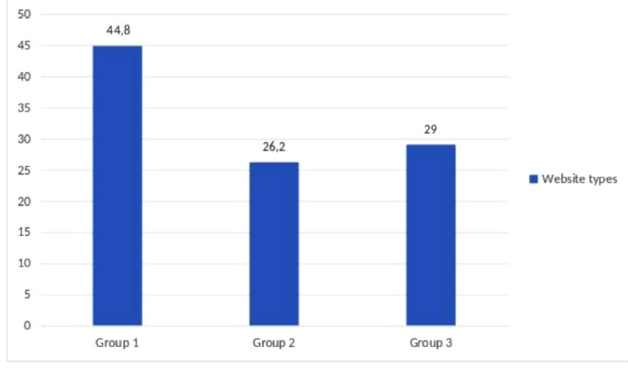


**Figure 1.** Frequency of website groups by creator (%)
Group 1; prepared by a hospital, medical center, university, health-related associations, or other official institutions
Group 2; prepared by health professionals
Group 3; other (news sites, blogs, anonymous, unclassifiable)

The overall JAMA benchmark median scores of websites were 2.0 (min=0, max=4) (1.46±0.768). Hundred and two (95.2%) of these sites were classified as low-reliable (JAMA score ≤2), and 5 (4.7%) of them were classified as high-reliable (JAMA score ≥3). The inter-rater reliability for determining the JAMA score of the websites was almost perfect agreement (Cohen's κ=0.823, p=0.000). There was no significant difference between the groups (typology of the websites) in terms of the JAMA scores (p=0.705) (Table 1).

The mean Ateşman readability value of all websites included in the study was 46.74±9.15 (median=47.3, min=21.6, max=80.2), and the mean Bezirci-Yılmaz readability value was 13.30±3.17 (median=13.1, min=4.8, max=22.7). The mean Ateşman readability value of all websites included in the study was found to be "difficult". The Bezirci-Yılmaz readability value of the websites included in the study corresponds to the 13$^{th}$ grade (undergraduate) in the Turkish education system. No statistically significant differences were detected between the Ateşman readability values of the study groups (p=0.754) and the Bezirci-Yılmaz readability values (p=0.650) (Table 1).

When the readability ranges are examined according to the Ateşman formula, 73 (68.2%) websites are found to be "very difficult" or "difficult" to read. No statistically significant differences were detected between the readability ranges (very difficult + difficult vs. medium + easy + very easy) of the types of websites (p=0.558) (Table 2).

Most (75%) of the websites on the first two pages (n=16) were in group 1, whereas the websites on the last 18 pages had a more homogeneous distribution (p=0.006). Contrary to expectations, it was observed that the JAMA score of the websites on the first two pages was slightly lower than the following pages (p=0.011) (Table 3). There was no significant difference between these groups in terms of information content and readability values for the Ateşman and Bezirci-Yılmaz (p=0.56, p=0.82, and p=0.78, respectively) (Table 3). Furthermore, there was no significant correlation between the JAMA scores of the websites and Ateşman and Bezirci-Yılmaz's readability values (r=0.04, p=0.97; and r=-0.02; p=0.87, respectively).

## Discussion

This study aimed to evaluate the information coverage, readability, and reliability levels of Turkish websites containing information about fibromyalgia. Almost all (95%) of the 107 websites examined were found to have a low level of reliability according to the JAMA score. In terms of readability, it is difficult to understand according to the Ateşman formula, and according to the Bezirci-Yılmaz formula, it is at an understandable level with 13 years of undergraduate education according to the Turkish education system. It was also observed that there was insufficient information in terms of content.

With the rapid increase in the use of the Internet, especially in the last decade, people are trying to get access to a lot of health-related information from the Internet. Most of the time, in this process, which is

**Table 1. Information content, readability and reliability levels of websites by groups**

| Website type | Group 1 (n=48, 45%) mean ± SD median (min.-max.) | Group 2 (n=28, 26%) mean ± SD median (min.-max.) | Group 3 (n=31, 29%) mean ± SD median (min.-max.) | p-value |
|---|---|---|---|---|
| Information content* | 5.02±1.37<br>5.0 (1-7) | 5.04±0.92<br>5.0 (3-6) | 4.94±1.31<br>5.0 (2-7) | 0.877[a] |
| JAMA score | 1.38±0.84<br>1 (0-3) | 1.54±0.51<br>2 (1-2) | 1.52±0.85<br>2 (0-4) | 0.705[a] |
| Ateşman value | 46.7±7.67<br>47.46 (23.6-63.4) | 47.8±10.4<br>47.53 (23.7-80.2) | 46.0±10.42<br>47.08 (21.6-63.4) | 0.754[b] |
| Bezirci-Yılmaz value | 13.3±2.84<br>13.4 (7.8-21.9) | 12.9±3.52<br>12.2 (4.8-22.5) | 13.6±3.40<br>12.7 (8.5-22.7) | 0.650[b] |

*According to the information booklet prepared by the Turkish Physical Medicine and Rehabilitation Association for fibromyalgia patients.
[a]Kruskal-Wallis test; [b]one-way ANOVA test, p<0.05 is significant
JAMA: Journal of the American Medical Association, min.-max.: Minimum-maximum, SD: Standard deviation

**Table 2. Evaluation of the readability ranges of the groups according to the Ateşman value**

| Website type | Group 1 48 (45%) | Group 2 28 (26%) | Group 3 31 (29%) | p-value* |
|---|---|---|---|---|
| Very difficult + difficult | 35 (73%) | 19 (68%) | 19 (61%) | 0.558[a] |
| Very easy + easy + medium | 13 (27%) | 9 (32%) | 12 (39%) | |

[a]Kruskal-Wallis test, p<0.05 is significant

| Table 3. Comparison of the websites on the first two pages and the websites on the remaining pages | | | |
|---|---|---|---|
| | **First two page (n=16)<br>mean ± SD<br>median (min.-max.)** | **Other 18 page (n=91)<br>mean ± SD<br>median (min.-max.)** | **p-value** |
| Information content | 5.19±1.28<br>5 (3-7) | 4.97±1.23<br>5 (1-7) | 0.560[a] |
| JAMA score | 1.0±0.73<br>1 (0-2) | 1.54±0.75<br>2 (0-4) | 0.011[a] |
| Ateşman value | 46.3±6.9<br>47.3 (33.2-60.6) | 46.8±9.5<br>47.3 (21.6-80.2) | 0.820[b] |
| Bezirci-Yılmaz value | 13.1±2.38<br>13.5 (8.8-18.3) | 13.3±3.3<br>12.9 (4.8-22.7) | 0.779[b] |
| [a]Mann-Whitney U test; [b]Student's t-test; p<0.05 is significant<br>JAMA: Journal of the American Medical Association, min.-max.: Minimum-maximum, SD: Standard deviation | | | |

conducted through search engines, individuals try to obtain information about the characteristics of the diseases, diagnostic methods, treatment options, or which disease their current symptoms may indicate (20). Although it has been reported that online health information can improve people's ability to cope with diseases and increase their quality of life by reducing their anxiety and fears, it seems very difficult to obtain reliable and readable information with sufficient and correct content (11-12,21). General medical information with low information content, low quality, and non-individual is deceptive and confusing because it cannot be correctly interpreted, ultimately leading to maladaptive behaviors and concerns (22).

Increased anxiety and social isolation during the COVID-19 pandemic adversely affected fibromyalgia symptoms (23). In this process, it has been reported that the incidence of chronic widespread pain, including fibromyalgia, increases (24,25). The chronic, difficult, and wearisome nature of fibromyalgia, the cause of which is unknown without objective diagnostic criteria and effective treatment, increases the search for a cure in these patients. Indeed, fibromyalgia patients report a preference for engaging with online health information (26). Additionally, considering that patient education for treating fibromyalgia is recommended with a strong level of evidence (level 1A), it is critical to access reliable and quality information on the internet (27).

Daraz et al. (11) examined the first 25 English-language websites on Google that provide online information about fibromyalgia in terms of information content, quality, and readability. The DISCERN tool was used for information quality and reliability, but they also used the Quality Checklist, which consists of seven items such as authorship, content, currency, and disclosure, considering that this DISCERN scale would not be an adequate assessment on its own. Because of the research, they reported that the websites did not contain comprehensive information, were of low quality, and were difficult to read. It has been observed that only 16% of the websites can provide the 6-8 year education level recommended for ideal readability.

In another recent study, the top 200 websites on Google offering fibromyalgia information online in English in the United States were examined for information completeness and trustworthiness (28). It was determined that the information content did not meet the inquiry needs of the patients, and the median value of the JAMA score was 2.0. It has been reported that 43% of websites could achieve the sufficient quality threshold of ≥3 JAMA scores, and only 8% were at the recommended readability grade of 6.

In a study conducted on Spanish-language websites, the third most frequently used language on the internet in the world in 2020, the content, quality, and readability of online information about fibromyalgia were evaluated (13). This study, which included 73 sites, found that the information content was very limited, the quality was medium-low, and the readability was poor. There is no quality, readable, reliable, and sufficient content online information presentation that can benefit a population with a high tendency and need to access online information, such as fibromyalgia patients.

The results obtained in this study are similar to those obtained from research conducted in other countries and languages. In the information content review, the patient information booklet of a very active association on fibromyalgia in Turkey was taken as a reference, and it was observed that only 11% of the websites had complete subject integrity. The fact that online resources have not specifically addressed how the diagnosis is made and the issue of differential diagnosis is far from meeting the needs of a patient group with a high tendency to cyberchondria, such as fibromyalgia.

According to the 2020 Human Development Report, the average education period in Turkey is 8.1 years (29). According to the Bezirci-Yılmaz formula, the online resources examined in our study were 5 years above the national education average. This result, which shows that it is very difficult for individuals with average education to understand the texts, agrees with studies on different

subjects who evaluated the readability of both fibromyalgia-related websites in other languages and Turkish websites (11,13,15,28).

The top 20 results on the first two pages are generally clicked on in searches made via search engines on the Internet (30). Considering this behavior pattern in our study, the websites on the first two pages were compared with those on the other pages, and we observed that the majority of the first two pages (75%) were in group 1. We think that this heterogeneous distribution is due to the recognition of hospitals and the belief that they can be a more reliable source of information. However, contrary to expectations, the JAMA score of the websites on the first two pages was slightly lower. Whereas, Basavakumar et al. (28) found the JAMA score and information coverage of the top 10 websites to be slightly higher and the readability level to be easier to understand. In a study examining information about osteoporosis on English-language websites, similar to the results obtained, no difference was observed between the first 10 websites and the remaining 141 websites in terms of the JAMA score and readability (31).

It is surprising that the websites prepared by health professionals in our study were indistinguishable from those of other groups in terms of the parameters examined, but this is not consistent with the literature (31). Failure to pay attention to academic writing principles such as date, reference, and disclosure to these sites caused the JAMA score to lower. The fact that the texts were prepared by copying from previously written on online sources may have led to similar results in different website types.

In a fairly recent study, 80 websites in four different search engines (Google, Yandex, Bing, and Yahoo) providing online information about fibromyalgia in Turkey were examined (32). Similar to the results of our study, it was emphasized that the information content was weak, the least loss of libido (2.5%) was mentioned among the symptoms of the disease, and only 3.8% of the websites had references. The websites were found to be of low quality (median=30) according to the DISCERN score, and "moderately difficult" (median=55.5) according to the Ateşman formula. The JAMA score and the education level corresponding to the Bezirci-Yılmaz formula have not been examined in this study. Similar to our study, no difference was observed between the website types in terms of quality and readability. Search engines other than Google (1-15%) are used at a negligible level in Turkey (14,33). The DISCERN score is a tool that primarily assesses the quality of treatment, not the overall quality. In our study, the JAMA score, which is a more objective reliability and quality scale, was used, and the evaluations were made by two independent researchers. Considering all of these, we think that the results obtained in this study are more comprehensive and powerful.

### Study Limitations

The most important limitation of this study is that the analyzed online information belongs to a certain period. With a cross-sectional assessment, it cannot be ruled out that changing trends on the internet or search engines may offer different best results to different users. As in all similar studies, the formulas used for readability were calculated by considering the technical aspect of grammar. Therefore, the fact that the words in the texts are simple, close to the average folk language, or consist of technical and medical terms does not affect the calculated readability value. In other words, it is a difficult text to understand because of the heavy use of medical terms. If the number of words and syllables in the sentences is low, it can be calculated at an easily readable level according to the readability formulas. Another limitation is that although critical parameters in terms of reliability have been examined with the JAMA score, this and similar studies are methodologically far from being able to definitively reveal the academic accuracy and currency of online information content. Despite these limitations, we believe that our study presented a current and comprehensive review with an original and robust methodology by a team of authors experienced in fibromyalgia and health literacy.

## Conclusion

Turkish websites are far from properly illuminating fibromyalgia.The inadequacy of the information content, especially on diagnosis and differential diagnosis, makes it difficult to understand the subject. Considering that patient education is an important element for treating fibromyalgia and that these patients have a high tendency to access online information, the results obtained reveal a deficiency in this regard. Misinformation with insufficient content can cause confusion, anxiety, and maladaptive behavior. Official institutions related to health policies and sources providing online information should make the necessary improvements within the framework of this data. Patients should also be made aware of the fact that the existing websites are far too inadequate and unreliable to be useful to them.

### Ethics

**Ethics Committee Approval:** The study approval was obtained from the University of Health Sciences Turkey, Hamidiye Scientific Research Ethics Committee (date: 06.04.2022, and approval number: 9/13).

**Informed Consent:** Not necessary.

**Peer-review:** Externally peer-reviewed

**Authorship Contributions**

Concept: R.Y., S.K., H.H.G., H.Y., Design: R.Y., S.K., Data Collection and/or Processing: R.Y., S.K., H.H.G., Analysis and/or Interpretation: R.Y., S.K., H.H.G., H.Y., Literature Research: R.Y., S.K., H.H.G., Writing: R.Y., S.K.

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

**Financial Disclosure:** The authors declared that this study received no financial support.

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Original Article

DOI: 10.4274/haseki.galenos.2022.8651
Med Bull Haseki 2022;60:433-438

# Relationship Between Smell Disorders and Pulmonary Involvement in COVID-19

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## Abstract

**Aim:** Some symptoms of coronavirus disease-2019 (COVID-19) are more common in patients without pulmonary involvement and in patients with a good prognosis. Although it is known that smelling disorders are more common in patients with a good prognosis, their relationship with pulmonary involvement is unknown. This study ianvestigated the relationship between smell disorders and pulmonary involvement in COVID-19.

**Methods:** This cross-sectional study was conducted between May 2022 and July 2022 and included 60 COVID-19 patients with pulmonary involvement and 60 COVID-19 patients without pulmonary involvement. Phone-call interviews were performed with all patients 1 month after the diagnosis of COVID-19 and their sense of smell was questioned with a questionnaire. The prevalence of smell disorders, type and severity of smell disorders were questioned, and participants were asked to grade their answers from 0 to 10.

**Results:** In 58 (48.3%) of the patients, smell disorders were found to be present. Hyposmia was detected in 35 (60.34%), and anosmia was detected in 23 (39.66%) of these patients. Smell disorder was present in 20 (33.3%) patients with pulmonary involvement and in 38 (63.3%) patients without pulmonary involvement. The prevalence of smell disorders was significantly higher in patients without pulmonary involvement (p=0.001). Hyposmia in 15 patients (25%) and anosmia in 5 patients (8.3%) were found in patients with pulmonary involvement. Hyposmia in 20 patients (33.3%) and anosmia in 5 patients (8.3%) were found in patients without pulmonary involvement. The prevalence of anosmia was significantly higher in patients without pulmonary involvement (p=0.003). The smell disorders were significantly more severe in patients without pulmonary involvement (p=0.042).

**Conclusion:** Smell disorders are seen more frequently and more severely in patients without pulmonary involvement due to COVID-19 than in patients with pulmonary involvement.

**Keywords:** COVID-19, olfaction disorders, prevalence, SARS-CoV-2, smell

## Introduction

Coronavirus disease-2019 (COVID-19) is a disease that causes a pandemic and has changed life in all areas for about 3 years (1). This disease, caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), is the largest global epidemic that humanity has faced since the 1918 influenza pandemic (2,3). The virus, which is taken by inhaled air or contact, first settles in the upper respiratory tract, and after replicating there, it reaches the lungs and causes a systemic infection (2).

COVID-19 can show a clinical course of very different severity. It can be asymptomatic or can lead to death by causing complications (1-4). Symptoms of the disease appear between 2 and 14 days, an average of 5 days, after exposure to the virus (5-6). In COVID-19, symptoms of typical respiratory tract infections such as fever, cough, fatigue, muscle pain, nasal congestion, runny nose, and dyspnea can be seen, as well as symptoms uncommon in respiratory tract infections, such as diarrhea (5).

Another group of symptoms of COVID-19 is olfactory disorders, which are more common than coronavirus infections before SARS-CoV-2 and typical upper respiratory tract infections (5,7). Smell disorders can be divided into two main classes, such as odor detection disorders and odor identification disorders. While hyperosmia, hyposmia, and

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**Received:** 26.07.2022 **Accepted:** 26.08.2022

anosmia constitute odor detection disorders, parosmia, phantosmia, and cacosmia constitute odor identification disorders (7).

The most important stage affecting the prognosis of COVID-19 is the infection of the lung by the virus, which makes the infection systemic (2). The most important method for detecting viral pneumonia caused by SARS-CoV-2 is computed tomography (CT) (8). The relationship between pulmonary involvement due to SARS-CoV-2 and COVID-19 symptoms has been investigated in several studies (9,10). Although smell disorders are more common in patients with a good prognosis, their relationship with pulmonary involvement has not been investigated.

This study was designed with the hypothesis that olfactory disorders would be less common in patients with pulmonary involvement due to COVID-19. Thus, the aim was to determine the relationship between olfactory disorders in COVID-19 patients and pulmonary involvement of the disease.

## Materials and Methods

### Ethical Standards

This cross-sectional study was conducted between May 2022 and July 2022 in, Istanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine and Eyüpsultan State Hospital in accordance with the approval of the Istanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine Clinical Research Ethics Committee dated July 9, 2021 and numbered 133532. All steps of this study were conducted in accordance with the Declaration of Helsinki and informed consent was obtained from all patients.

### Subjects and Study Criteria

In this study, we planned to use parametric tests to obtain more statistically significant results. The sample size was kept high because some patients could not be reached or they might want to leave the study. Therefore, 60 subjects, which is twice the minimum number of samples required for parametric tests, were included in each study group (11). Additionally, at the end of the study, it was planned to calculate the statistical power with post-hoc tests.

All patients included in the study were selected from among the patients who applied to Eyup Sultan State Hospital Emergency Service. All subjects were patients with a positive SARS-CoV-2 real-time polymerase chain reaction test, followed in outpatient isolation, and one month had passed since the diagnosis of COVID-19. All patients had thorax CT images taken at admission. Patients with chronic, neurological, mental, and psychiatric diseases; patients with a history of upper respiratory tract and/or otological surgery; prior any type of odor disorder; head trauma, facial trauma, and regular drug use in the previous 3 months; and patients with alcohol dependence and/or smoking were all excluded from the study.

### Study Design and Data Collection

A stratified sampling method was used in this study. COVID-19 patients were divided into two groups: those with pulmonary involvement due to the disease on thorax CT (group 1) and those without (group 2). The subjects were randomly selected from the start using the Microsoft Excel (Microsoft, USA) program. A total of 120 patients, 60 in each group, were included in the study.

CT scans of the patients were performed at the same center. Pulmonary involvement was evaluated by the same radiologist on images obtained with high-resolution tomography with 1 millimeter thick sections and was scored according to the COVID-19 Reporting and Data System (CO-RADS) classification. Group 1 patients were selected from patients in the CO-RADS 1 class. Group 2 patients were selected from patients in the CO-RADS 3-5 class (12).

The contact information of the patients included in the study was obtained from the hospital records. A self-reported questionnaire was applied to all patients. Patients were asked whether they had an olfactory disorder within one month of being diagnosed with COVID-19. The type of smell disorder seen in patients who stated that they had an olfactory disorder was questioned. The olfactory disorders were explained to the patients to clarify the selection in the questionnaire. Hyposmia was described as the decreased perception of smell; anosmia as the absence of all odor perception; parosmia as the perception of odors as different from what they are; and phantosmia as the perception of smell without any odor present (13). The severity of the olfactory disorder seen in the patients was determined by the patients themselves with a score from 0 to 10. Questionnaires were administered blindly by the same person without knowing which patient was in which group.

### Statistical Analysis

Statistical analysis was performed using the SPSS 23.0 program (IBM, USA). The normal distribution of the obtained data was evaluated with the Kolmogorov-Smirnov test and its homogeneity was evaluated with the Levene test. Statistical comparisons were made with the Independent sample t-test and the Pearson chi-square test. The statistical significance value was set as $p<0.05$. The determination of the study power was done using the G*Power program.

## Results

The demographic data of the patients is given in Table 1. The study groups were statistically similar in

| Table 1. The demographic characteristics of patients | | | | |
|---|---|---|---|---|
| **Parameters** | | **Group 1 (n=60)** | **Group 2 (n=60)** | **p-value** |
| Gender | Male, n (%) | 36 (60) | 38 (63.3) | 0.707* |
| | Female, n (%) | 24 (40) | 22 (36.7) | |
| Age (years) | Mean ± SD (median, min-max) | 52.02±12.707 (55.5, 24-65) | 47.28±14.042 (51, 21-65) | 0.059** |

*Pearson chi-square test, value: 0.141; df: 1, p>0.05.
**Independent samples t-test p>0.05.
SD: Standard deviation, min: Minimum, max: Maximum

terms of age and patient gender (p=0.059 and p=0.707, respectively).

Smell disorders were detected in 58 (48.3%) patients. (Figure 1). Thirty-five (29.2% of all patients, 60.34% of those with smell disorders) patients had hyposmia, and 23 (19.17% of all patients, 39.66% of those with smell disorders) patients had anosmia (Figure 1). In the examination of smell disorder frequency in the study groups, the presence of smell disorders was found in 20 (33.3%) patients in group 1 and 38 (66.3%) patients in group 2. While smell disorders were one of the initial symptoms in 11 (55%) patients in group 1, and in 21 (55.2%) patients in group 2, when both groups were evaluated together, these symptoms were one of the initial symptoms in 52.17% of the patients with smell disorders. The frequency of smell disorders was significantly higher in group 2 compared to in group 1 (p=0.001) (Table 2). The sensitivity and specificity of the smell disorders for detecting pulmonary involvement were 33.3% and 36.7%, respectively. The sensitivity and specificity of olfactory disorders detected as the initial symptoms in detecting pulmonary involvement were 18.3% and 65%, respectively.

In the examination of smell disorder types, hyposmia was detected in 15 (25% of group 1 patients, 75% of group 1 patients with smell disorders) patients, and anosmia was detected in 5 (8.3% of group 1 patients, 25% of group 1 patients with smell disorders) patients in group 1. In group 2, hyposmia was detected in 20 patients in group 2 (33.3% of patients in group 2, and 52.63% of patients with smell disorders in group 2), and anosmia was detected in 18 patients (30% of group 2 patients, and 47.37% of patients with smell disorders in group 2). None of the patients stated the presence of parosmia or phantosmia. While there was no significant difference between the groups in terms of hyposmia frequency, the frequency of anosmia was significantly higher in group 2 compared to group 1 (p=0.003) (Table 3).

The mean values of the severity of the smell disorders, which were evaluated by the patients between 0 and 10, are given in Table 4. When the severity of the observed smell disorders was evaluated, the smell disorders in group 2 were found to be more severe than in group 1 (p=0.042) (Table 4).

A post-hoc test, which was used to calculate the power of this study, was performed with a 5% error possibility according to the subject size used. The statistical power (1-β error probability) was 0.965.

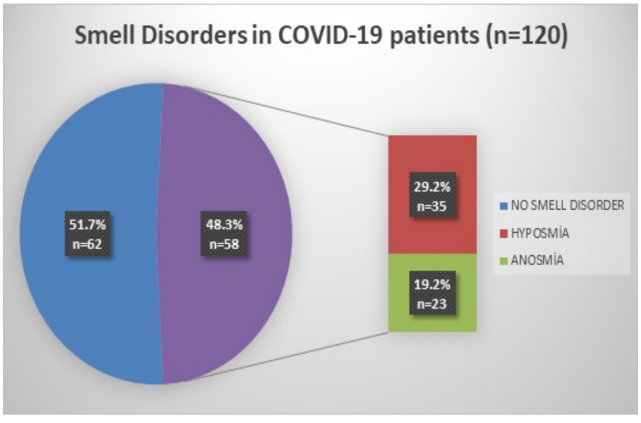


**Figure 1.** The frequency and types of smell disorders in COVID-19 patients
*COVID-19: Coronavirus disease-2019*

## Discussion

Smell disorders are on the COVID-19 symptom lists of national and international organizations (5,14). There

| Table 2. Evaluation of the presence of smell disorders according to pulmonary involvement in COVID-19 patients | | | |
|---|---|---|---|
| **The symptom** | **Group 1 (n=60) n (%)** | **Group 2 (n=60) n (%)** | **p** |
| Smell disorder + | 20 (33.3) | 38 (63.3) | **0.001*** |
| Smell disorder - | 40 (66.7) | 22 (36.7) | |

*Pearson chi-square test, value: 10.812; df: 1, p<0.05.
COVID-19: Coronavirus disease-2019

| Table 3. Evaluation of the relationship between subtypes of smell disorders and pulmonary involvement in COVID-19 patients | | | |
|---|---|---|---|
| **Smell disorders** | **Group 1 (n=60) n (%)** | **Group 2 (n=60) n (%)** | **p** |
| Hyposmia | 15 (25) | 20 (33.3) | 0.315* |
| Anosmia | 5 (8.3) | 18 (30) | **0.003**** |

*Pearson chi-square test, value: 1.008; df: 1, p>0.05.
**Pearson chi-square test, value: 9.090; df: 1, p<0.05.
COVID-19: Coronavirus disease-2019

**Table 4. The relationship between the severity of smell disorders and pulmonary involvement**

| Smell disorders | Group 1 mean ± SD (median, min-max) | Group 2 mean ± SD (median, min-max) | p |
|---|---|---|---|
| **Symptom severity (0-10)** | 4.3±1.261 (4, 2-7) | 5.21±1.527 (5, 3-8) | **0.042*** |

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

are several studies examining the relationship between COVID-19 symptoms and lung involvement due to COVID-19 (9,10). This study showed that smell disorders were significantly more frequent, anosmia was significantly more common, and the observed smell disorders were significantly more severe in patients without pulmonary involvement.

Although otorhinolaryngological symptoms such as flu-like symptoms, hearing loss, weakness or paralysis in facial movements, cervical swelling, pain, and sensibility in the cervical region can be seen in COVID-19 patients, smell and taste disorders are the most common (15). Hyposmia and anosmia belonging to this symptom group, which can be detected at a high rate of 85.6% in COVID-19 patients, are seen commonly in these patients (16). Although it is stated that smell disorders improve in time intervals ranging from one week to one month in the early stages of the pandemic, it is now known that COVID-19 may cause permanent loss of smell (17,18).

It has been reported in previous studies that smell disorders are more common in patients with mild COVID-19 (17,19). COVID-19, which can cause permanent sequelae, is divided into 3 periods (20). This study examines the first 4-week period, defined as the acute period of COVID-19 (20). The smell disorders seen in COVID-19 are more common in women and smokers (19). Smokers were excluded from this study, and the study groups were established to be statistically similar according to patient age and gender so that the results would not be affected by patient gender and smoking factors. The frequency of smell disorders seen in COVID-19 is different in inpatients and outpatients (17,19). Therefore, only outpatients were included in the study.

The mechanisms involved in the occurrence of smell disorders in patients with COVID-19 are still unclear and several pathophysiological mechanisms have been proposed. One of those hypotheses is that SARS-CoV-2 binds to angiotensin-converting enzyme 2 receptors and transmembrane serine protease 2 receptors in the nasal cavity and then damages the supporting cells and olfactory cells (21). One of the proposed pathophysiological mechanisms is conduction disorder due to direct damage or edema of the olfactory bulb (22).

In a previous meta-analysis study, the prevalence of smell disorder in COVID-19 was reported as 44% with subjective tests (23). In another meta-analysis study, this prevalence was reported as 41% (24). In this study, the frequency of smell disorders in COVID-19 patients was 48%. In a previous study, the rate of presence of these symptoms at the time of diagnosis was 51.4% in patients with olfactory disorders (25). In this study, this rate was found to be 52.17%. In most of the previous studies, hyposmia and anosmia were considered together (23,24). Different prevalence rates have been reported in studies dealing with these two symptoms separately. In a previous study, the frequency of anosmia was 32.7% in COVID-19 patients and the frequency of hyposmia was 20.3% (26). In a meta-analysis study, the anosmia rate was reported as 35.39% and the hyposmia rate as 36.15% (27). In this study, the prevalence of hyposmia was 29.1% and the prevalence of anosmia was 19.2%. Different results reported in previous studies can be attributed to the fact that the studies were self-reported questionnaire studies, and odor sensitivity varies by population.

In previous studies, it was reported that cough and shortness of breath symptoms were more common in patients with pulmonary involvement compared to patients without pulmonary involvement, and there was no significant difference in terms of other symptoms (9,10). This study showed that olfactory disorders are less common and less severe in patients with pulmonary involvement. It may also explain the higher prevalence of olfactory disorders in the patient group with a milder clinical course, less need for follow-up in the intensive care unit, and a lower mortality rate (17). However, the sensitivity and specificity values of smell disorders for detecting pulmonary involvement were not sufficient to eliminate the need for lung tomography to detect pulmonary involvement.

**Study Limitations**

There are some limitations to our study. The first limitation is that this study is a self-reported questionnaire study. The prevalence of olfactory disorders in COVID-19 differs between objective and subjective testing (23). Most of the previous studies were questionnaire studies (24). In this study, the questionnaire method was preferred to reduce the risk of transmission. The second and most important limitation of this study is that all patients included in this study used favipiravir. Favipiravir can affect the nervous system (28). Smell disorders in some patients may be due to this drug. However, the statistical results of the study do not change because all patients included received favipiravir. Another limitation of the study is that the minimum sample size was not calculated at the beginning of the study. The effect of this limitation was

limited by performing a post-hoc power analysis test at the end of the study, and the statistical power of the study was found to be high with a value of 0.965. Along with all these limitations, the study's strengths are that it is a statistically powerful study; it covers the entire acute period of COVID-19; its standardization is optimal; and it is the first in the literature with its subject.

## Conclusion

Smell disorders are one of the common symptoms of COVID-19. These symptoms may be seen more frequently and more severely in patients without pulmonary involvement. Based on this, we can say that the presence of olfactory disorders may be an indicator of good prognosis in patients with COVID-19.

**Acknowledgment**

The authors thank Dr. Zeliha Kubra CAKAN for her contributions.

**Ethics**

**Ethics Committee Approval:** Ethical approval for this study was obtained from the Istanbul University Cerrahpasa, Cerrahpasa Faculty of Medicine Clinical Research Ethics Committee (decision date/number: 09.07.2021/133532).

**Informed Consent:** All steps of this study were conducted in accordance with the Declaration of Helsinki and informed consent was obtained from all patients.

**Peer-review:** Externally and internally peer-reviewed.

**Authorship Contributions**

Surgical and Medical Practices: D.C., Concept: D.C., S.U., Design: D.C., S.U., Data Collection and/or Processing: D.C., Analysis and/or Interpretation: D.C., S.U., Literature Research: D.C., S.U., Writing: D.C., S.U.

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

**Financial Disclosure:** The authors declared that this study received no financial support.

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Original Article

DOI: 10.4274/haseki.galenos.2022.8501
Med Bull Haseki 2022;60:439-446

# Risk Factors and Predictors of 1-year Overall Mortality in Patients with COVID-19

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## Abstract

**Aim:** To date, limited data exists on 1-year mortality and associated factors in patients with coronavirus diseases-2019 (COVID-19). We determined risk factors and predictors of 1-year mortality.

**Methods:** In this retrospective and single-center study, hospitalized patients with COVID-19 were enrolled between March 11 and March 11, 2020. The primary outcome was 1-year all-cause mortality after discharge from the hospital. Secondary outcomes were the risk factors and predictors of 1-year mortality. A comparative analysis was applied to patients who died after recovering from acute COVID-19 and patients who survived.

**Results:** A total of 567 patients were analyzed. The 1-year mortality occurred in 18 (3.2%) patients. Older age (p=0.001), chronic obstructive pulmonary disease (p=0.001), chronic artery disease (p=0.001), chronic renal failure (p=0.001), presence of pleural fluid (p=0.001), high levels of leukocyte (p=0.001), neutrophil (p=0.001), monocyte (p=0.026), C-reactive protein (p=0.042), procalcitonin (p=0.004), urea (p=0.001), creatinine (p=0.001), troponin (p=0.001), lactate dehydrogenase (p=0.019), potassium (p=0.003), and a low level of alanine aminotransferase (p=0.001) at the first admission were associated with increased long-term mortality. Additionally, the need for intensive care unit (ICU) admission (p=0.007) and invasive ventilation (p=0.019) during the hospital stay for COVID-19 were associated with increased 1-year mortality.

**Conclusion:** This study suggests that age, underlying diseases, pleural fluid, certain laboratory parameters, and ICU care are somewhat associated with 1-year mortality.

**Keywords:** COVID-19, 1-year mortality, risk factors, predictors

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**Received:** 25.05.2022 **Accepted:** 05.10.2022

## Introduction

The coronavirus disease-2019 (COVID-19) has had a global impact, resulting in over 6 million deaths as of April 2022 (1). Hospitalized patients with COVID-19 frequently have pneumonia, which causes respiratory failure and results in multiorgan dysfunction, the need for invasive ventilation, and death (2,3). While most survivors have a full recovery after discharge from the hospital, some patients need long-term follow-up care due to the complications of COVID-19 and long-COVID symptoms (4,5).

To date, limited data exists on 1-year mortality in patients with COVID-19, although 30-day and 3-6-month outcomes of COVID-19 are well-known (6,7). Therefore, in this study, we aimed to determine the prevalence of 1-year mortality among survivors and to explore the risk factors and predictors of long-term mortality after discharge from the hospital.

## Materials and Methods

### Compliance with Ethical Standards

All procedures performed in this study were in accordance with the ethical standards of the Declaration of Helsinki. This study was approved by the Ethics Committee of University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital (approval number: 102-2022, date number: 08.06.2022) and the Advisory Board on Coronavirus Research of the Republic of Turkey Ministry of Health (approval number: 2022-01-26T10_14_12, date: 27.01.2022). Written informed consent was waived because of the retrospective nature of this study.

### Study Design

In this single-center study, all hospitalized adult patients (older than 18 years old) with laboratory-confirmed COVID-19 between March 11 and March 11, 2020, were retrospectively enrolled. For laboratory confirmation, positive severe acute respiratory syndromecoronavirus-2 real-time reverse transcriptase polymerase chain reaction testing from oropharyngeal and/or nasopharyngeal swabs was used. We excluded patients with asymptomatic COVID-19 and patients who died during the hospital admission.

### Patients' Evaluation

This study was designed as a continuation of our previous study (8). In the study, demographic and clinical features, laboratory test results, radiological findings, and short-term outcomes were obtained from medical charts and recorded via a follow-up data sheet. The primary outcome was 1-year all-cause mortality after discharge from the hospital. Secondary outcomes were the risk factors and predictors of 1-year mortality. For mortality, the National Death Report Database was used to obtain the 1-year mortality. The patients were divided into two groups: deceased and surviving patients. A comparative analysis was applied to patients who died after recovery from acute COVID-19 and patients who survived.

### Statistical Analysis

Categorical parameters were represented as frequencies (n) and percentages (%), whereas quantitative parameters were represented as median and interquartile ranges (IQR). The chi-square test or Fisher's exact test were used to compare categorical data.The Kolmogorov-Smirnov test was used for normal distribution analysis. The Independent sample t-test was applied for normally distributed variables, while the Mann-Whitney U test was performed for variables without normal distribution. A p value less than 0.05 was considered significant. Odds ratios (OR) with 95% confidence intervals were determined. The analyses were performed using IBM SPSS-21 (Statistical Package for Social Sciences, IL, USA).

## Results

A total of 567 patients were enrolled in the study. Of those, 298 (52.6%) were male, and the median (IQR) age was 53 (41-62) years. The 1-year mortality occurred in 18 (3.2%) patients. One-year mortality was found to be higher in older patients (65 years old) than in younger patients (10.9% vs. 1.3%, OR=9.09, p=0.001). The 1-year mortality rate was more frequent in patients with at least one comorbid disease (5.1% vs. 0.8%, OR=6.74, p=0.004), chronic obstructive pulmonary disease (COPD) (25.0% vs. 2.4%, OR=13.69, p=0.001), chronic artery disease (11.5 vs. 2.3%, OR=5.47, p=0.001), and chronic renal failure (29.2% vs. 2.0%, OR=19.9, p=0.001) compared to those with none (Table 1). Figure 1 demonstrates the risk factors for 1-year mortality in patients with COVID-19 in the post-discharge period. However, no significant relationship was detected between the 1-year mortality and the initial symptoms at admission (Table 2).

On chest computed tomography (CT), patients with pleural fluid had a higher 1-year mortality rate than patients without pleural fluid (27.3% vs. 2.3%, OR=16.2, p=0.001) (Table 3).

The median values of leukocyte count (7860/$mm^3$ vs. 5850/$mm^3$, p=0.001), neutrophil count (5690/$mm^3$ vs. 3650/$mm^3$, p=0.001), monocyte count (740/$mm^3$ vs. 510/$mm^3$, p=0.026), C-reactive protein (CRP) (60 mg/L vs. 36 mg/L, p=0.042), procalcitonin (0.13 ng/mL vs. 0.05 ng/mL, p=0.004), urea (44 mmol/L vs. 27 mmol/L, p=0.001), creatinine (1.12 mg/dL vs. 0.73 mg/dL, p=0.001), troponin (59.2 ng/L vs. 3.9 ng/L, p=0.001), lactate dehydrogenase (LDH) (312 UI/L vs. 264 UI/L, p=0.019), and potassium (4.5 mmol/L vs. 4.1 mmol/L, p=0.003) at admission were higher in deceased patients

**Table 1. Comparison of the demographic characteristics of deceased and survived patients in the post-discharge 1-year period**

| | | Deceased | | Survived | | In total | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | n | % | n | % | n | % | p-value | OR |
| Sex | Male | 11 | 3.70 | 287 | 96.30 | 298 | 52.56 | 0.46* | 1.44 |
| | Female | 7 | 2.60 | 262 | 97.40 | 269 | 47.44 | | |
| Age, years | <65 | 6 | 1.30 | 451 | 98.70 | 457 | 80.60 | **0.001*** | 0.11 |
| | ≥65 | 12 | 10.90 | 98 | 89.10 | 110 | 19.40 | | |
| Underlying diseases | Yes | 16 | 5.10 | 298 | 94.90 | 314 | 55.38 | **0.004**† | 6.74 |
| | No | 2 | 0.80 | 251 | 99.20 | 253 | 44.62 | | |
| COPD | Yes | 5 | 25.00 | 15 | 75.00 | 20 | 3.53 | **0.001*** | 13.69 |
| | No | 13 | 2.40 | 534 | 97.60 | 547 | 96.47 | | |
| Diabetes mellitus | Yes | 8 | 5.30 | 144 | 94.70 | 152 | 26.81 | 0.09* | 2.25 |
| | No | 10 | 2.40 | 405 | 97.60 | 415 | 73.19 | | |
| Hypertension | Yes | 9 | 5.20 | 163 | 94.80 | 172 | 30.34 | 0.07† | 2.37 |
| | No | 9 | 2.30 | 386 | 97.70 | 395 | 69.66 | | |
| Congestive heart failure | Yes | 1 | 11.10 | 8 | 88.90 | 9 | 1.59 | 0.17† | 3.98 |
| | No | 17 | 3.00 | 541 | 97.00 | 558 | 98.41 | | |
| Chronic artery disease | Yes | 6 | 11.50 | 46 | 88.50 | 52 | 9.17 | **0.001*** | 5.47 |
| | No | 12 | 2.30 | 503 | 97.70 | 515 | 90.83 | | |
| Chronic renal failure | Yes | 7 | 29.20 | 17 | 70.80 | 24 | 4.23 | **0.001*** | 19.9 |
| | No | 11 | 2.00 | 532 | 98.00 | 543 | 95.77 | | |
| Malignancy | Yes | 0 | 0.00 | 8 | 100.00 | 8 | 1.41 | 1.00† | - |
| | No | 18 | 3.20 | 541 | 96.80 | 559 | 98.59 | | |
| Chronic lung disease | Yes | 1 | 11.10 | 8 | 88.90 | 9 | 1.59 | 0.17† | 3.98 |
| | No | 17 | 3.00 | 541 | 97.00 | 558 | 98.41 | | |
| Bronchial asthma | Yes | 2 | 4.50 | 42 | 95.50 | 44 | 7.76 | 0.59† | 1.51 |
| | No | 16 | 3.10 | 507 | 96.90 | 523 | 92.24 | | |

Bold values represent statistical significance at the level of p<0.05. The 1-year mortality was more frequent in patients with at least one comorbid disease, patients with COPD, chronic artery disease, and chronic renal failure compared to those with none.
*Chi-square test, †: Fisher's exact test, COPD: Chronic obstructive pulmonary disease, OR: Odds ratios

than in surviving patients. Only alanine aminotransferase (ALT) at admission was lower in deceased patients than in surviving patients (16 UI/L vs. 23 UI/L, p=0.001) (Table 4).

The 1-year mortality after discharge from the hospital was higher in patients requiring invasive ventilation (12.0% vs. 2.8%, OR=4.79, p=0.019) and intensive care unit (ICU) admission (11.8% vs. 2.6%, OR=4.94, p=0.007) than those with none (Table 5).

## Discussion

In this study, we presented a detailed analysis of the predictors of 1-year mortality in 567 hospitalized patients with COVID-19. The 1-year mortality rate was relatively low (3.2%). Older age, COPD, chronic artery disease, chronic renal failure, presence of pleural fluid on chest CT, high levels of leukocyte, neutrophil, monocyte, CRP, procalcitonin, urea, creatinine, troponin, LDH, potassium, and a low level of ALT were associated with increased long-term mortality. Additionally, the need for ICU admission and ventilatory support, including non-invasive ventilation, during the hospital stay for COVID-19 was associated with about a 5-fold increased 1-year mortality.

Recently, new concerns about increased long-term mortality in patients with certain risk factors have arisen (9). Nevertheless, only a few studies have provided information on risk factors or predictors of 1-year mortality (10-12). The 1-year mortality rate was decisively lower in this study compared to the previous studies on community-acquired pneumonia in Turkey (13,14). This might be partly explained by the difference between COVID-19 and other etiological agents of community-acquired pneumonia in the disease severity and their nature. Most patients with COVID-19 during the first period of the pandemic were admitted to isolated wards according to the national guidelines due to the unknown consequences. Thus, hospitalized patients with COVID-19 were younger and had fewer previous history of comorbid diseases. This also explains the long-term better outcomes of COVID-19 in

**Table 2. Comparison of the clinical characteristics at first admission of deceased and survived patients in the post-discharge 1-year period**

| | | Deceased | | Survived | | In total | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | % | n | % | n | % | p-value | OR |
| Fever | Yes | 7 | 2.20 | 312 | 97.80 | 319 | 56.26 | 0.15* | 0.48 |
| | No | 11 | 4.40 | 237 | 95.60 | 248 | 43.74 | | |
| Cough | Yes | 14 | 3.20 | 424 | 96.80 | 438 | 77.25 | 0.96† | 1.03 |
| | No | 4 | 3.10 | 125 | 96.90 | 129 | 22.75 | | |
| Chest pain | Yes | 1 | 6.30 | 15 | 93.80 | 16 | 2.82 | 0.48† | 2.09 |
| | No | 17 | 3.10 | 534 | 96.90 | 551 | 97.18 | | |
| Myalgia | Yes | 1 | 1.40 | 72 | 98.60 | 73 | 12.87 | 0.35† | 0.39 |
| | No | 17 | 3.40 | 477 | 96.60 | 494 | 87.13 | | |
| Arthralgia | Yes | 0 | 0.00 | 21 | 100.00 | 21 | 3.70 | 0.40† | 1.03 |
| | No | 18 | 3.30 | 528 | 96.70 | 546 | 96.30 | | |
| Fatigue | Yes | 3 | 1.50 | 196 | 98.50 | 199 | 35.10 | 0.11† | 0.36 |
| | No | 15 | 4.10 | 353 | 95.90 | 368 | 64.90 | | |
| Nausea | Yes | 1 | 2.80 | 35 | 97.20 | 36 | 6.35 | 0.89† | 0.86 |
| | No | 17 | 3.20 | 514 | 96.80 | 531 | 93.65 | | |
| Vomiting | Yes | 0 | 0.00 | 19 | 100.00 | 19 | 3.35 | 0.42† | 1.03 |
| | No | 18 | 3.30 | 530 | 96.70 | 548 | 96.65 | | |
| Diarrhea | Yes | 2 | 8.00 | 23 | 92.00 | 25 | 4.41 | 0.16† | 2.86 |
| | No | 16 | 3.00 | 526 | 97.00 | 542 | 95.59 | | |

No significant relationship was detected between 1-year mortality and initial sypmtoms at admission.
*Chi-square test, †: Fisher's Exact test, OR: Odds ratios

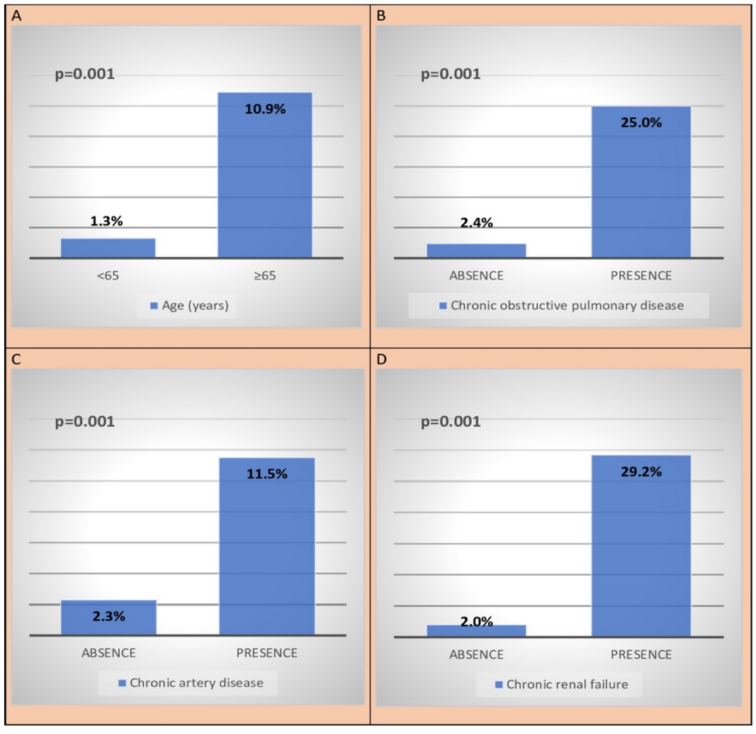


**Figure 1.** Risk factors for mortality in patients with COVID-19 in the post-dicharge 1-year period (A. Age B. Chronic obstructive pulmonary disease C. Chronic artery disease D. Chronic renal failure)
*COVID-19: Coronavirus disease-2019*

**Table 3. Comparison of the radiological findings at first admission of deceased and survived patients in the post-discharge 1-year period**

| | | Deceased | | Survived | | In total | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | n | % | n | % | n | % | p-value | OR |
| Chest graphy findings | Yes | 14 | 4.30 | 312 | 95.70 | 326 | 70.56 | 0.13† | 3.01 |
| | No | 2 | 1.50 | 134 | 98.50 | 136 | 29.44 | | |
| | Unilateral | 2 | 5.60 | 34 | 94.40 | 36 | 11.36 | 0.72† | 1.32 |
| | Bilateral | 12 | 4.30 | 269 | 95.70 | 281 | 88.64 | | |
| Chest CT findings | Yes | 17 | 3.10 | 533 | 96.90 | 550 | 98.39 | 0.18† | 0.26 |
| | No | 1 | 11.10 | 8 | 88.90 | 9 | 1.61 | | |
| Plevral fluid | Yes | 6 | 27.30 | 16 | 72.70 | 22 | 3.99 | **0.001*** | 16.16 |
| | No | 12 | 2.30 | 517 | 97.70 | 529 | 96.01 | | |
| | Unilateral | 2 | 28.60 | 5 | 71.40 | 7 | 30.43 | 1.00† | 0.88 |
| | Bilateral | 5 | 31.30 | 11 | 68.80 | 16 | 69.57 | | |
| Small patch | Yes | 2 | 1.60 | 124 | 98.40 | 126 | 22.83 | 0.23† | 0.41 |
| | No | 16 | 3.80 | 410 | 96.20 | 426 | 77.17 | | |
| Ground-glass opacity | Yes | 15 | 3.10 | 473 | 96.90 | 488 | 88.41 | 0.49† | 0.65 |
| | No | 3 | 4.70 | 61 | 95.30 | 64 | 11.59 | | |
| Consolidation | Yes | 6 | 3.80 | 151 | 96.20 | 157 | 28.39 | 0.64* | 1.27 |
| | No | 12 | 3.00 | 384 | 97.00 | 396 | 71.6 | | |
| Air bronchogram | Yes | 0 | 0.00 | 21 | 100.00 | 21 | 3.80 | 0.39† | - |
| | No | 18 | 3.40 | 514 | 96.60 | 532 | 96.20 | | |
| Interlobuler septal thickening | Yes | 5 | 10.40 | 43 | 89.60 | 48 | 8.68 | **0.003*** | 4.4 |
| | No | 13 | 2.60 | 492 | 97.40 | 505 | 91.32 | | |
| Pulmonary nodules | Yes | 0 | 0.00 | 43 | 100.00 | 43 | 7.78 | 0.21† | - |
| | No | 18 | 3.50 | 492 | 96.50 | 510 | 92.22 | | |
| Pathological lymph node | Yes | 1 | 11.10 | 8 | 88.90 | 9 | 1.62 | 0.18† | 3.88 |
| | No | 17 | 3.10 | 528 | 96.90 | 545 | 98.38 | | |

Bold values represent statistical significance at the level of p<0.05. The 1-year mortality was observed more frequent in patients with pleural fluid on chest CT compared to patients without pleural fluid.
*Chi-square test, †: Fisher's Exact test, CT: Computed tomography, OR: Odds ratios

our study compared to community-acquired pneumonia in previous studies.

The 1-year mortality rates vary between studies and range from 1% to 39% depending on the study population (10-12,15-18). Maestre-Muñiz et al. (10) reported that the 1-year mortality in COVID-19 patients applying to emergency departments but not hospitalized was 3.1% (n=10). Additionally, they revealed that the 1-year mortality rate in patients with COVID-19 after discharge from the hospital was 12.8% (n=34). However, they did not evaluate the risk factors or predictors of 1-year mortality. In their study, the higher mortality rates might be explained by the older age of their study population and the higher comorbidities in hospitalized patients. In the study by Maestre-Muñiz et al. (10), of the hospitalized patients with COVID-19, about 70% were older than 65 years and about 90% had at least one underlying disease. In our study, only 19.4% of the cohort was over 65 years old, and 55.3% of patients had a previous history of any comorbidity.

In the study by Akhtar et al. (15), they demonstrated that a high rate of subsequent 1-year mortality (n=28, 17.6%) was associated with increased poor outcomes. They revealed that older age, diabetes mellitus, and post-COVID electrocardiographic findings were associated with an increased risk of long-term mortality. Akhtar et al. (15) showed that about a quarter of patients with diabetes mellitus and 17% of patients with hypertension died one year after recovery from acute COVID-19. In our study, 25% of patients with COPD, 11.5% of patients with chronic artery disease, and 29.2% of patients with chronic renal failure died after discharge in the long-term period.

Chai et al. (11) reported that 3.5% (n=17) of the discharged patients with COVID-19 (n=488) died within the 1-year follow-up in the cohort, while the 1-year mortality rate was 11.4% (n=15) in patients with cancer who had COVID-19. Interestingly, Ceccato et al. (12) demonstrated a low 1-year mortality rate in ICU admitted patients after discharge (1.3%, n=28). Similarly, in another study with comparable findings to our study in terms of

**Table 4. Comparison of the vital signs and laboratory parameters at first admission of deceased and survived patients in the post-discharge 1-year period**

| Parameters | Deceased | Survived | In total | p-value |
|---|---|---|---|---|
| | Median (IQR) | Median (IQR) | Median (IQR) | |
| $SpO_2$ (%) | 93 (90-95) | 94 (92-96) | 94 (92-96) | 0.17* |
| Systolic Blood Pressure (mmHg) | 115 (105-120) | 120 (110-130) | 120 (110-130) | 0.293* |
| Diastolic Blood Pressure (mmHg) | 70 (63-80) | 70 (70-80) | 70 (70-80) | 0.536* |
| Body temperature (°C) | 37 (36-37) | 37 (36-37) | 37 (36-37) | 0.653* |
| Respiratory rate/minute | 20 (18-21) | 20 (20-22) | 20 (20-22) | 0.198* |
| Heart rate/minute | 84 (72-97) | 87 (80-95) | 86 (80-95) | 0.614† |
| Leukocyte count/$mm^3$ | 7860 (6400-12130) | 5850 (4500-7480) | 5900 (4540-7530) | **0.001*** |
| Neutrophil count/$mm^3$ | 5690 (4370-8400) | 3650 (2790-5130) | 3730 (2800-5300) | **0.001*** |
| Lymphocyte count/$mm^3$ | 1140 (680-1390) | 1380 (1010-1810) | 1370 (1005-1800) | 0.063* |
| Monocyte (/*µl*) | 740 (430-1010) | 510 (370-690) | 510 (370-700) | **0.026*** |
| Monocyte (%) | 7.7 (5.7-9.9) | 8.3 (6.5-10.8) | 8.3 (6.5-10.8) | 0.353† |
| Platelet count/$mm^3$ | 199 (162-341) | 196 (156-240) | 196 (156-241) | 0.403* |
| Hemoglobin, (g/dL) | 12.6 (12.1-13.7) | 13 (12-14) | 13 (12-14) | 0.423† |
| Hematocrit, (g/dL) | 38.3 (37-41) | 39 (36.3-41.5) | 39 (36.3-41.5) | 0.968* |
| Glucose, (mg/dL) | 107 (90-149) | 114 (100-147) | 114 (100-147) | 0.492* |
| C-reactive protein, (mg/L) | 60 (27.4-166) | 36 (13.1-81) | 37 (13.9-81.2) | **0.042*** |
| Procalcitonin, (ng/mL) | 0.13 (0.07- 0.44) | 0.05 (0.03-0.08) | 0.05 (0.03-0.08) | **0.004*** |
| Urea, (mmol/L) | 44 (37-79) | 27 (21-33) | 27 (21-34) | **0.001*** |
| Creatinine, (mg/dL) | 1.12 (0.8-2.5) | 0.73 (0.6-0.9) | 0.74 (0.6-0.9) | **0.001*** |
| Ferritin, (ng/L) | 97.5 (94-119) | 155 (80-307) | 152 (80-307) | 0.322* |
| Troponin (ng/L) | 59.2 (12.4-288) | 3.9 (2.6-7) | 3.95 (2.6-7.2) | **0.001*** |
| Fibrinogen (mg/dL) | 566 (365-640) | 481 (376-574) | 482 (376-576) | 0.357* |
| LDH, (UI/L) | 312 (261-543) | 264 (218-340) | 265 (219-341) | **0.019*** |
| Creatine kinase (IU/L) | 91 (70-245) | 110 (58-194) | 109 (59-194) | 0.834* |
| D-dimer, (mg/L) | 1.28 (0.4-1.32) | 0.64 (0.4-1.04) | 0.64 (0.4-1.07) | 0.382* |
| Albumin (g/dL) | 38 (36-39) | 37 (35-40) | 37 (35-40) | 0.981† |
| AST, (UI/L) | 27 (18- 34) | 31 (24-43) | 31 (24-42) | 0.057* |
| ALT, (UI/L) | 16 (12-19) | 23 (16-35) | 23 (16-35) | **0.001*** |
| Sodium (mmol/L) | 136 (133-138) | 138 (135-139) | 138 (135-139) | 0.208† |
| Potassium (mmol/L) | 4.5 (4.1-4.8) | 4.1 (3.8-4.3) | 4.1 (3.8-4.3) | **0.003*** |
| Calcium (mmol/L) | 8.7 (8.1-9.2) | 8.9 (8.5-9.2) | 8.9 (8.5-9.2) | 0.187† |

Bold values represent statistical significance at the level of p<0.05. The median values of leukocyte count, neutrophil count, monocyte count, C-reactive protein, procalcitonin, urea, creatinine, troponin, lactate dehyrogenase, and potassium at admission were significantly higher in deceased patients than in survived patients. Only ALT at admisson was significantly lower in deceased patients than in survived patients.
*Mann-Whitney U test, †: Independent sample t-test, LDH: Lactate dehydrogenase, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, IQR: Interquartile ranges

**Table 5. Comparison of the need for supportive care during the first hospitalisation for COVID-19 of deceased and survived patients in the post-discharge 1-year period**

| | | Deceased | | Survived | | In total | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | n | % | n | % | n | % | p-value | OR |
| Oxygen need | Yes | 14 | 3.8 | 357 | 96.2 | 371 | 65.4 | 0.270* | 1.88 |
| | No | 4 | 2.0 | 192 | 98.0 | 196 | 34.6 | | |
| Invasive ventilation | Yes | 3 | 12.0 | 22 | 88.0 | 25 | 4.4 | **0.019*** | 4.79 |
| | No | 15 | 2.8 | 527 | 97.2 | 542 | 95.6 | | |
| Vasopressor need | Yes | 1 | 7.1 | 13 | 92.9 | 14 | 2.5 | 0.406* | 2.43 |
| | No | 17 | 3.1 | 536 | 96.9 | 553 | 97.5 | | |
| ICU admission | Yes | 4 | 11.8 | 30 | 88.2 | 34 | 6.0 | **0.007*** | 4.94 |
| | No | 14 | 2.6 | 519 | 97.4 | 533 | 94.0 | | |

Bold values represent statistical significance at the level of p<0.05. The 1-year mortality after discharge from hospital was higher in patients requiring invasive ventilation and ICU admission than those with none.
*Fisher's exact test, ICU: Intensive care unit, COVID-19: Coronavirus disease-2019, OR: Odds ratios

age and comorbidities, the 1-year post-discharge mortality rate was 1.3% in the cohort (n=32) and 1.8% (n=8) in patients with diabetes mellitus (16). The researchers found that fasting blood glucose was associated with a 4-fold increased risk of 1-year mortality in patients with no history of diabetes mellitus and about an 11-fold increased risk of 1-year mortality in patients with diabetes. However, they did not find a relationship between post-discharge long-term mortality and diabetes mellitus. Akhtar et al. (15) found that a high red cell distribution width and low albumin level on discharge were associated with long-term mortality.

In a prospective cohort of chronic renal failure patients who needed hemodialysis, 25% of the survived patients (n=14) died within the first year (17). Similarly, a quarter of the survivors with chronic renal failure died within the first year in this study. The prevalence of 6-month mortality after hospitalization in mechanically ventilated patients was 38.6% (n=335) in a multicenter Spanish study. However, their analysis included patients who died during the hospital stay, since they did not exclude patients who were discharged from the hospital. The researchers revealed age, diabetes mellitus, neutrophil to lymphocyte ratio, and other factors measured during the ICU stay as predictors of 6-month survival. Chojnicki et al. (18) analyzed patients over 60 years of age and showed that 13.2% (n=30) of surviving patients (n=227) died during the 6-month post-discharge period. They demonstrated that age, cognitive functions, functional capacity, hemoglobin level, and urea were associated with mortality. As a result, various rates of mortality have been observed depending on the characteristics of the cohorts. Additionally, different risk factors and predictors from different studies have been determined for 1-year mortality in COVID-19.

### Study Limitations

This study had some limitations. First, this study was retrospectively conducted in a single center. Second, our sample size was small and not generalizable to different populations. Third, we used crude all-cause mortality since causes of death were not determined in the study. Some deaths may not be directly attributable to COVID-19. However, the observed increased re-hospitalisation rates and high prevalence of multiorgan dysfunction in patients with COVID-19 compared to the general population prove that there is a certain association between COVID-19 and the 1-year consequences, including death (15). Finally, we did not evaluate long-term persistent symptoms, pulmonary sequelae and other complications or secondary outcomes including readmission, need for ventilation support, respiratory or multiorgan failure, since the only outcome that we measured was the 1-year mortality, due to the primary objective of this study. However, we had several strengths. First, to our knowledge, this is the first comprehensive study to evaluate 1-year mortality and its predictors in hospitalized patients with laboratory confirmed COVID-19 in Turkey. Second, we included all hospitalized patients during the first period of the COVID-19 pandemic. Third, we could include multiple comorbidities and different types of variables in the analysis.

### Conclusion

This study proves that surviving patients still have an ongoing mortality risk even after recovery from acute COVID-19. Additionally, our study provides a list of predictors of 1-year mortality in patients with COVID-19 and suggests that age, underlying diseases, pleural fluid, certain laboratory parameters, and ICU care during the first admission are somewhat associated with 1-year mortality.

Therefore, clinicians should define a comprehensive follow-up plan for survivors and consider close monitoring of patients with these risk factors after discharge from the hospital.

### Ethics

**Ethics Committee Approval:** This study was approved by the Ethics Committee of University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital (approval number: 102-2022, date number: 08.06.2022).

**Informed Consent:** Written informed consent was waived because of the retrospective nature of this study.

**Peer-review:** Externally and internally peer-reviewed.

### Authorship Contributions

Concept: S.S., Design: S.S., O.F.B., Data Collection or Processing: S.S., G.T., O.F.B., H.T., B.C., M.Y., E.Z., I.Y.N., Analysis or Interpretation: S.S., O.F.B., Literature Search: S.S., G.T., O.F.B., G.S., F.P., Writing: S.S.

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

**Financial Disclosure:** The authors declared that this study received no financial support.

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Original Article

DOI: 10.4274/haseki.galenos.2022.8721
Med Bull Haseki 2022;60:447-452

# Anesthesia Management in Cesarian Section in Pregnant Patients with COVID-19 Diagnoses

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## Abstract

**Aim:** The recommendation to avoid general anesthesia in pregnant women with coronavirus disease-2019 (COVID-19) and to use neuraxial blockade techniques, if possible, has not changed over time. On the other hand, general anesthesia also has to be applied to some patients in clinical practice. In this study, we evaluated anesthesia management, maternal outcomes, and clinical course in pregnant women with COVID-19 who delivered by cesarean section.

**Methods:** One hundred and seven pregnant women with COVID-19 who underwent cesarean sections between October 2020 and April 2021 were included in the study. Anesthesia methods, presenting symptoms, comorbidities, laboratory test results, and radiological data at admission, length of hospital stay, intensive care unit admissions, and mortality rates were retrospectively analyzed.

**Results:** Out of 107 pregnant women, 85 underwent cesarean surgery under spinal anesthesia and 22 under general anesthesia. Forty patients (37%) had at least one symptom, whereas sixty-seven (63%) had no symptoms at all. Fifty percent of symptomatic and only 6% of asymptomatic pregnant women were admitted to the intensive care unit, and there was a significant difference between them. Mortality was 30% in symptomatic patients and only 1% in asymptomatic patients, and the difference in mortality was significant ($p<0.05$).

**Conclusion:** Since the risk of intensive care and mortality is higher, particularly in symptomatic pregnant women with COVID-19, these patients should be evaluated, operated and followed up by experienced teams.

**Keywords:** COVID-19, anesthesia, obstetrical, spinal, intensive care units

## Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), the cause of coronavirus disease-2019 (COVID-19), started in Wuhan, China, in December 2019, is a novel coronavirus that causes a spectrum of diseases ranging from asymptomatic to severe acute respiratory distress syndrome (ARDS), septic shock, cardiovascular symptoms, and death (1,2).

COVID-19 infection was discovered in 10% of pregnant women who presented to the hospital for any reason, according to a meta-analysis of 192 studies (3). However, compared with non-pregnant women, pregnant women have a higher risk of having more severe symptoms and being admitted to an intensive care unit (ICU) or hospital (4). Since the lungs are the main target of the coronavirus disease, anesthesia management during cesarean surgery is essential (5,6).

The use of neuraxial blockade techniques has advantages over general anesthesia and causes less respiratory depression. It is also thought to reduce the spread of the virus to healthcare workers via aerosol. For all these reasons, the recommendation to avoid general

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**Received:** 18.08.2022 **Accepted:** 14.11.2022

anesthesia in pregnant women with COVID-19 and to use neuraxial blockade techniques, if possible, has not changed over time (4,7). On the other hand, general anesthesia also has to be applied to some patients in clinical practice.

We evaluated anesthesia management, maternal outcomes, and clinical course in pregnant women with COVID-19 who delivered by cesarean section.

## Materials and Methods

### Compliance with Ethical Standards

The study was carried out in accordance with the principles of the Helsinki Declaration, with the approval of the local Ethics Committees of University of Health Sciences Turkey, Basaksehir Cam and Sakura City Hospital (decision no: 2021.04.71, date: 28.04.2021). This article was not funded. Written informed consent was obtained from all patients in this study before participation.

### Study Design

The study was conducted as a single-center and cross-sectional study. Pregnant women who underwent cesarean sections with COVID-19 between October 2020 and April 2021 were included in the study. Anesthesia methods (general or regional), patient characteristics (age, symptoms at admission, comorbidities), laboratory test results and radiological findings at admission, length of hospital stay, ICU needs, and mortality were analyzed. The patients' medical data were obtained from our hospital's digital automation system and anesthesia records. Patients were divided into two groups, symptomatic and asymptomatic, and the data were analyzed statistically.

### Patient Management

Patients were taken to the negative pressure operating room by personnel wearing personal protective equipment, and routine monitoring was performed. Oxygen therapy was given only to those who needed it. For the spinal block, 0.5% hyperbaric bupivacaine was administered with a 25-gauge needle, and sedation was given to the patients after the baby was discharged if necessary. General anesthesia was administered when spinal anesthesia failed or was contraindicated, in cases of fetal distress with insufficient time for spinal anesthesia, and when the patient was orotracheally intubated from the ICU.

### Statistical Analysis

The SPSS 24.0 (Statistical Package for the Social Sciences) program was used to evaluate and statistically analyze the data obtained in the study. Descriptive statistics were expressed as numbers and percentages (%) for discrete variables and median (minimum-maximum) for continuous variables. The Kolmogorov-Smirnov test was used to determine the normal distribution of quantitative data, and since the assumption of normal distribution was not met, the analyses were performed using the Mann-Whitney U test. Chi-square test statistics were used to analyze the relationship between categorical variables. The statistical significance level was set at a p-value less than 0.05.

## Results

In 85 of the 107 women who had cesarean surgery, spinal anesthesia was used, and general anesthesia was used in 22. Sixty-four patients had no comorbidity; fifty-seven had anemia, nine had hypothyroidism, and six had diabetes mellitus. A patient had diabetic ketoacidosis. Others had chronic bronchitis, allergic asthma, hypertension, cholestasis, preeclampsia, epilepsy, and lymphoma (Table 1).

Of the 107 pregnant women, 67 (63%) were asymptomatic. The symptoms of symptomatic women included dyspnea (30%), cough (20%), fever (4%), diarrhea (3%), and vomiting (3%). One patient had a headache, and another patient had chest pain (Table 2). All 107 patients were PCR-positive for SARS-CoV-2. There were signs of pneumonic infiltration in the chest radiograms of 25 patients (Table 3).

**Table 1. Mean age and comorbidities of patients**

| | Number of patients (n=107) |
|---|---|
| Average age, mean | 30.7 |
| Additional disease, No, n | 64 |
| Additional disease, Yes, n | 43 |
| Anemia, n | 57 |
| Chronic bronchitis, n | 1 |
| Allergic Asthma, n | 4 |
| Hypertension, n | 4 |
| Preeclampsia, n | 2 |
| Valvular heart disease, n | 1 |
| History of thrombus, n | 1 |
| Cholestasis of pregnancy, n | 5 |
| Fatty liver, n | 1 |
| Diabetes, n | 6 |
| Insulin resistance, n | 1 |
| Diabetic ketoacidosis, n | 1 |
| Hypothyroidism, n | 9 |
| Hepatitis, n | 2 |
| Scoliosis, n | 1 |
| Migraine, n | 1 |
| Epilepsy, n | 2 |
| Lymphoma, n | 2 |
| Thalassemia, n | 1 |

*Unless otherwise stated, results are given as n (%)

| Table 2. Patient symptoms assessment (n=107) | |
|---|---|
| | Number of patients |
| **Symptoms and findings** | |
| No symptoms, n (%) | 67 (63%) |
| Fever, n (%) | 4 (4%) |
| Cough, n (%) | 21 (20%) |
| Palpitations, n (%) | 1 (1%) |
| Shortness of breath, n (%) | 32 (30%) |
| Diarrhea, n (%) | 3 (3%) |
| Chest pain, n (%) | 1 (1%) |
| Headache, n (%) | 1 (1%) |
| Vomiting, n (%) | 3 (3%) |
| Itching, n (%) | 1 (1%) |
| *Unless otherwise stated, results are given as n (%) | |

Leucocytosis was present in 27 (25%) patients, and lymphopenia in 34 (32%) patients. Twenty-four patients without preeclampsia showed thrombocytopenia. The lowest thrombocyte counts were 63,000 and 65,000, and these patients were under general anesthesia. A patient with a thrombocyte count of 70,000 underwent spinal anesthesia without any neurological sequelae. Patients with thrombocyte counts of 91,000 and 99,000 were operated on under general anesthesia. Seventy-three patients had an elevated C-reactive protein level, 16 had an elevated PCT level, and 71 had an elevated LDH level (Table 3).

The mean length of hospitalization was 9 days for pregnant women who were operated on under spinal anesthesia and 15 days for those who were operated on under general anesthesia. Twenty-four pregnant women were admitted to the ICU. In 107 pregnant women with COVID-19, the overall mortality rate was 12%. Among them, those who were operated on under spinal anesthesia had a mortality rate of 11%, and those who were operated on under general anesthesia had a mortality rate of 18 (Table 4).

| Table 3. Laboratory results (n=107) | |
|---|---|
| | Number of patients, n |
| **Laboratory results** | |
| Leucocytosis, n | 27 |
| Lymphopenia, n | 34 |
| Thrombocytopenia, n | 24 |
| Elevated CRP concentrations, n | 73 |
| Elevated ALT concentrations, n | 24 |
| Elevated AST concentrations, n | 47 |
| Elevated PCT levels, n | 16 |
| Elevated LDH levels, n | 71 |
| Radiographic evidence of pneumonia, n | 25 |
| *Unless otherwise stated, results are given as n (%). (Leucocytosis >10.000, lymphopenia <1.000, thrombocytopenia <150.000, elevated CRP >10, elevated ALT >33, elevated AST >31, elevated LDH >214, elevated PCT >0.5) CRP: C-reactive protein, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, PCT: Procalcitonin, LDH: Lactate dehydrogenase | |

Forty of 107 pregnant women had at least one symptom, and 67 had none. While at least one comorbidity in 43 of them, 64 had no comorbidity. Fifty percent of symptomatic and only 6% of asymptomatic pregnant women were admitted to the ICU, and there was a significant difference between them ($p<0.05$). Mortality was 30% in symptomatic patients and only 1% in asymptomatic patients, and there was a significant difference in mortality ($p<0.05$). ICU admission was 21% in patients with comorbidity and 23% in those without comorbidity, and the difference was insignificant. Mortality was 16% in patients with comorbidity and 9% in those without comorbidity. There was no significant difference in mortality between patients with comorbidity and those without comorbidity (Table 5).

## Discussion

SARS-CoV-2 infection enters the respiratory tract through nasopharyngeal mucosal membranes. A mild form affecting the upper respiratory tract occurs in approximately 80% of the cases. In contrast, a very severe form of the disease occurs in 20% of cases, affecting pulmonary alveolar cells and causing a systemic inflammatory response due to the cytokine storm. It has been shown that disease severity is related to advanced age and the presence of comorbidities (2,7). Most COVID-19-positive pregnant women are asymptomatic, but it has been reported that pregnancy increases the risk of having severe COVID-19 (8-10). Many studies have shown that pregnant women admitted to the hospital with critical coronavirus disease are more likely than non-pregnant women of reproductive age to be admitted to an ICU, be mechanically ventilated, or have a higher morbidity burden. Pre-existing maternal comorbidities, in particular, increase the risk (6,11-13).

| Table 4. Evaluation of mortality, hospital and intensive care unit locations | | |
|---|---|---|
| | Spinal anesthesia (n=85) | General anesthesia (n=22) |
| Length of hospitalization, days | 9 | 15 |
| Number of patients admitted to ICU, n | 12 | 12 |
| Length of stay in ICU, days | 14 | 16 |
| Mortality, n (%) | 9 (11) | 4 (18) |
| *Unless otherwise stated, results are given as n (%). ICU: Intensive care unit | | |

| Table 5. The effect of patients' symptoms and comorbidities on ICU hospitalization and mortality | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Admission to ICU | | | | p-value | Mortality | | | | p-value |
| Number of patients | | A | | N/A | | | A | | N/A | | |
| Symptom | Yes | 20 | (50%) | 20 | (50%) | **0.000** | 12 | (30%) | 28 | (70%) | **0.000** |
| | No | 4 | (6%) | 63 | (94%) | | 1 | (1%) | 66 | (99%) | |
| No | Yes | 9 | (21%) | 34 | (79%) | **0.760** | 7 | (16%) | 36 | (84%) | **0.284** |
| | No | 15 | (23%) | 49 | (77%) | | 6 | (9%) | 58 | (91%) | |

*Unless otherwise stated, results are given as n (%).
ICU: Intensive care unit

In a cohort study of 126 obstetric patients by Keita et al. (14), 17% of cases with COVID-19 were hospitalized in the ICU. It has been reported that symptomatic pregnant women are more likely to be admitted to the ICU and require mechanical ventilation (15). ICU hospitalization was 22.4% in our study. While the rate of ICU admission was 50% in pregnant women with symptoms, it was only 6% in those without symptoms, and there was a significant difference between them ($p<0.05$). While 21% of patients with comorbidity were admitted to the ICU, 23% of those without comorbidity were admitted.

Fever, coughing, dyspnea, sore throat, myalgia, nasal discharge, smell or taste abnormalities, ARDS, arrhythmias, acute cardiac damage, and shock are all signs and symptoms of COVID-19 in pregnant women (2). Sutton et al. (16) evaluated 454 women who gave birth and found COVID-19 in 79 (17%). 27.9% of pregnant women were symptomatic, with symptoms including cough (13.9%), fever (10.1%), chest pain (5.1%), and myalgia (5.1%). In our study, all the patients had a positive SARS-CoV-2 polymerase chain reaction (PCR) test, and 63% were asymptomatic. Of those who were symptomatic, 30% had dyspnea, 20% were coughing, and 4% had a fever. Nine percent% complained of diarrhea, vomiting, palpitations, chest pain, headache, and itching.

Pregnant women may be more susceptible to respiratory tract pathogen infection due to elevated diaphragm muscles, airway oedema, increased oxygen demand, and immunological changes.Simultaneously, all these pregnancy-related changes make pregnant women more susceptible to hypoxemia (17). Pregnant women with COVID-19 are managed according to the disease's severity. Depending on the clinical course of the disease, arterial blood gas analysis, lactate, liver and kidney function tests, and cardiac enzymes should be serially measured. Monitoring vital signs and oxygen saturation are important. Maternal vital signs should be closely monitored.

Maintain maternal oxygen saturation ($SpO_2$) of 95%; if $SpO_2$ drops below 95%, an arterial blood gas analysis should be performed to evaluate $PaO_2$. To maintain an adequate oxygen gradient between the mother and the fetus, PaO2 should be maintained above 70 mmHg. Depending on the severity of hypoxemia, inhaled oxygen can be administered. To achieve adequate oxygenation, high-flow oxygenation, intubation or mechanical ventilation, and extracorporeal membrane oxygenation (ECMO) can be used (18). COVID-19 by itself is not a reason to change the delivery method. If pregnancy is beyond 32 weeks and delivery would improve respiratory function in pregnant women, delivery is recommended (19). In this study, 20 (18%) pregnant women needed oxygen therapy, of whom 2 were intubated and mechanically ventilated before cesarean surgery.

When an anesthesia technique for cesarean surgery is selected for a COVID-19-positive pregnant woman, the urgency of the operation should be the primary consideration. COVID-19 is not a contraindication for neuraxial anesthesia. Evaluation of thrombocytopenia should be given priority when managing patients suspected of having confirmed COVID-19. It should be remembered that respiratory distress may be aggravated due to a further decline in functional residual capacity caused by neuraxial anesthesia (20). Regional anesthesia is recommended because the target organs of the SARS-CoV-2 infection are the lungs, and regional anesthesia will reduce intubation-related pulmonary complications and aerosol release (4,8). Binyamin et al. (21) found that the rate of neuraxial block in elective cesarean surgery was 44.8% before the SARS-CoV-2 pandemic, whereas it rose to 79.3% during the pandemic.

In our study, spinal anesthesia was the anesthesia technique of choice during cesarean surgery. In 79% of the 107 pregnant women, spinal anesthesia was used, while general anesthesia was used in 21%. General anesthesia was used when any maternal or fetal emergency condition existed (when there was no waiting time for regional anesthesia), when spinal anesthesia was contraindicated, when a patient was brought to the operating room from the ICU while intubated, or when intrathecal anesthesia failed. A study from the United Kingdom reported a significant drop in the rate of general anesthesia for cesarean surgery during the COVID-19 pandemic (22). Since our hospital was opened during the COVID-19 pandemic, we could

not compare the anesthesia management in cesarean deliveries during and before the pandemic.

Studies have reported thrombocytopenia in one-third of patients with COVID-19 infection (23). A thrombocyte count of 75,000 and above is recommended as an acceptable level for neuroanesthesia (20,23-25). Lee et al. (26) recommend that regional anesthesia be performed at lower thrombocyte counts (70,000 or lower) in pregnant women who may develop respiratory failure with general anesthesia. In this study, 24 pregnant women without preeclampsia developed thrombocytopenia. Patients with thrombocytopenia underwent cesarean surgery under general anesthesia. Only one patient with a thrombocyte count of 70,000 was operated on under spinal anesthesia without any neurological complications. Studies have recommended using neuraxial procedures for pregnant women with COVID-19 without contraindications (8). Sangroula et al. (27) also demonstrated that neuraxial anesthesia with standard-dose local anesthetic agent administration was safe and effective in COVID-19-positive pregnant women who were asymptomatic or mildly symptomatic.

According to Villar et al. (28), 11 out of 706 pregnant women diagnosed with COVID-19 died. COVID-19 symptoms were also linked to higher morbidity and mortality, with a 22-fold increase in the probability of death. In our study, on the other hand, 13 (12%) of 107 pregnant women with COVID-19 died. Of these, seven had comorbidities (hypothyroidism, diabetic ketoacidosis, hypertension, a history of intracerebral thrombus, epilepsy, asthma, and Hodgkin lymphoma), while six had none. Twelve patients died in the ICU, and a patient who refused treatment after cesarean surgery died after discharge. There was no significant difference in mortality between patients with and without comorbidities. Mortality was 30% in symptomatic pregnant women and 1% in asymptomatic women. In the study, mortality was significantly higher in the presence of symptoms in pregnant women with COVID-19.

According to the data provided by the Turkish Ministry of Health, maternal mortality increased after the COVID-19 pandemic compared with pre-pandemic figures. Increased morbidity and mortality have been observed in COVID-19-positive pregnant women with comorbidities. Despite a multidisciplinary approach, mortality rates are particularly high during peripartum care in advanced centers. Our hospital is also a leading referral center for pregnant patients with multiple comorbidities and clinical findings, as well as pregnant women from other hospitals. All available treatments, including ECMO, can be performed at our center. This explains the increased ICU admission and mortality rates among our pregnant patients. In our study, patients with COVID-19 who underwent cesarean surgery had a mortality rate of 12%.

### Study Limitations

The most important limitation of the study is that it is retrospective in nature. The lack of long-term results is another important limitation. Despite these limitations, the relatively high number of patients in the study and the fact that we are a center with many treatment possibilities make the study valuable.

## Conclusion

In this study, the incidence of cesarean delivery under spinal anesthesia was higher than that under general anesthesia in pregnant women with COVID-19. Spinal anesthesia is safe for pregnant women with COVID-19. Symptoms and comorbidity increase the rate of intensive care hospitalization, mechanical ventilation, and morbidity, and in our study, we found that intensive care and mortality rates were higher in symptomatic COVID-19 pregnant women. These patients should be evaluated, operated and followed up by experienced teams.

### Ethics

**Ethics Committee Approval:** The study was approved by the local ethics committees of University of Health Sciences Turkey, Basaksehir Cam and Sakura City Hospital (decision no. 2021.04.71, date: 28.04.2021).

**Informed Consent:** Written informed consent was obtained from all patients in this study before participation.

**Peer-review:** Externally peer-reviewed.

### Authorship Contributions

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

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

**Financial Disclosure:** The authors declared that this study received no financial support.

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Original Article

DOI: 10.4274/haseki.galenos.2022.8327
Med Bull Haseki 2022;60:453-460

# Clinical Characteristics of COVID-19 in Active or Previously Treated Tuberculosis Patients in Turkey

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## Abstract

**Aim:** There is limited literature on coronavirus disease-2019 (COVID-19) and tuberculosis (TB) coinfection, although high rates of coinfection between COVID-19 and other respiratory pathogens are expected. To the best of our knowledge, this is the first study to examine COVID-19 infection in patients diagnosed with active or previously treated TB in Turkey. In this study, the aim was to examine the frequency of COVID-19 and the factors affecting the frequency of COVID-19 in patients with active or previously treated TB.

**Methods:** The population of the retrospective cohort type study consisted of patients with TB enrolled in the Elazig Tuberculosis Dispensary between January 2015 and April 2021. The TB-related data of the patients was obtained from the Public Health Management System Tuberculosis System, and the COVID-19 information was obtained from the COVID-19 Case Tracking System. The status of being alive or dead and the date of death if they were dead were obtained from the Central Population Management System.

**Results:** 23.92% (n=105) of 439 patients with TB were COVID-19 cases. Advanced age, having at least one comorbid disease, and the presence of chronic pulmonary disease, diabetes mellitus, and heart disease increased the risk of developing COVID-19 in active or previously treated patients with TB.

**Conclusion:** COVID-19 was detected more frequently in active or previously treated TB patients than in the general population. Within the scope of public health services implemented to prevent the spread of COVID-19 infection, priority should be given to the TB patient group and older people, especially those with comorbid chronic pulmonary disease, diabetes mellitus, and heart disease in this group.

**Keywords:** COVID-19, coinfection, tuberculosis, retrospective studies, diabetes mellitus

## Introduction

Tuberculosis (TB) is a public health problem that affects millions of people worldwide. In the World Health Organization (WHO) "2020 Global Tuberculosis Report", it was stated that around 7.1 million people worldwide were diagnosed with TB in 2019, and approximately 1.4 million people died from TB (1). Tuberculosis dispensaries were opened in order to provide assistance, solidarity, and health services in the fight against TB in Turkey. According to the "Tuberculosis War 2019 Report", 11,101 people were newly diagnosed in 2017, and 732 died in 2016 (2).

Coronavirus disease-2019 (COVID-19), which emerged in Wuhan, China, in December 2019 and spread widely in a short time, was declared a pandemic by the WHO on March 11, 2020 (3). On the same day, the first case was seen in Turkey (4). COVID-19 can cause a wide range of clinical symptoms, from asymptomatic infection to severe respiratory failure (5). It has been reported that 396 million people worldwide were diagnosed with COVID-19 on February 8, 2022, and 5.7 million died because of COVID-19 on February 6, 2022 (6). The total number of cases in Turkey has exceeded 12 million, and COVID-19 has caused the death of 89 thousand people (as of February 9, 2022) (7).

Although high coinfection rates are expected between COVID-19 and other respiratory pathogens (8), there is limited literature on COVID-19 and TB coinfection (9). TB infection can cause respiratory dysfunction and specific ventilation defects. This situation is associated with inflammation and proteases that develop to fight infection

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**Received:** 16.03.2022 **Accepted:** 25.11.2022

and cause lung damage. Thus, a history of TB constitutes a risk factor for chronic respiratory disorders (10). For these reasons, it is critical to investigate the coexistence of TB and COVID-19.

Although there are few studies examining the TB-COVID-19 coinfection, these studies generally have insignificant sample sizes and short follow-up periods. Another important issue is the lack of information about comorbidities in these studies. In most studies, it is even difficult to determine whether TB was diagnosed before or during treatment for COVID-19 (11). To the best of our knowledge, this is the first study to examine COVID-19 infection in patients diagnosed with active or previously treated TB in Turkey. In this study, the aim was to examine the frequency of COVID-19 and the factors affecting the frequency of COVID-19 in patients with active/previously treated TB.

## Materials and Methods

### Compliance with Ethical Standards

The ethical permission for the research was obtained from Firat University's Non-Interventional Research Ethics Committee with a letter dated April 27, 2021 and numbered 1908, and the institutional permission was obtained from the Public Health Directorate of the Elazig Provincial Health Directorate with a letter dated June 16, 2021.

### Study Design, Setting, and Participants

The universe of the retrospective cohort type study consisted of patients with TB enrolled in the Tuberculosis Dispensary in Elazig province between January 2015 and April 2021. We reached the entire population without using the sample selection method.

Since this study is a retrospective cohort, the starting point of the study was January 2015. From January 2015 to April 2021, patients were followed through their records. A group of people with a certain trait is called a cohort (12). The cohort of this study consists of patients diagnosed with active or previous TB. In cohort studies, exposure status (independent variables, e.g., comorbid diseases) must occur before the outcome (COVID-19) occurs (12). For these reasons, people who have not yet been diagnosed with TB cannot be included in the cohort, so those who were diagnosed with COVID-19 before being diagnosed with TB were excluded from the study. Additionally, those who died before the start of the pandemic in Turkey (the first case of COVID-19 in Turkey) were excluded from the study because they could not be examined in terms of whether they were COVID-19 or not. In conclusion, the criteria for inclusion and exclusion from the study are as follows: The inclusion criterion was the TB diagnosis. Exclusion criteria: i) diagnosed with COVID-19 before being diagnosed with TB; ii) died before March 11, 2020, which is the first COVID-19 case in Turkey (13).

### Variables

The dependent variable was whether the patient had COVID-19. Sex, age, comorbidities, the diagnosis year of TB, the case definition of TB, the sites of involvement of the TB disease, culture or smear positivity, drug-resistant TB, the multi-drug regimen used in the treatment and treatment result of patients with TB, and active or previously treated TB were independent variables. Comorbid diseases diagnosed before the COVID-19 diagnosis date were included in the analysis, and comorbid diseases diagnosed later were excluded from the study.

Active TB patients refer to people who are still receiving treatment, and previously treated TB patients refer to people whose treatment has been completed or who have been cured.

According to the 'Tuberculosis Diagnosis and Treatment Guidelines of the Ministry of Health of the Republic of Turkey', the definitions of the variables used in the current study are given below (14):

### Case Definitions of TB

New case: patients who have not been treated for TB before or have received treatment for less than a month.

Relapse cases: patients who were previously diagnosed with TB and whose treatment was completed successfully, and who were re-diagnosed with TB with sputum positivity or clinical and radiological findings.

### Multi-drug Regimen

First-line drugs: isoniazid, rifampicin, ethambutol, and pyrazinamide. Sensitive ones were used in the treatment.

Second-line drugs: ethionamide, prothionamide, cycloserine, and terizidone (since they were similar drugs, one of ethionamide and prothionamide, one of cycloserine and terizidone were used).

### Treatment Results

Cured: it was the demonstration of a negative sputum smear at least twice in a patient with a positive sputum smear at baseline, one during the maintenance period of the treatment and the other at the completion of the treatment, with clinical and radiological improvement.

Completed treatment: it was the termination of the treatment by considering the clinical and radiological findings that was successful in cases where sputum analysis could not be performed during the maintenance period of the treatment or at the end of the treatment for the patient who completed the prescribed treatment within the prescribed time.

Death: death of a patient with TB during treatment.

Abandonment of treatment: tuberculosis patients did not take their medication for two months or longer during treatment.

Transferred: it was the case that the results of the treatment were not known because the patient went to another dispensary area (or abroad).

Ongoing treatment: if the patient's treatment was ongoing, it was considered in this group.

### Data Sources

The TB-related data of the patients were obtained from the Public Health Management System Tuberculosis System, and the COVID-19 information was obtained from the Public Health Management System COVID-19 Case Tracking System. The patients' status as being alive or dead and their death dates were obtained from the Central Population Management System.

### Statistical Analysis

The data obtained in the study were recorded in the SPSS 21.0 program and analyzed. Descriptive statistics are presented with frequency (n) and percentage (%) for categorical variables; mean ± standard deviation or median; and 1st quarter-3rd quarter or minimum (min.)-maximum (max.) for continuous variables. Normal distribution was tested with the Kolmogorov-Smirnov test. Chi-square and Mann-Whitney U tests were used in bivariate analyses. While presenting the results of the regression analysis, the unadjusted odds ratio (UOR) was used in the univariate logistic regression analysis, and the hazard OR (HOR) was used in the COX regression analysis. Odds ratios are presented with a 95% confidence interval (CI). Statistical significance was evaluated at $p<0.05$.

## Results

Between January 2015 and April 2021, there were 496 patients with TB registered in the Elazig Tuberculosis Dispensary. One hundred and twenty-eight of these patients had COVID-19. Twenty-three patients were diagnosed with COVID-19 before being diagnosed with TB; eight patients were diagnosed with TB in 2020 and 15 patients in 2021; they were excluded from the study, and 34 patients died before the first COVID-19 case in Turkey. The remaining 439 patients with TB were included in the study (Figure 1). Of these patients, 23.92% (105/439) were cases of COVID-19 (Table 1).

The demographic, clinical, and laboratory characteristics and frequency of COVID-19 of the patients with TB included in the study are given in Table 1. They were 186 (42.37%) males and 253 (57.63%) females, with a mean age of 42.65±20.29 (median=43, min.=0, max.=95). The average time elapsed between the TB diagnosis date and the COVID-19 process start date for the patients with TB who caught COVID-19 was 35.20±21.74 months (min.=0, max.=71).

A regression analysis was performed using the independent variables (age, having at least one comorbidity, chronic lung disease, diabetes mellitus, and heart disease) that were significant in the bivariate analysis and the dependent variable of the presence or absence of COVID-19. The results of a binary regression analysis with one independent variable are shown in Figure 2. Increasing age by 1 year increased the incidence of COVID-19 by 2% (UOR=1.02, 95% CI=1.01-1.03, $p<0.001$). The incidence of COVID-19 was 81% higher in patients with at least one comorbidity than in those without (UOR=1.81, 95% CI=1.16-2.82, p=0.009). Additionally, the incidence of COVID-19 was significantly higher in patients with chronic pulmonary disease (UOR=2.93, 95% CI=1.42-6.04, p=0.004), diabetes mellitus (UOR=2.27, 95% CI=1.05-4, 87, p=0.036), and chronic cardiac disease (UOR=2.51, 95% CI=1.48-4.28, p=0.001) than in those without. The results of the COX regression analysis with the model created using these five independent variables are presented in Figure 3. The variables of having at least one comorbid disease, diabetes mellitus and chronic cardiac diseases lost their significance in the model. Age (HOR=1.01, 95% CI=1.00-1.03, p=0.009) and chronic pulmonary disease (HOR=2.05, 95% CI=1.10-3.81; p=0.024) variables remained significant.

The clinical characteristics of COVID-19 cases are presented in Table 2. Only one COVID-19 case died; he was a 68-year-old male patient. Here, diabetes mellitus and epilepsy were comorbidities, and TB involvement was extrapulmonary. It had a computed tomography result that was compatible with COVID-19. The COVID-19 fatality rate was determined at 0.95%.

## Discussion

In this study, the frequency of COVID-19 in patients with active/previously treated TB and the factors affecting the frequency of COVID-19 were investigated. To the best of our knowledge, the current study is the first to examine COVID-19 infection in patients diagnosed with active or previously treated TB in Turkey. According to the results of the study; the incidence of COVID-19 in the current cohort was found to be 23.92%. Advanced age, having at least one comorbid disease, and the presence of chronic pulmonary disease, diabetes mellitus, and heart disease increase the risk of developing COVID-19 in active or previously treated patients with TB.

The prevalence of COVID-19 in active or previous patients with TB in the current study (23.92%, Table 1) was higher than the prevalence in the population in Turkey (5.78%, when the data from the onset of the pandemic to

| Table 1. Demographic, clinical, laboratory characteristics and frequency of COVID-19 of tuberculosis patients | | | | | |
|---|---|---|---|---|---|
| **Variables** | **Total, n (%)** | **COVID-19 case, n (%)** | | **p-value** | **COVID-19 frequency %** |
| | | **Yes** | **No** | | |
| Total | 439 (100) | 105 (100) | 334 (100) | | 23.92 |
| **Sex** | | | | 0.430* | |
| Male | 186 (42.37) | 41 (39.05) | 145 (43.41) | | 22.04 |
| Female | 253 (57.63) | 64 (60.95) | 189 (56.59) | | 25.30 |
| Age [median (Q1-Q3)] | 43 (25-61) | 49 (29-67) | 41 (24-57) | **<0.001**** | - |
| At least one comorbid disease | 158 (35.99) | 49 (46.67) | 109 (32.63) | **0.009*** | 31.01 |
| **Comorbidities** | | | | | |
| Chronic pulmonary diseases | 33 (7.52) | 15 (14.29) | 18 (5.39) | 0.003* | 45.45 |
| Chronic renal disease | 14 (3.19) | 6 (5.71) | 8 (2.40) | 0.110* | 42.86 |
| Cerebrovascular diseases | 7 (1.59) | 3 (2.86) | 4 (1.20) | 0.365* | 42.86 |
| Diabetes mellitus | 30 (6.83) | 12 (11.43) | 18 (5.39) | **0.032*** | 40.00 |
| Chronic cardiac diseases | 73 (16.63) | 29 (27.62) | 44 (13.17) | **0.001*** | 39.73 |
| Cancer | 21 (4.78) | 7 (6.67) | 14 (4.19) | 0.300* | 33.33 |
| Neurological diseases | 11 (2.51) | 3 (2.86) | 8 (2.40) | 0.729* | 22.27 |
| Gastrointestinal system diseases | 8 (1.82) | 1 (0.95) | 7 (2.10) | 0.686* | 12.50 |
| Rheumatological diseases | 17 (3.87) | 2 (1.90) | 15 (4.49) | 0.383* | 11.76 |
| **Diagnosis year of TB** | | | | 0.119* | |
| 2015 | 86 (19.59) | 18 (17.14) | 68 (20.36) | | 20.93 |
| 2016 | 77 (17.54) | 22 (20.95) | 55 (16.47) | | 28.57 |
| 2017 | 65 (14.81) | 16 (15.24) | 49 (14.67) | | 24.62 |
| 2018 | 69 (15.72) | 13 (12.38) | 56 (16.77) | | 18.84 |
| 2019 | 71 (16.17) | 15 (14.29) | 56 (16.77) | | 21.13 |
| 2020 | 60 (13.67) | 21 (20.00) | 39 (11.68) | | 35.00 |
| 2021 | 11 (2.51) | 0 | 11 (3.29) | | 0 |
| **Case definition of TB (n=416)** | | | | 0.694* | |
| New | 388 (93.27) | 96 (94.12) | 292 (92.99) | | 24.74 |
| Relapse | 28 (6.73) | 6 (5.88) | 22 (7.01) | | 21.43 |
| **The involvement sites of the TB disease** | | | | 0.334* | |
| Pulmonary | 197 (44.87) | 41 (39.05) | 156 (46.71) | | 20.81 |
| Pulmonary + extrapulmonary | 19 (4.33) | 6 (5.71) | 13 (3.89) | | 31.58 |
| Extrapulmonary | 223 (50.80) | 58 (55.24) | 165 (49.40) | | 26.01 |
| **Extrapulmonary involvement (n=235)** | | | | | |
| Bone involvement | 17 (7.23) | 7 (11.29) | 10 (5.78) | 0.160* | 41.18 |
| Breast involvement | 15 (6.38) | 5 (8.06) | 10 (5.78) | 0.549* | 33.33 |
| Pleural membrane involvement | 40 (17.02) | 13 (20.97) | 27 (15.61) | 0.335* | 32.50 |
| Lymphatic system involvement | 123 (52.34) | 35 (56.45) | 88 (50.87) | 0.450* | 28.46 |
| Abdominal involvement | 27 (11.49) | 6 (9.68) | 21 (12.14) | 0.602* | 22.22 |
| Central nervous system involvement | 10 (4.26) | 2 (3.23) | 8 (4.62) | 1.000* | 20.00 |
| Cutaneous involvement | 27 (11.49) | 5 (8.06) | 22 (12.72) | 0.324* | 18.52 |
| Culture positivity | 95 (50.80) | 26 (59.09) | 69 (48.25) | 0.209* | 27.37 |
| Smear positivity | 115 (61.50) | 23 (52.27) | 92 (64.34) | 0.150* | 20.00 |
| Resistance to at least one drug | 20 (4.56) | 4 (3.81) | 16 (4.79) | 0.794* | 20.00 |
| **Multi-drug regimen (n=424)** | | | | 0.397* | |
| First-line drugs | 402 (94.81) | 97 (97.00) | 305 (94.14) | | 24.13 |

| Table 1. Continued | | | | | |
|---|---|---|---|---|---|
| **Variables** | **Total, n (%)** | **COVID-19 case, n (%)** | | **p-value** | **COVID-19 frequency %** |
| | | **Yes** | **No** | | |
| First-line drugs and second-line drugs | 17 (4.01) | 3 (3.00) | 14 (4.32) | | 17.65 |
| Second-line drugs | 5 (1.18) | 0 | 5 (1.54) | | 0 |
| **Treatment result (n=438)** | | | | 0.716* | |
| Cure | 99 (22.60) | 27 (25.71) | 72 (21.62) | | 27.27 |
| Completed treatment | 282 (64.38) | 66 (62.86) | 216 (64.86) | | 23.40 |
| Death | 2 (0.46) | 0 | 2 (0.60) | | 0 |
| Abandonment of treatment | 3 (0.68) | 0 | 3 (0.90) | | 0 |
| Transferred | 18 (4.11) | 3 (2.86) | 15 (4.50) | | 16.67 |
| Ongoing treatment | 34 (7.76) | 9 (8.57) | 25 (7.51) | | 26.47 |
| **Active/previously treated TB (n=415)** | | | | 0.789* | |
| Active tuberculosis | 34 (8.19) | 9 (8.82) | 25 (7.99) | | 26.47 |
| Previously treated tuberculosis | 381 (91.81) | 93 (91.18) | 288 (92.01) | | 24.41 |
| *Chi-square were used, **Mann-Whitney U were used<br>COVID-19: Coronavirus disease-2019, TB: Tuberculosis | | | | | |

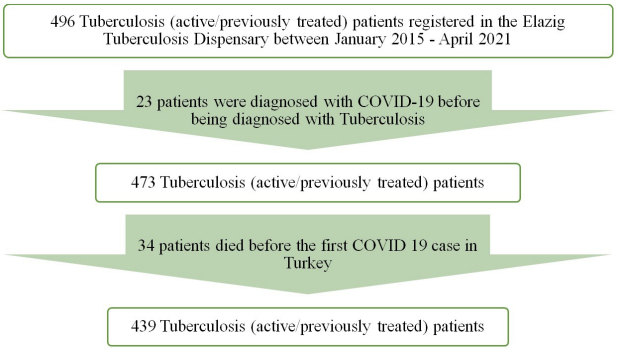


**Figure 1.** Flow chart of study sample identification

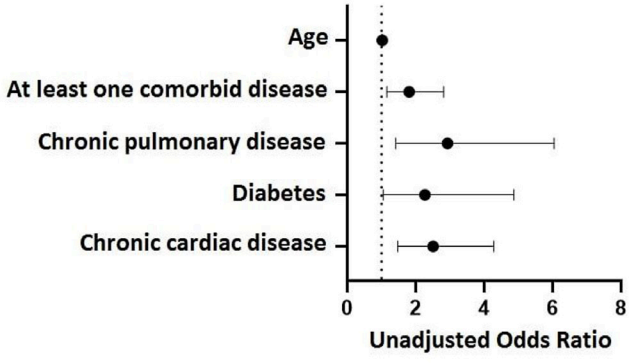


**Figure 2.** Univariate logistic regression analysis predicting COVID-19 with factors associated with the frequency of COVID-19 in tuberculosis patients
*COVID-19: Coronavirus disease-2019*

April 30, 2021 were analyzed) (7,15). Patients who have previously been affected by a respiratory disease have impaired lung function and decreased resistance to the virus, and they tend to develop Acute Respiratory Distress Syndrome (16). Therefore, the incidence of COVID-19 in

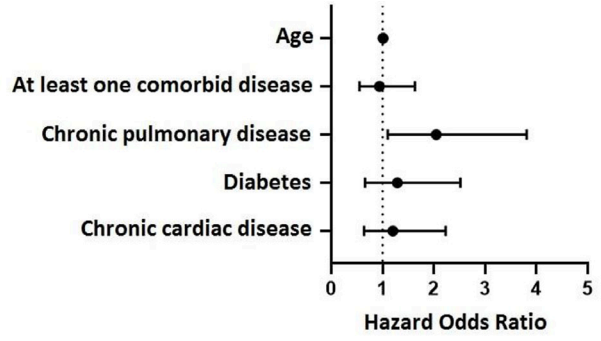


**Figure 3.** Multivariate logistic regression analysis predicting COVID-19 with factors associated with the frequency of COVID-19 in tuberculosis patients
*COVID-19: Coronavirus disease-2019*

| Table 2. Clinical characteristics of COVID-19 cases | |
|---|---|
| **Variables** | **n (%)** |
| Total | 105 (100) |
| Tuberculosis and COVID-19 status | |
| COVID-19 after the previously treated tuberculosis | 89 (84.76) |
| COVID-19 while active tuberculosis (now tuberculosis is not active) | 4 (3.81) |
| COVID-19 during active tuberculosis (also active now) | 9 (8.57) |
| Unknown due to transferred | 3 (2.86) |
| Symptomatic case | 67 (63.81) |
| Contacted | 26 (24.76) |
| COVID-19 case status | |
| Recovered from COVID-19 | 100 (95.24) |
| Currently in treatment | 4 (3.81) |
| Death | 1 (0.95) |
| Hospitalization in intensive care | 1 (0.95) |
| Intubation | 0 |
| COVID-19: Coronavirus disease-2019 | |

patients with TB may be higher than that in the general population. Another possible cause of TB-COVID-19 infection may be that both diseases reinforce each other, with a temporary reduction in cellular immunity leading to new infection or exaggerated reactivation of latent infection (17).

Due to biological factors, social roles, and behavioral differences, the distribution of some diseases by sex differs. It has been reported that TB is more common in males in Turkey (2). However, with the increase in extrapulmonary TB, which is more common in females recently, female dominance can be observed in TB cases (18,19). Therefore, the fact that more than half (50.80%) of the TB cases in the current study were extrapulmonary TB can be explained by the fact that the frequency of female patients (57.63%) is higher than that of males (Table 1). It was reported that the frequency of COVID-19 did not change according to sex (Table 1), in accordance with the current study (20).

In the study of Tadolini et al. (21) examining the TB - COVID-19 coinfection, the median age of the patients was 48 (32-69), and in the study of Sy et al. (9), 48.92±19.63. In this study, the median age of TB-COVID-19 co-infected patients was 49 (29-67), and this finding was consistent with the literature (Table 1). TB and COVID-19 have overlapping risk factors such as advanced age, diabetes, smoking, and other chronic respiratory diseases (17). According to the results of the current study, age was significantly associated with the frequency of COVID-19 both when examined alone and in the presence of comorbid diseases (Table 1, Figure 2, Figure 3).

In studies examining both COVID-19 patients (22-24) and TB-COVID-19 co-infected patients (21,25), the most frequently reported comorbidities were cardiovascular diseases, diabetes, and chronic lung diseases (Table 1), which was consistent with the findings of the present study. The coexistence of these diseases with COVID-19 may be related to the pathogenesis of COVID-19 (23). Although the underlying mechanism of COVID-19 remains unclear, it has been determined that the virus uses angiotensin converting enzyme-2 (ACE-2) receptors on the surface of host cells to enter the cell (26). The association between cardiovascular diseases and COVID-19 may be due to the weakening of the immune system in people with cardiovascular disease (23,27) and/or the presence of ACE-2 receptors in cardiac muscle cells (28). People with diabetes tend to get infections due to impaired phagocytic cell abilities. Elevated ACE-2 receptor levels have been associated with diabetes and may sensitize people with diabetes to COVID-19 infection (29). Additionally, impaired function of T cells and elevated interleukin-6 levels may also play a decisive role in the development of COVID-19 in diabetics (27,30).

In this cohort of patients with TB, although there was no correlation between pulmonary and extrapulmonary TB disease and the frequency of COVID-19 infection, COVID-19 infection was observed most frequently in those with chronic pulmonary disease compared with other comorbidities (Table 1). Additionally, in the presence of other comorbid diseases, chronic pulmonary diseases were found to be the only risk factor for comorbid COVID-19 infection (Figure 3). Further studies are needed to examine the effect of chronic respiratory system diseases as a mediator variable in the TB-COVID-19 relationship. Additionally, experimental data on the immunopathological mechanism underlying the TB-COVID-19 coinfection may further explain this relationship (11).

In this study, the most common extrapulmonary involvement in COVID-19 patients with TB was found to be lymphatic system, pleura, and bone involvement (Table 1), consistent with the literature (21).

In this study, the incidence of COVID-19 was found to be higher in patients with active TB than in patients with previously treated TB, in patients diagnosed with TB in 2020 compared with patients with TB diagnosed in previous years (Table 1). However, no significant relationship was found between being a patient with active or previously treated TB or the year of diagnosis of TB and the incidence of COVID-19 (Table 1). The relationship between TB and COVID-19 coinfection can be explained by the presence of damage to the lungs due to fibrosis or cavitation in patients with previously treated TB and impaired lung function in patients with active TB (31). Although there is limited information on the TB-COVID-19 relationship in the literature, there is also limited information on the distinction between active and previously treated TB as a risk factor for COVID-19 (32).

In a study conducted in India, a country with a high TB burden, examining TB and COVID-19 coinfected patients, the mortality rate among TB and COVID-19 coinfected patients was found to be 27.3% (31). In another study conducted in eight countries examining TB and COVID-19 coinfected patients, this frequency was found to be 12.3% (21), and in a study conducted in Italy, it was 11.6% (33). In the study, which included the data of 37 countries, the mortality rates were 14.2% in Europe, 9.2% outside Europe, and 11.08% (34). However, in the current study, only one of the 105 TB-COVID-19 coinfected patients died (Table 2). This can be explained by the fact that both the TB estimated incidence rate and the TB estimated mortality rate in Turkey are lower than the rates of both the world and all WHO regions, including the European and American regions (35). Additionally, according to the results of the study evaluating TB-COVID-19 infection in South Africa, another country with a high TB burden,

it was determined that underlying conditions such as advanced age, male sex, and diabetes mellitus increase COVID-19-related hospital mortality (25). Therefore, it should be emphasized that the TB-COVID-19 coinfected patient who died in this study was an advanced-age male patient who was diagnosed with diabetes mellitus. When the data from the beginning of the epidemic to the date of April 30, 2021, in Turkey showed a COVID-19 fatality rate of 0.83% (7), it was calculated as 0.95% in the current study. In this study, in which we examined COVID-19 patients in the patient population with TB, it was seen that the COVID-19 fatality of the population with TB is similar to that of the general population.

### Study Limitations

This study has some limitations. First, COVID-19 is rapidly evolving globally. Therefore, information regarding COVID-19 may change as new literature continues to be reported. Second, the results may not be representative of COVID-19 cases nationwide or globally, as the current research only includes data for one city. Third, some data are missing because the study's data was derived from health information systems.

This study has some strengths. Compared to similar studies, a larger sample size was used in the study, and a longer follow-up period was determined. The comorbid diseases of patients with TB were also examined. Additionally, it was clearly stated that the patients with TB included in the study were people who had not been diagnosed with COVID-19 yet since the study was a retrospective cohort. For all these reasons, this study offers stronger and more precise results than similar studies.

## Conclusion

COVID-19 was detected more frequently in active or previously treated patients with TB than in the general population. Advanced age, chronic pulmonary diseases, diabetes mellitus, and chronic cardiac diseases have also been identified as risk factors for COVID-19 infection in patients with TB. For these reasons, within the scope of public health services implemented to prevent the spread of COVID-19 infection, priority should be given to the TB patient group and those with advanced age and comorbid diseases in this group. Furthermore, there was no correlation between the frequency of COVID-19 and the year of TB diagnosis, TB case definition (new or relapse), TB involvement sites (pulmonary or extrapulmonary TB), culture or smear positivity, anti-tuberculosis drug resistance status, the multi-drug regimen used in treatment, or active or previously treated TB. The fatality of COVID-19 in patients with TB has been found to be similar to that in the general population. The relationship between TB and COVID-19 severity was not evaluated in this study. Evaluation of this issue in future studies may contribute to further elucidating the TB-COVID-19 relationship.

### Ethics

**Ethics Committee Approval:** The ethical permission for the research was obtained from Firat University's Non-Interventional Research Ethics Committee with a letter dated April 27, 2021 and numbered 1908, and the institutional permission was obtained from the Public Health Directorate of the Elazig Provincial Health Directorate with a letter dated June 16, 2021.

**Informed Consent:** Retrospective cohort type study.

**Peer-review:** Externally and internally peer-reviewed.

### Authorship Contributions

Concept: S.K., F.N.K., M.Y., Z.A.T., E.P., Design: S.K., F.N.K., M.Y., Z.A.T., E.P., Data Collection and/or Processing: S.K., F.N.K., Analysis and/or Interpretation: S.K., F.N.K., Literature Research: S.K., F.N.K., Writing: S.K., F.N.K., M.Y., Z.A.T., E.P.

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

**Financial Disclosure:** The authors declared that this study received no financial support.

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Original Article

DOI: 10.4274/haseki.galenos.2022.8469
Med Bull Haseki 2022;60:461-467

# A Comparative Analysis of the Blood Products used in the Emergency Room and other Clinics with the Pre-pandemic Period

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**Ministry of Health, Medical Specialty Board, Emergency Medicine, Ankara, Turkey

## Abstract

**Aim:** In this study, we evaluated the blood transfusion statistics by determining the frequency of blood component transfusions by year and the total number of transfusions administered in emergency departments (EDs) and all inpatient clinics across Turkey, to provide a foresight of the future and to guide planning.

**Methods:** The study was conducted retrospectively, covering the period between January 1, 2016, and January 1, 2022. The numerical data of the blood transfusions applied in the 2nd and 3rd level public hospitals in Turkey were collected as the number of units, and the data were used by obtaining the necessary permissions from the Ministry of Health. The most frequently used blood components in EDsand inpatient clinics in our country were examined. The total number of transfusions in EDs and all inpatient clinics was calculated, and the frequency changes over time were investigated. In the study, the 4-year period of 2016-2019 was specified as the prepandemic period. The 2-year data for 2020 and 2021 are also stated as the pandemic period. The mean values of the data belonging to both periods were taken, and their significance was evaluated with Fisher's exact test. Blood transfusion statistics for each year were recorded on the tabulation software, and the frequency changes were calculated using the statistical formulas of the tabulation software. Patient consent was waived because of the study.

**Results:** The most common types of blood components transfused in Turkey were packed red blood cell (PRBC), fresh frozen plasma (FFP), platelet concentrate, whole blood, and cryoprecipitate. When the blood component transfusion rates in the EDs were evaluated, the most frequently transfused blood component was found to be PRBC, followed by FFP (64.4% and 29.8%, respectively). Platelet concentrate, cryoprecipitate, and whole blood transfusion rates were found to be 5.5%, 0.17%, and 0.13%, respectively. 6.6% of all blood transfusions were administered in EDs. The use of all blood and blood products, except PRBC, has decreased in the ED. In all departments, there was a decrease in the use of platelets and whole blood and an increase in the use of cryoprecipitate.

**Conclusion:** Since the current study shows blood and blood product replacement and includes a broad comparison with the pandemic and pre-pandemic periods, it can guide the blood replacement strategies of the ED and all departments.

**Keywords:** Blood components, emergency department, transfusion

## Introduction

Circulating blood consists of shaped elements such as erythrocytes, leukocytes, and platelets, suspended in a liquid medium called plasma. Blood transfusions can be defined as a special type of tissue transplantation. With the discovery of blood group antigens, blood typing methods, and crossmatching at the beginning of the 20th century, blood transfusions became available (1).

While "blood products" are all therapeutic substances derived from blood, including both blood components and plasma products, the term "blood components" includes packed red blood cell (PRBC), leukocytes,

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**Received:** 11.05.2022 **Accepted:** 22.11.2022

platelet concentrates, plasma, and cryoprecipitate. Major transfusion indications include replacement of blood volume and missing blood components, exchange transfusion, correction of bleeding and coagulation disorders, and correction of immunological deficiencies. When deciding whether to transfuse a patient, it is important to consider whether the patient truly requires transfusion, if so, which blood component is needed, how many units should be transfused to the patient, and what the potential benefit-to-harm ratio of the transfusion is (2,3).

A unit of whole blood collected from a healthy donor is usually separated into PRBC, platelet concentrate, white blood cell concentrate, fresh frozen plasma (FFP), and cryoprecipitate, as this facilitates the preparation, storage, and use of blood components. Immunoglobulin and coagulation factors are obtained with more advanced technology in manufacturing conditions with large plasma pools (4). Emergency departments (EDs) are places that are not only a step in the diagnosis of diseases but also the primary clinics where many treatment plans are applied. Most patients who need blood transfusions but do not need hospitalization are treated in the ED and safely discharged. Some patients with additional comorbidities who required both hospitalization and blood transfusions received the primary treatment in the EDs, and their treatment continued in the inpatient clinics. In previous studies, anemia was found to be the most common indication for transfusion in EDs, and gastrointestinal system bleeding, hemorrhages in oncology and hemato-oncology patients, chronic anemia, and trauma were found to be other important causes (5).

In this study, we evaluated the blood transfusion statistics by determining the frequency of blood component transfusions by year and the total number of transfusions administered in EDs and all inpatient clinics across 2nd and 3rd public hospitals in Turkey, to provide foresight for the future and to guide planning.

## Materials and Methods

### Compliance with Ethical Standards

The study was conducted retrospectively, covering the period between January 1, 2016, and January 1, 2022, after obtaining the approval of the Clinical Research Ethics Committee No 2 of Ankara City Hospital (date: 30.03.2022; approval number: E2-22-1619).

### Study Design

The data were obtained from the information data system of the Ministry of Health, Department of Blood and Blood Products. These data were used by obtaining the necessary permissions from the Ministry of Health. The numerical data of blood transfusions used in Turkey's second and third level public hospitals were collected as many units. The study was conducted on the total data of 758 hospitals, of which 552 were second-level and 206 were third-level public hospitals.

The most frequently used blood components in EDs and inpatient clinics in our country were examined. The total number of transfusions in EDs and in all inpatient clinics were determined, and the frequency changes according to year were examined. In our study, data on the coronavirus disease-2019 (COVID-19) pandemic process, before and after, were also shared. The effect of the COVID-19 pandemic on the transfusion of blood and blood products was also evaluated.

### Statistical Analysis

In the study, the 4-year period of 2016-2019 was specified as the prepandemic period. The 2-year data for 2020 and 2021 are also stated as the pandemic period. The mean values of the data belonging to both periods were taken, and their significance was evaluated with Fisher's exact test. Blood transfusion statistics for each year were recorded on the tabulation software, and the frequency changes were calculated using the statistical formulas of the tabulation software. Patient consent was waived because of the study.

## Results

The total number of blood transfusions administered in all clinics has increased continuously except for 2020. There was no regular increase or decrease in the blood transfusion numbers of EDs (Table 1). When all of the blood component transfusions were evaluated, the most frequently transfused blood component was found to be PRBC, followed by FFP (60.8% and 30.7%, respectively). While the platelet concentrate transfusion rate was 8.3%, the whole blood and cryoprecipitate transfusion rates were 0.11% and 0.09%, respectively (Figure 1). When the blood component transfusion rates in the EDs were evaluated, the most frequently transfused blood component was found to be PRBC with a rate of 64.4%. It was followed by FFP (29.8%). Platelet concentrate, cryoprecipitate, and

**Table 1. Number of blood transfusions by years and annual change rates**

| Blood product | 2016 | 2017 | 2018 | 2019 | 2020 | 2021 | Mean |
|---|---|---|---|---|---|---|---|
| All clinics-total (number/unit) | 2.038.400 | 2.347.838 | 2.461.927 | 2.739.322 | 2.274.517 | 2.471.499 | 2.388.917 |
| Emergency department (number/unit) | 145.339 | 166.922 | 161.307 | 162.639 | 148.182 | 153.377 | 156.294 |

whole blood transfusion rates were found to be 5.5%, 0.17%, and 0.13%, respectively (Figure 2).

The average number of blood and blood product transfusions in all clinics during the 4-year pre-pandemic period, including 2016-2019, and the 2-year pandemic period, including 2020-2021, were evaluated. Comparisons of both periods were made (Table 2). Likewise, comparisons and results for emergency services are shown in Table 3. The rates of blood transfusions administered in EDs compared to blood transfusions administered in all clinics are shown in Table 4. Additionally, the comparison of these data for the prepandemic and pandemic periods is shown in Figure 3. Platelet transfusions were determined separately as random, pooled, and apheresis platelet concentrates. Statistics for all clinics are shown in Figure 4, and transfusions administered in the ED are shown in Figure 5.

## Discussion

In our study, the total number of blood transfusions administered in all clinics of 758 2nd and 3rd level public hospitals in Turkey and the number of blood transfusions administered in EDs were examined. It was found that 6.6% of total transfusions in the last 6 years were administered in the EDs. The total number of blood transfusions administered in all clinics has increased continuously except for 2020. There was no regular increase or decrease in the blood transfusion numbers of EDs (Table 1).

PRBC was the most commonly administered blood product, with a rate of 60.8% and a rate of 64.4% in ED transfusions. Similarly, in a study conducted in Korea, PRBC transfusion was found to be the most common of all transfusions, just as it is in our country (6). Previous

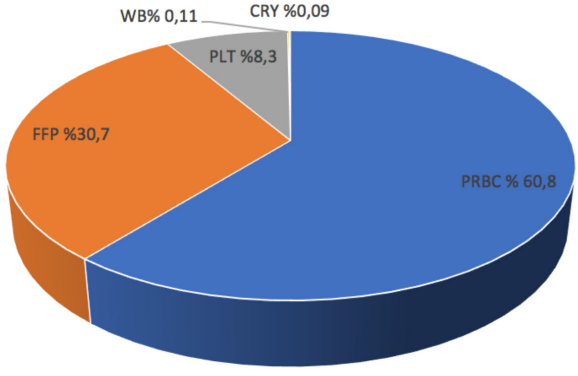


**Figure 1.** Average PRBC, platelet, FFP, whole blood, cryoprecipitate transfusions in emergency departments

*FFP: Fresh frozen plasma, PRBC: Packed red blood cells, PLT: Platelet, CRY: Cryoprecipitate, WB: Whole blood*

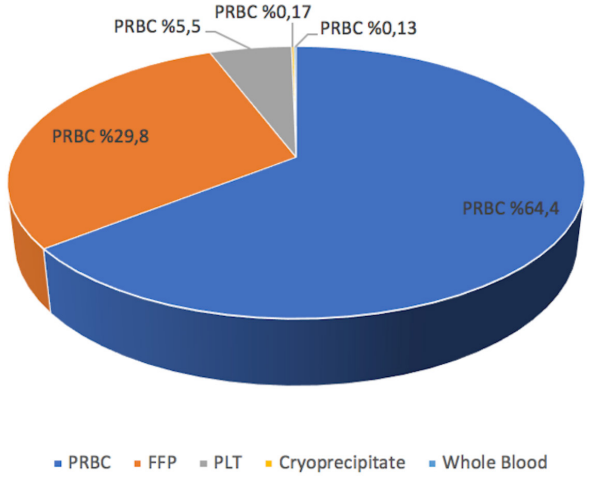


**Figure 2.** Average PRBC, platelet, FFP, whole blood, cryoprecipitate transfusions across all departments

*FFP: Fresh frozen plasma, PRBC: Packed red blood cells, PLT: Platelet, CRY: Cryoprecipitate, WB: Whole blood*

**Table 2. Average of PRBC, PLT, FFP, WB, CRY transfusions in all departments in pre-pandemic and pandemic periods**

| Blood product | All departments | Prepandemic | Pandemic | p-value |
|---|---|---|---|---|
| PRBC | Count | 1.427.481 | 1.441.739 | |
| | % within group | 49.8% | 50.2% | >0.05 |
| FFP | Count | 720,907 | 731,896 | |
| | % within group | 49.6% | 50.4% | >0.05 |
| PLT | Count | 209,083 | 169,127 | |
| | % within group | 55.3% | 44.7% | <0.001 |
| CRY | Count | 12,663 | 24,969 | |
| | % within group | 33.6% | 66.4% | <0.001 |
| WB | Count | 26,738 | 5,279 | |
| | % within group | 83.5% | 16.5% | <0.001 |

The mean values of the data belonging to both periods were taken and their significance was evaluated with Fisher's exact test
FFP: Fresh frozen plasma, PRBC: Packed red blood cells, PLT: Platelet, CRY: Cryoprecipitate, WB: Whole blood

| Table 3. Average of PRBC, PLT, FFP, WB, CRY transfusions in emergency departments in pre-pandemic and pandemic periods | | | | |
|---|---|---|---|---|
| **Blood product** | **Emergency departments** | **Prepandemic** | **Pandemic** | **p-value** |
| PRBC | Count | 95,941 | 109,768 | |
| | % within group | 46.6% | 53.4% | <0.001 |
| FFP | Count | 52,366 | 34,993 | |
| | % within group | 59.9% | 40.1% | <0.001 |
| PLT | Count | 9,982 | 5,618 | |
| | % within group | 64.0% | 36.0% | <0.001 |
| CRY | Count | 445 | 230 | |
| | % within group | 65.9% | 34.1% | <0.001 |
| WB | Count | 318 | 171 | |
| | % within group | 65.0% | 35.0% | <0.001 |
| The mean values of the data belonging to both periods were taken and their significance was evaluated with Fisher's exact test<br>FFP: Fresh frozen plasma, PRBC: Packed red blood cells, PLT: Platelet, CRY: Cryoprecipitate, WB: Whole blood | | | | |

| Table 4. Emergency departments/all clinics blood transfusion rates | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Blood product** | **2016** | **2017** | **2018** | **2019** | **2020** | **2021** | **Mean** |
| PRBC (single unit) | 6.8 | 7.1 | 6.5 | 6.4 | 7.5 | 7.6 | 6.98 |
| FFP (single unit) | 8.8 | 8.2 | 7.1 | 5.5 | 5.2 | 4.3 | 6.51 |
| Platelet (single unit, apheresis, random, and pooled in total) | 5.2 | 4.7 | 4.6 | 4 | 3.7 | 2.9 | 4.22 |
| Cryoprecipitate (single unit) | 4.3 | 6 | 4 | 1.2 | 1.4 | 0.5 | 2.9 |
| Whole blood (single unit) | 1.3 | 1.1 | 0.8 | 1.7 | 2.8 | 3.7 | 1.9 |
| The values expressed as "%".<br>FFP: Fresh frozen plasma, PRBC: Packed red blood cells | | | | | | | |

studies found that the rates of PRBC transfusions for all blood transfusions were 70%, 59%, 63%, and 84%, respectively (7-10). The changes in PRBC transfusions in all clinics before and during the pandemic were not statistically significant. However, a significant increase was observed in the use of emergency services during the pandemic period (p<0.001).

EDs are the first point of contact for patients with anemia and symptoms, patients with gastrointestinal bleeding, and patients with major traumas. Therefore, it is natural to expect an increase in prpc transfusions. Another study examining the departments administering blood and blood products revealed that 50.6% of the transfusions were administered by the internal medicine department, followed by the ED at a rate of 44.9% (10,11). Similar to our study, in a study conducted in the USA and covering all departments, PRBC transfusions were evaluated between 2017 and 2019, and no significant change was found in transfusion levels during this 3-year period (12).

FFP was found to be the second most frequently administered blood component following PRBC, both in the EDs and in total. When the total number of FFP transfusions was examined, a continuous increase was observed from 2016 to 2020, and the increase rate was approximately 45% in this 4-year period. In 2020, a decrease of approximately 20% was observed in FFP transfusions. The fact that FFP has a wide area of use is the main reason for its high frequency of use (13-15). Although there was an increase in the use of FFP during the pandemic period in all clinics compared to the pre-pandemic period, it was found to be statistically insignificant. When the usage levels in the emergency services were compared, a significant decrease was found during the pandemic period (p<0.001). While total FFP usage is increasing in all areas, the usage rate in emergency services is decreasing. The earlier transfer of patients diagnosed and treated in the emergency room to services, operating rooms, and intensive care units may explain this decrease in their use in emergency services. Although the use of FFP in emergency services is decreasing, its share (6.51%) in total transfusions in all units is still close to the share of erythrocyte suspension (6.98%) (Table 4).

Among the total transfusions in all units, platelet transfusion was the most frequently used blood component with a rate of 8.3%, after erythrocyte and FFP. It has a rate of 5.5% among transfusions in emergency services and 4.2% among all transfusions. The total number of random platelet transfusions given in all units decreased year after year, eventually falling by 93% to 14,705 units at the end of six years. The use of pooled

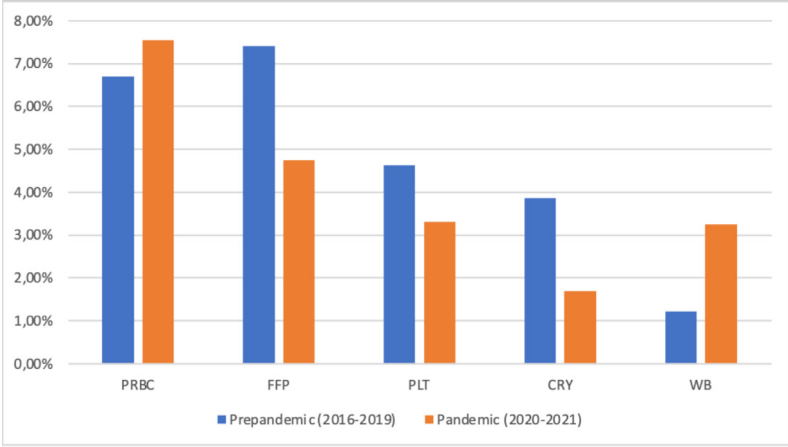


**Figure 3.** Emergency departments blood transfusions/all departments blood transfusions

*FFP: Fresh frozen plasma, PRBC: Packed red blood cells, PLT: Platelet, CRY: Cryoprecipitate, WB: Whole blood*

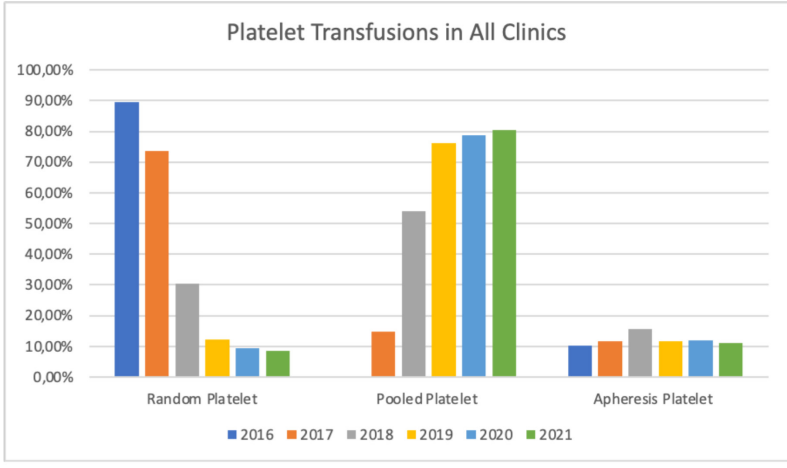


**Figure 4.** Change of platelet transfusions by years in all clinics

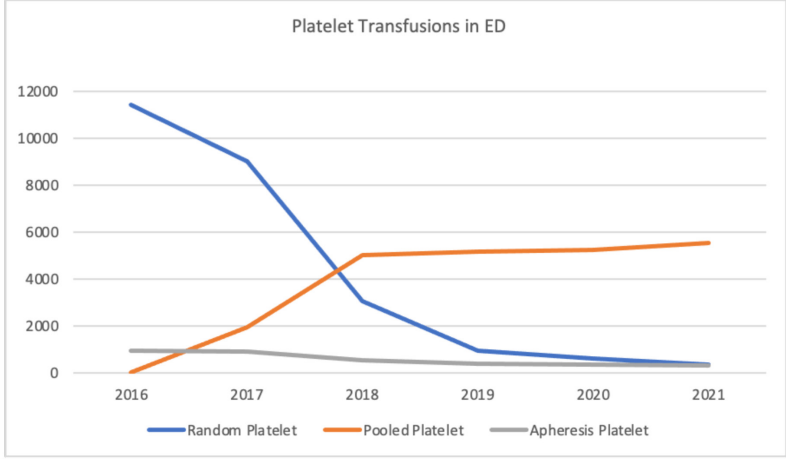


**Figure 5.** Change of platelet transfusions by years in emergency department (unit/year)

*ED: Emergency department*

platelets significantly increased every year, except for a partial decrease in 2020, and increased from 329 units to 141,598 units in six years. Apheresis platelet transfusion, on the other hand, increased between 2016 and 2017, then decreased to 19,678 units with an annual average decrease of about 7% each year (Figure 4). Random platelets, which were used 11,424 units in emergency services in 2016, decreased to only 363 units in 2021. Similarly, the use of apheresis platelets also decreased continuously, from 932 units to 323 units within 6 years. When platelet transfusions are examined according to the prepandemic period in the pandemic period, a statistically significant decrease was found both in all clinics and in the ED ($p<0.001$).

These data show that the priority of platelet transfusion in hospitals has shifted from random platelets to pooled platelets over the years. Although the use of apheresis platelets still maintains its importance, it is seen that transfusion levels have decreased over the years, although not as much as random platelets.

The use of whole blood remained very limited compared with other blood components. The ratio of whole blood in all blood transfusions was found to be 0.11% on average. Platelets contained in the whole blood product lose their effectiveness within 2 days at +1-6 °C. FV and FVIII, in particular, lose their effects quickly. While factor V is 80% active on the fifth day and 50% active on the 14$^{th}$ day, factor VIII levels decrease to 50% of normal within 1-2 days and to 30% of normal after 5 days. The factor XI level was only 20% of normal after 7 days. For these reasons, the use of whole blood has decreased by approximately 92% in the last 6 years (1,2).

Considering the decrease in the use of whole blood during the pandemic process, during the pandemic period, a statistically significant decrease was detected both in the emergency services and in all other clinics compared to the pre-pandemic period ($p<0.001$).

The use of cryoprecipitate has been increasing continuously over the years in all units of the hospital. Its use in 2021 has quadrupled from its 2016 level. The use of cryoprecipitate in all clinics increased statistically during the pandemic period compared to the prepandemic period ($p<0.001$). The opposite situation was observed in emergency services, where cryo use decreased significantly during the pandemic period ($p<0.001$). The reason for this is thought to be able to meet the transfusion needs of patients in need of cryo use in areas such as the service, intensive care, and operating rooms without waiting in the emergency services. In a study by Morrow et al. (16) it was shown that cryotransfusion restores essential fibrinolytic regulators and limits plasmin formation to form stronger clots. Clot structure and stability, as well as additional factors in cryoprecipitate, enable a stronger and more stable clot formation. The use of cryoprecipitate increases survival in patients with bleeding (16).

Although cryoprecipitate transfusions in the ED peaked in 2017, they decreased drastically in 2021. While the rate of total cryoprecipitate transfusion in all units was 6% in 2017, when it was used the most in the ED, this rate decreased to 0.5% in 2021. Generally, the decrease in cryoprecipitate transfusions in EDs is similar to the decrease in other transfusions. The reason for this can be shown as the effect of the understanding that, recently, the hospitalization of individuals in need of specialty transfusions such as fibrinogen, factor 8, factor 13, and vWF should be made earlier and these treatments should be administered in inpatient services, not in EDs.

### Study Limitations

The most important limitation of this study was the lack of data from universities and private hospitals. Another limitation is that the transfusion indications could not be reached. Although there are limitations, the most crucial aspect of the study is that the data containing blood transfusions belonging to the emergency services and other departments of our country are shared for the first time with such a large amount of data.

## Conclusion

Since the current study shows blood and blood product replacement and includes a broad comparison with the pandemic and pre-pandemic periods, it can guide the blood replacement strategies of the ED and all departments.

## Ethics

**Ethics Committee Approval:** Ethics committee approval was received for this study from the Clinical Research Ethics Committee No 2 of Ankara City Hospital (date: 30.03.2022; approval number: E2-22-1619).

**Informed Consent:** Patient consent was waived because of the study.

**Peer-review:** Internally peer-reviewed.

### Authorship Contributions

Concept: A.B., Design: A.B., Data Collection or Processing: A.B., A.T., Analysis or Interpretation: A.B., A.T., Literature Search: A.B., A.T.,

Writing: A.B.

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

**Financial Disclosure:** The authors declared that this study received no financial support.

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Original Article

DOI: 10.4274/haseki.galenos.2022.8668
Med Bull Haseki 2022;60:468-475

# Predictive Value of the Hematopoietic Stem Cell Transplantation - Comorbidity Index for Overall Survival in Patients with Multiple Myeloma

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## Abstract

**Aim:** The scoring system of the hematopoietic cell transplantation comorbidity index (HCT-CI) was used in patients with multiple myeloma (MM) undergoing autologous stem cell transplantation (ASCT), and it could predict progress-free survival and overall survival. Our study aims to determine the ideal cut-off value for the HCT-CI score, which can be effective in showing overall survival in patients with MM undergoing ASCT.

**Methods:** The files of all MM patients with ASCT between January 2015 and December 2020 were retrospectively scanned. The X-tile model was used to determine the cut-off values of the HCT-CI score. Survival probabilities were calculated using the Kaplan-Meier estimator. The Cox proportional hazard regression model was used for univariate and multivariate analyses.

**Results:** Patients were divided into two categories according to HCT-CI. Score ≤6 was defined as low-risk (n=93, 81.6%), and score >6 was defined as high-risk (n=21, 18.4%). The low-risk group had one-year and two-year OS rates of 96.7% and 86.9%, respectively, while the high-risk group had rates of 69.9% and 40.3% (p<0.001). In multivariate regression analysis, only being older than 70 years and having a HCT-CI >6 were found to be significant, with an HR of 3,718 and 5,543, respectively.

**Conclusion:** Hematopoietic stem cell transplantation - comorbidity index score >6 can aid physicians in deciding whether to perform ASCT in MM patients and predict the overall survival of those patients.

**Keywords:** Multiple myeloma, autologous stem cell transplantation, hematopoietic stem cell transplantation - comorbidity index, survival

## Introduction

High-dose therapy with autologous stem cell transplantation (ASCT) is an effective treatment for patients with multiple myeloma (MM) who are eligible for transplantation (1). Choosing the appropriate patient for transplantation and anticipating issues that may occur during ASCT is still a paramount problem for patients of all ages; when it can be done, various studies (2,3) have stated that favorable results have been obtained with ASCT even in elderly patients with MM.

The scoring system of the hematopoietic cell transplantation comorbidity index (HCT-CI), developed by Sorror et al. (4) to show early non-relapse mortality in patients undergoing allogeneic stem cell transplant, was also used in patients undergoing ASCT and included patients with MM. Although it does not effectively show transplant-related early mortality in MM patients, some studies (5,6) in the past few years have shown that it could predict progress-free survival (PFS) and overall survival (OS).

As research conducted in the current treatment era uses many new medications, we intended to evaluate the impact of medical comorbidities on the outcome of MM patients undergoing ASCT using the HCT-CI. The current study determines the ideal cut-off value for the HCT-CI score, a value that can be effective in showing OS in patients

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**Received:** 09.07.2022 **Accepted:** 22.11.2022

with MM who are treated with ASCT. The secondary endpoints are comparing the patients' characteristics and comorbidities before ASCT, transplant outcomes, and OS according to the cut-off value determined by HCT-CI.

## Materials and Methods

### Compliance with Ethical Standards

The present study was approved by the University of Health Sciences Turkey, Istanbul Medeniyet University, Goztepe Training and Research Hospital Clinical Research Ethic Committee (date: 16.06.2021, approval no: 2021/0315). The ethics committee of the institution approved all protocols, experimental studies, and clinical trials involving human subjects before the study began. Protocols have been developed in accordance with the Helsinki Declaration of 1975.

### Study Design

The files of all MM patients who underwent high-dose melphalan with ASCT between January 2015 and December 2020 were retrospectively scanned. Treatments were selected by the hematologist who made the diagnosis of the patients, according to the current international guidelines (NCCN, ESMO, etc.), labels, and practices. In all patients included in the study, MM panel tests (serum biochemistry, serum protein electrophoresis, serum plasma, and spot urine immune electrophoresis), serum plasma free light chain kappa/lambda, and 24-hour urine total light chain kappa/lambda), beta-2 microglobulin analysis, and whole-body 18-fluorodeoxyglucose using positron emission tomography-computed tomography (PET-CT) were performed in the pre-transplant setting. ECOG performance scores and ISS stages were recorded before transplantation.

The HCT-CI score determined by Sorror et al. (4) was calculated for all patients before transplantation (Supplementary Table 1). If information about any comorbidity of the patient could not be reached, that patient was considered to have no comorbidity, and scoring was done accordingly.

Melphalan was administered at doses of 200 mg/m² or 140 mg/m² as a conditioning regimen on day -2 according to the measurements of creatinine clearance and the patients' ages. All patients received levofloxacin for bacterial prophylaxis, fluconazole for fungal prophylaxis, and valaciclovir for viral prophylaxis starting from day -2.

Myeloma panel tests and PET-CT imaging were repeated with all patients at the end of the third month after transplantation. Post-transplant response status was determined by comparing the results obtained on day 100 after transplantation with those obtained before transplantation. All patients who survived had at least a 100-day follow-up.

### Statistical Analysis

The X-tile model (version 3.6.1) was used to determine the cut-off values of the HCT-CI score. The Kaplan-Meier method was used to plot survival curves, and the log-rank test was used to determine whether differences existed between the individual groups.

Descriptive statistics, frequency, and percentage were used to summarize the characteristics of the study population. Group comparisons were done using the Mann-Whitney U test, the chi-square test, and the Fisher's exact test. Based on Kaplan-Meier estimates, survival probabilities were calculated. To compare the survival of different groups, point-wise comparisons were made and log-rank analyses were conducted. The Cox proportional hazard regression model was used for univariate and multivariate analysis. Variables analyzed included HCT-CI (>2, and >6), age (>65 and >70 years), ECOG, gender, myeloma subgroup, ISS stage, melphalan dose, and biochemical parameters (albumin, LDH, creatinine, and B2-microglobulin at the time of transplantation). A univariate Cox regression was performed for variable selection at a .05 significance level was used to identify covariates; multivariate Cox regression analysis was performed using all significant covariates. IBM SPSS Version 25 was used for statistical analyses.

## Results

### Patients Characteristics

One hundred fourteen patients who had ASCT in concordance with a diagnosis of MM were included in the study. There was a predominance of males, with 64 patients (56.1%) examined, and the median age was 61 years (26-76). The median HCT-CI score was 4 for all patients (0-11). The distribution of patients due to the HCT-CI score is given in Figure 1, and the distribution of comorbidities among patients between the groups is given in Table 1.

### X-tile Modeling & Group Comparisons

By using the X-tile model according to the HCT-CI score, patients were divided into 2 categories according to OS: HCT-CI scores ≤6 as low-risk (n=93, 81.6%), HCT-CI score >6 as high-risk (n=21, 18.4%).


**Figure 1.** Distribution of patients due to HCT-CI score
*HCT-CI: Hematopoietic cell transplantation comorbidity index*

| Table 1. Distribution of comorbidities among patients between the groups | | | | |
|---|---|---|---|---|
| | **All patients** | **HCT-CI ≤6** | **HCT-CI >6** | **p-value** |
| Psychiatric disturbance | 47 (41.2%) | 33 (35.5%) | 14 (66.7%) | 0,009 |
| Peptic ulcer | 34 (29.8%) | 21 (22.6%) | 13 (61.9%) | 0.000 |
| Heart valve disease | 21 (18.4%) | 12 (12.9%) | 9 (42.9%) | 0,003 |
| Pulmonary disease | 51 (44.7%) | 34 (36.6%) | 17 (81%) | 0.000 |
| Diabetes/steroid-induced hyperglycemia | 36 (31.6%) | 24 (25.8%) | 12 (57.1%) | 0.005 |
| Infection | 26 (22.8%) | 19 (20.4%) | 7 (33.3%) | 0.250 |
| Renal disease | 9 (7.9%) | 3 (3.2%) | 6 (28.6%) | 0.001 |
| Cardiac disease | 17 (14.9%) | 12 (12.9%) | 5 (23.8%) | 0.305 |
| Arrhythmia | 5 (4.4%) | 1 (1.1%) | 4 (19%) | 0.004 |
| Hepatic disease | 21 (18.4%) | 17 (18.3%) | 4 (19%) | 1,000 |
| Prior solid tumor | 9 (7.9%) | 4 (4.3%) | 5 (23.8%) | 0.010 |
| Inflammatory bowel disease | 0 (0%) | 0 (0%) | 0 (0%) | |
| Cerebrovascular disease | 1 (0.9%) | 1 (1.1%) | 0 (0%) | 1,000 |
| Obesity | 10 (8.8%) | 5 (5.4%) | 5 (23.8%) | 0.018 |
| Rheumatologic disease | 2 (1.8%) | 1 (1.1%) | 1 (4.8%) | 0.336 |

According to the new risk score, most patients in the high-risk group were female (12 patients, 57.1%). The median ages were 58 (26-76), and 66 (35-72) in the low-risk and high-risk groups, respectively. The number of patients with an ECOG score of zero showed a significant difference between the groups (50 patients (53.8%) in low-risk vs. a total of 2 (9.5%) in high-risk groups, p <0.001). The number of patients with left ventricular ejection fraction above 50% was similar between the groups (89 patients (95.7%) in the low-risk group vs. 19 patients (90.5%) in the high-risk group, respectively), but there were statistically significantly more patients with an estimated glomerular filtration rate (eGFR) below 60 mL/min/1.73 $m^2$ in the high-risk group (10 patients, 47.6%) than the low-risk group (21 patients, 22.6%) (p=0.020).

Myeloma subgroups, ISS stages of patients, and pre-transplant and post-transplant response rates were similar among both groups. Although a decreased tendency was observed without significant statistical difference in stem cell mobilization success with G-CSF in the high-risk group (p=0.255), in most of the patients it was successfully mobilized with G-CSF: 84 patients (90.3%) in the low-risk group, and 17 patients (81%) in the high-risk group, respectively. As expected, melphalan dose reduction was performed more frequently in the high-risk group (10 patients in the high-risk group; 47.6% and 24 patients in the low-risk group; 25.8%, p=0.048) (Table 2).

Concerning the post-transplant complications presenting on the 100$^{th}$ day after the transplantation, death due to septic shock was observed in one patient from each risk group, while death due to cardiorenal toxicity was observed in one patient in the high-risk group. Renal toxicity and hepatobiliary toxicities were more frequent in high-risk patients [p=0.020, hazard ratio (HR): 3.72, 95% confidence interval (CI): 1,236-11,244], but cardiac toxicity, pulmonary toxicity, bleeding, and deep vein thrombosis were comparable between groups (Table 3).

**Survival Analysis**

Patients were followed for an average of 21 months (0-79). The median duration of survival could not be reached for the low-risk group and the entire cohort, but it was 22 months for high-risk patients. One-year and 2-year OS rates were 96.7% and 86.9% in the low-risk group; 69.9% and 40.3% in the high-risk group (p<0.001), respectively (Figure 2).

In univariate cox-regression analysis, being more than 70 years old, HCT-CI >6, ECOG >0, reduced melphalan dose, and creatinine levels of patients before ASCT were found to be significant in terms of decreased OS. In multivariate regression analysis, only being older than 70 years and having an HCT-CI >6 were found to be significant with an HR of 3.718 (p=0.011, 95% CI: 1,344-10,291) and 5.543 (p=0.001, 95% CI: 2,072-14,833), respectively (Supplementary Table 2).

In univariate cox-regression analysis, the HCT-CI score > 2 was also found to be significant in terms of OS, with an HR of 3.457 (p=0.023, 95% CI: 1.19-10,043) compared with HCT-CI ≤2. Considering this information, patients were divided into 3 risk groups for OS according to their HCT-CI scores: 0-2 (very low risk), 3-6 (low risk), and more than 6 (high-risk). The median OS of patients was 58 months in low-risk patients and 22 months in high-risk patients; it could not be reached in the very low-risk group. One-year and two-year OS of patients were 100%

| Table 2. Patients, disease and treatment characteristics between groups | | | | |
|---|---|---|---|---|
| | **All patients** | **HCT-CI ≤6** | **HCT-CI >6** | **p-value** |
| **HCT-CI** | 4 (0-11) | 3 (0-6) | 8 (7-11) | 0.000 |
| **Male (n,%)** | 64 (56.1%) | 55 (59.1%) | 9 (42.9%) | 0.174 |
| **Age (years, range)** | 61 (26-76) | 58 (26-76) | 66 (35-72) | 0.410 |
| 18-39 | 8 (7%) | 7 (7.5%) | 1 (4.8%) | 0.395 |
| 40-49 | 15 (13.2%) | 14 (15.1%) | 1 (4.8%) | |
| 50-59 | 34 (29.8%) | 28 (30.1%) | 6 (28.6%) | |
| 60-65 | 9 (7.9%) | 7 (7.5%) | 2 (9.5%) | |
| 66-69 | 25 (12.9%) | 17 (18.3%) | 8 (38.1%) | |
| 70-80 | 23 (20.2%) | 20 (12.5%) | 3 (14.3%) | |
| **ISS** | | | | |
| Stage I | 54 (47.4%) | 48 (51.6%) | 6 (28.6%) | 0.080 |
| Stage II | 25 (21.9%) | 17 (18.3%) | 8 (38.1%) | |
| Stage III | 35 (30.7%) | 28 (30.1%) | 7 (33.3%) | |
| **Myeloma subgroups** | | | | |
| IgG | 76 (67.9%) | 63 (68.5%) | 13 (65%) | 0.460 |
| IgA | 22 (19.6%) | 18 (19.6%) | 4 (20%) | |
| Light Chain | 9 (8%) | 6 (6.5%) | 3 (15%) | |
| Other | 5 (4.5%) | 5 (5.4%) | - | |
| **Lines of chemotherapy** | 1 (1-5) | 1 (1-3) | 1 (1-5) | 0.973 |
| **Response before transplant** | | | | |
| CR | 17 (14.9%) | 15 (16.1%) | 2 (9.5%) | 0.634 |
| VGPR | 64 (56.1%) | 53 (57%) | 11 (52.4%) | |
| PR | 32 (28.1%) | 24 (25.8%) | 8 (38.1%) | |
| SD | 1 (0.9%) | 1(1.1%) | - | |
| **ECOG** | | | | |
| 0 | 52 (45.6%) | 50 (53.8%) | 2 (9.5%) | **0.000** |
| ≥1 | 62 (54.4%) | 43 (46.2%) | 19 (90.5%) | |
| **LVEF** | | | | |
| ≥%50 | 108 (94.7%) | 89 (95.7%) | 19 (90.5%) | 0.305 |
| <%50 | 6 (5.3%) | 4 (4.3%) | 2 (9.5%) | |
| **eGFR** | | | | |
| ≥60 mL/min | 83 (72.8%) | 72 (77.4%) | 11 (52.4%) | **0.020** |
| <60 mL/min | 31 (27.2%) | 21 (22.6%) | 10 (47.6%) | |
| **Stem cell mobilization** | | | | |
| G-CSF | 101 (88.6%) | 84 (90.3%) | 17 (81%) | 0.077 |
| Cyclo & G-CSF | 9 (7.9%) | 5 (5.4%) | 4 (19%) | |
| Plerixafor & G-CSF | 4 (3.5%) | 4 (4.3%) | - | |
| **Melphalan dose** | | | | |
| <200 mg/m$^2$ | 34 (29.8%) | 24 (25.8%) | 10 (47.6%) | 0.048 |
| 200 mg/m$^2$ | 80 (70.2%) | 69 (74.2%) | 11 (52.4%) | |

| Table 3. Outcomes of patients after ASCT | | | | |
|---|---|---|---|---|
| | **All patients** | **HCTCI ≤6** | **HCT-CI >6** | **p-value** |
| Treatment-related mortality | 3 (2.6%) | 1 (1.1%) | 2 (9.5%) | 0.087 |
| Febrile neutropenia | 61 (53.5%) | 47 (50.5%) | 14 (66.7%) | 0.181 |
| Renal toxicity | 18 (15.8%) | 11 (11.8%) | 7 (33.3%) | **0.023** |
| Cardiac toxicity | 7 (6.1%) | 5 (5.4%) | 2 (9.5%) | 0.611 |
| Pulmonary toxicity | 1 (0.9%) | 1 (1.1%) | 0 | 1,000 |
| Hepatobiliary toxicity | 25 (21.9%) | 16 (17.2%) | 9 (42.9%) | **0.018** |
| Bleeding | 11 (9.6%) | 7 (7.5%) | 4 (19%) | 0.117 |
| Deep vein thrombosis | 7 (6.7%) | 5 (5.9%) | 2 (10.5%) | 0.609 |
| **Response after transplant** | | | | |
| CR | 37 (33.9%) | 32 (35.2%) | 5 (27.8%) | 0.186 |
| VGPR | 67 (61.5%) | 55 (60.4%) | 12 (66.7%) | |
| PR | 2 (1.8%) | 2 (2.2%) | - | |
| SD | 3 (2.7%) | 2 (2.2%) | 1 (5.6%) | |

and 89.9% in the very low-risk group; 94.2% and 84.6% in the low-risk group; and 69.9% and 40.3% in the high-risk group (Figure 3). While the HCT-CI score between 2 and 6 appeared to be associated with worse OS compared to the HCT-CI 0–1 score, it did not reach statistical significance (p=0.182, HR: 2.18, 95% CI: 0.694-6.849) in cox-regression analysis. HCT-CI Score >6 had a statistically significantly worse OS compared to both HCT-CI scores of 0-2 and 3-6 (with an HR of 8.7, p<0.001, 95% CI 2.74-27.6; HR 4, p=0.001, 95% CI 1.7-9.34).

## Discussion

The largest study showing the effects of the HCT-CI score on OS in 1154 MM patients was conducted by Saad et al. (5) in 2014. They reported that in univariate analysis, the patients with HCT-CI scores of 1 to 2 had a worse OS with an HR of 1.37 and HCT-CI >2 with an HR of 1.5 compared with an HCT-CI score of 0. In multivariate analysis, HCT-CI scores greater than 0 had a HR of 1.33 (p=0.04) compared to HCT-CI scores less than 0. In another study, Jaglowski et al. (7) reported that there was no statistical difference between groups with HCT-CI scores <3 vs. ≥3 (p=0.92). Obiozor et al. (8) also reported that an HCT-CI score >2 also appeared to be associated with worse OS than HCT-CI 0-1, but the difference did not reach statistical significance (HR 1,311, 95% CI: 0.72 to 2.76), similar to patients with an HCT-CI score between 2 and 6 in our study. We found that all patients with an HCT-CI >2 had a worse OS with an HR 3.45 than patients with a score ≤2; however, this difference was mostly due to the patients with an HCT-CI >6, not those with an HCT-CI between 3 and 6 (with an HR 8.7 compared to an HCT-CI score 0-2; p<0.001, and an HR 4 compared to an HCT-CI score 3-6; p=0.001).

In our study, we reported that the 2-year OS of patients with HCT-CI scores 0-2 was 89.9%. In Saad et al.'s (5) study, it was 89%, and only in patients with an HCT-CI score of 0. In patients with an HCT-CI score of 1-2, it was 84%. We reported that patients with higher HCT-CI scores (between 3-6) had a 2-year OS of 84.6%. HCT-CI score did not influence OS in patients aged >65 years at the time of transplant in Saad et al.'s (5), but HCT-CI score >6 influenced OS in all age groups in our study (data not shown). When comparing the comorbidities of patients in two studies, it was observed that pulmonary dysfunction (44.7% vs. 22.6%), psychiatric disturbances (41.2% vs. 12.2%), diabetes/steroid-induced hyperglycemia (31.6% vs. 13.7%), peptic ulcus (29.8% vs. 2.5%), and all other comorbidities were higher in our study. In both studies, the melphalan dose was reduced similarly in about 26-28% of patients, especially those with high HCT-CI scores. Although HCT-CI scores were higher and comorbidities were more common in our study, OS in patients with an HCT-CI score of 6 was comparable to that of patients in Saad's study with an HCT-CI score between 0 and 2. This was speculated to be because OS has significantly improved in patients with MM. Several factors contribute to this progress, including better biological insights into the disease, more sensitive tests and technologies allowing for easier detection of relapses, better combination therapies, and increased access to supportive care measures (6). So now, high-risk patients could be defined as patients with an HCT-CI score >6.

In Saad et al.'s (5) study, there was no difference in OS among patients who received a reduced melphalan dose. In our study, reduced melphalan was associated with worse outcomes in univariate cox-regression analysis but not in multivariate analysis. TRM was similar in both studies (1-2%). Saad et al. (5) also reports that age greater than 65 years did not influence OS as much as our study, although we found that age greater than 70 years influenced OS with an HR 3.7.

Not only was OS short, but treatment-related toxicities were more common in high-risk patients. Labonté et al. (9) report in their study that patients with an HCT-CI score ≥1 had severe organ toxicity 2.5 times higher than patients with an HCT-CI score 0. Also, parallel with our study, high-risk patients had more pulmonary and hepatotoxicity compared with the low-risk patients (with an HR of 3.7).

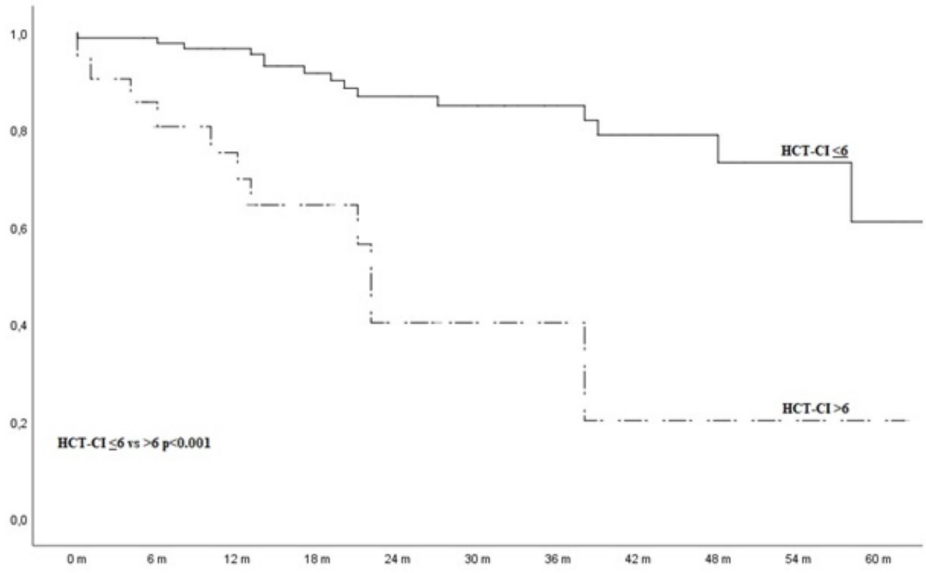


**Figure 2.** OS according to risk groups calculated from HCT-CI score (low risk vs. high-risk)
*OS: Overall survival, HCT-CI: Hematopoietic cell transplantation comorbidity index*

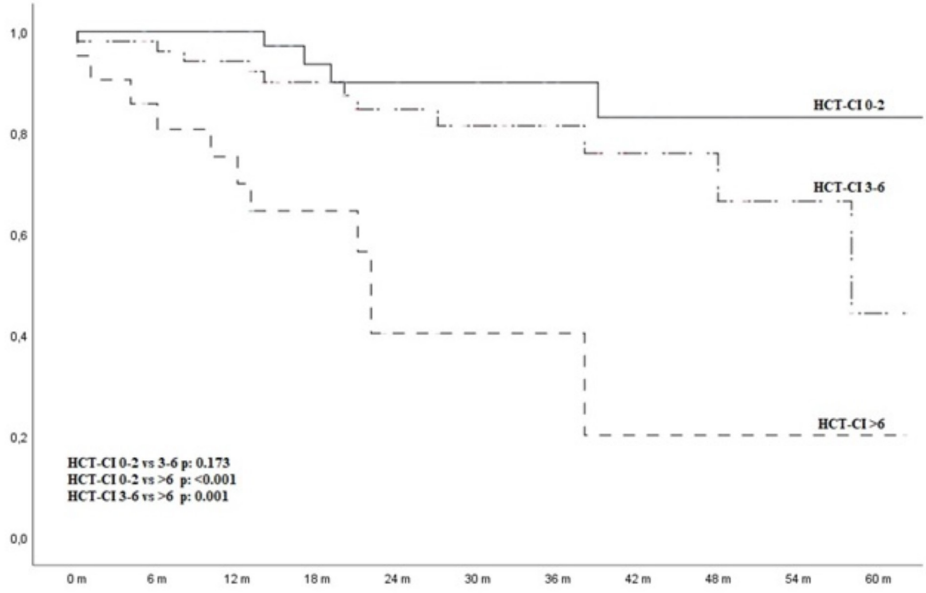


**Figure 3.** OS according to 3 risk groups calculated from HCT-CI score (very low-risk vs. low-risk vs. high-risk)
*OS: Overall survival, HCT-CI: Hematopoietic cell transplantation comorbidity index*

In Waszczuk-Gajda et al.'s (10) study on infection complications in 1374 patients with MM, Waszczuk-Gajda reported that 336 of the 1374 patients (24.4%) had infection episodes during ASCT, whereas Gil et al. (11) reported that 56 of 64 patients with MM had infection complications during neutropenia after ASCT. Febrile neutropenia was observed in 53.5% of our patients, with a tendency to occur more frequently in high-risk patients. Different rates of febrile neutropenia in these studies and our study may be related to the different comorbidity rates of the patients in these studies.

**Study Limitations**

The first and most important limitation is the retrospective nature of the study. Most of the patients included in the study were treated with different induction regimens (vincristine-doxorubicin-dexamethasone, bortezomib-cyclophosphamide-dexamethasone, bortezomib-thalidomide-dexamethasone, etc.) and variable use of maintenance therapy, thereby affecting the OS homogeneity. Because the genetic makeup of the majority of our patients was unknown, genetic analyses

could not be included in our study. We could also not make any comments on the PFS for most of the patients due to the lack of information beyond 100 days post-transplant.

## Conclusion

Successful results in studies conducted with both the elderly and patients with comorbidities showed that ASCT can be a treatment option for people of all ages with MM, as long as an accurate patient selection can be done. HCT-CI scores greater than 6 can help physicians make this difficult decision by predicting both overall patient survival and treatment-related toxicity incidence. Since similar survival times can be achieved with current combination therapies (monoclonal antibodies, etc.) in these patients, ASCT may not be considered. Randomized, controlled studies are needed on this subject. Also, there is still a need to develop a scoring system that can be easily performed and is more effective in showing morbidity and mortality in MM patients.

## Ethics

**Ethics Committee Approval:** The present study was approved by the University of Health Sciences Turkey, Istanbul Medeniyet University, Goztepe Training and Research Hospital Clinical Research Ethic Committee (date: 16.06.2021, approval no: 2021/0315).

**Informed Consent:** Retrospective study.

**Peer-review:** Externally peer-reviewed.

**Authorship Contributions**

Concept: T.E., O.K., Design: T.E., O.K., Data Collection or Processing: T.E., O.K., Analysis or Interpretation: T.E., O.K., Literature Search: T.E., O.K., Writing: T.E., O.K.

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

**Financial Disclosure:** The authors declared that this study received no financial support.

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| Supplementary Table 1. The HCT-CI score | | |
|---|---|---|
| **Comorbidities** | **Definitions** | **HCT-CI Score** |
| Arrhythmia | Atrial fibrillation or flutter, sick sinus syndrome, and ventricular arrhythmias | 1 |
| Cardiac | Coronary artery disease, congestive heart failure, myocardial infarction, or ejection fraction ≤50% | 1 |
| Inflammatory bowel disease | Crohn's disease or ulcerative colitis | 1 |
| Diabetes | Requiring treatment with insulin or oral hypoglycemics but not diet alone | 1 |
| Cerebrovascular disease | Transient ischemic attack or cerebrovascular accident | 1 |
| Psychiatric disturbance | Depression/anxiety requiring psychiatric consult or treatment | 1 |
| Hepatic, mild | Chronic hepatitis, bilirubin >ULN - 1.5 x ULN, or AST/ALT >ULN - 2.5 x ULN | 1 |
| Obesity | Patients with a body mass index >35 kg/m2 | 1 |
| Infection | Requiring continuation of antimicrobial treatment after day 0 | 1 |
| Rheumatologic | SLE, RA, polymyositis, mixed CTD, polymyalgia rheumatica | 2 |
| Peptic ulcer | Requiring treatment | 2 |
| Moderate/severe renal | Serum creatinine >2 mg/dL, on dialysis, or prior renal transplantation | 2 |
| Moderate pulmonary | DLCO and/or FEV1 >65%-80% or dyspnea on slight activity | 2 |
| Prior solid tumor | Treated at any time point in the patient's past history, excluding nonmelanoma skin cancer | 3 |
| Heart valve disease | Except mitral valve prolapse | 3 |
| Severe pulmonary | DLCO and/or FEV1 <65% or dyspnea at rest or requiring oxygen | 3 |
| Moderate/severe hepatic | Liver cirrhosis, bilirubin >1.5 x ULN, or AST/ALT > 2.5 x ULN | 3 |

ULN: Upper limit of normal, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, SLE: Systemic lupus erythematosus, RA: Rheumatoid arthritis, CTD: Connective tissue disease, DLco: Diffusion capacity of carbon monoxide, FEV1: Forced expiratory volume at 1 second

| Supplementary Table 2. Multivariate cox regression analysis for | | | | | | | |
|---|---|---|---|---|---|---|---|
| | **Mean** | **B** | **SE** | **p-value** | **HR** | **95% CI for Exp (B)** | |
| HCT-CI ≤6 vs. >6 | **0.184** | **1,713** | **0.502** | **0.001** | **5,543** | **2,072** | **14,833** |
| ECOG | 0.544 | -0.281 | 0.547 | 0.608 | 0.755 | 0.258 | 2,209 |
| Age ≤70 vs. >70 years old | **0.175** | **1,313** | **0.519** | **0.011** | **3,719** | **1,344** | **10,291** |
| Melphalane dose | 0.298 | 0.499 | 0.493 | 0.312 | 1,646 | 0.627 | 4,324 |
| Creatinine | 1,026 | 0,43 | 0.443 | 0.332 | 1,537 | 0.645 | 3,658 |

Original Article

DOI: 10.4274/haseki.galenos.2022.8449
Med Bull Haseki 2022;60:476-482

# Association Between Cerebral Small Vessel Disease and Intracranial Arterial Calcification

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**Abstract**

**Aim:** Cerebral small vessel disease (CSVD) is a representative cause of stroke, cognitive impairment, and age-related disability, and it is shown to be associated with some traditional atherosclerotic risk factors. This study investigated relationship between the presence and severity of intracranial arterial calcification (ICAS) and the findings of CSVD.

**Methods:** Three hundred eighty-nine patients over the age of 40 who underwent non-enhanced cranial computed tomography (CT) and magnetic resonance imaging between January 01 and December 31, 2018, were included in the retrospective study. ICAS was scored on CT. CSVD findings, enlarged perivascular spaces (BGPVS, CSPVS), white matter hyperintensities [white matter hyperintensity was scored at periventricular (PVWMHI), white matter hyperintensity was scored at subcortical (SCWMHI)], cortical atrophy [global atrophy (GA) score, and medial temporal atrophy (MTA), Koedam score] were scored in MR images. The presence of acute, chronic, and lacunar infarcts was recorded. After controlling for age and gender, the correlation between ICAS and CSVD markers was examined.

**Results:** A positive correlation was found between ICAS score and BGPVS (r: 0.463 p<0.001), PVWMHI (r: 0.235 p<0.001), and GA (r: 0.368 p<0.001). A negative correlation was found between ICAS score and MTA (r: -0.112 p<0.05) and Koedam score (r: -0.196 p<0.001). The ICAS score was significantly high in cases of lacunar and chronic infarcts (p<0.001). No correlation was found between the calcification score and the CSPVS and SCWMHI scores.

**Conclusion:** The results of this study show that ICAS is correlated with BGPVS, PVWMHI, GA, MTA, Koedam score, and chronic and lacunar infarct.

**Keywords:** Small vessel disease, intracranial calcification, atrophy, infarct

## Introduction

Calcification observed in intracranial arteries (ICAS) is an indicator of atherosclerosis. ICAS is a relatively easy biomarker to detect, which allows the evaluation of the diffuseness of intracranial atherosclerosis (1). There is literature evidence showing that ICAS may be associated with acute ischemic stroke, cerebral small vessel disease (CSVD), and cognitive impairment (1).

Cerebral small-vessel disease is a large group of diseases affecting the small vessels, arterial, venule, and capillary systems of the brain, which includes various pathological processes and etiological factors (2). CSVD is an important cause of stroke, cognitive impairment, and age-related disability (2). There are data showing that vascular brain diseases such as hypertension, aging, and amyloid angiopathy are also effective in CSVD (2). The imaging findings of CSVD include small subcortical infarcts, lacunar infarcts, white matter hyperintensities (WMHI), perivascular spaces, microhemorrhages, and brain atrophy (3). Because of the relationship between traditional atherosclerotic risk factors such as hypertension and CSVD, we hypothesized that ICAS, as an indicator of intracranial atherosclerosis, may also be associated with CSVD. In studies investigating the relationship between CSVD markers and ICAS, findings such as lacunar infarct and WMHI are evaluated separately (4-9). In this study, however, all findings of ICAS and CSVD markers other than microhemorrhage were evaluated together.

This study aimed to investigate the relationship between the presence and severity of ICAS and the findings of CSVD.

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**Received:** 02.05.2022 **Accepted:** 25.09.2022

## Materials and Methods

### Compliance with Ethical Standards

This retrospective study was approved by the University of Health Science Turkey, Ankara Kecioren Training and Research Hospital Institutional Review Board (date: 05.10.2018, approval number: 29).

### Study Design

Four hundred seventy-five patients over the age of 40 who underwent non-contrast cranial computed tomography (CT) and magnetic resonance imaging (MRI) between January 1 and December 31, 2018, not more than 3 months apart, were screened from PACS. Ninety-six cases were excluded due to poor imaging quality, trauma/operation history, presence of tumor/metastasis, and history of demyelinating disease. The study was completed with 379 cases. Informed consent was not obtained because the study was retrospective.

All MRI examinations were carried out with a 1.5-T Siemens Avanto MR device (Siemens AG, Healthcare Sector, Erlangen, Germany). MRI squences included two-dimensional multislice turbo spin-echo T1-weighted [repetition time (TR)/echo time (TE), 1200/11 ms], fluid-attenuated inversion recovery (FLAIR) (TR/TE, 7000/94 ms; inversion time, 2500 ms), T2-weighted [TR/TE, 4500/84 ms), diffusion-weighted imaging (DWI), TR/TE, 4800/102 Ms, b: 0 and 1000 s/mm$^2$] in the axial plane, as well as a T1-weighted sequence oriented in the sagittal plane. The slice thickness was 5 mm, with a 1-mm gap between slices.

All CT examinations were carried out with a Siemens 16-slice multislice CT device (Siemens, Sensations, Germany). The slice thickness was 3 mm, with no gap between the slices.

The CT and MR images were independently evaluated by two radiologists at the workstation (Syngo workstation, Earlengen, Germany).

### Patient Evaluation

The bone window was used in the detection and grading of ICAS. Foci above 130 HU in the evaluated vessel tracing were accepted as ICAS. The internal carotid artery (ICA) cavernous segment, middle cerebral artery (MCA) M1 segment, anterior cerebral artery A1 segment, vertebral artery V4 segment, and basilar artery were evaluated on the right and left sides. According to the visual 5-point ICAS scoring method defined by Hong et al. (8), grade 0 was scored as no calcification, grade 1 was scored as point calcification, grade 2 was scored as thin continuous or thick non-continuous calcification, grade 3 was scored as thick continuous calcification, and grade 4 was scored as double tract calcification (Figure 1). The total calcification score was determined by summing all scores (min-max: 0-36).

In the evaluation of small vessel disease, areas of cerebral spinal fluid intensity around penetrating vascular structures at the level of basal ganglia (BGPVS) and centrum semiovale (CSPVS) were considered perivascular space (PVS) enlargement on MRI. PVS was evaluated in axial T2A fast spin-echo (FSE) images and scored separately at these levels. Scores were done separately for both hemispheres and the highest score was included in the analyses (0: no PVS; 1: <10 PVS, 2:11- 20 PVS, 3: 21-40 PVS, and 4: >40 PVS) (10) (Figure 2). Scores of 2 and above were considered abnormal (6).

On MRI, WMHI was scored at periventricular (PVWMHI) and subcortical (SCWMHI) levels separately according to Fazekas et al. (11) staging (Figure 3). Scores of 2 and above were considered positive.

Cortical atrophy, global atrophy (GA) score, medial temporal atrophy (MTA) score, and Koedam score were recorded separately on MRI. The scoring methods were

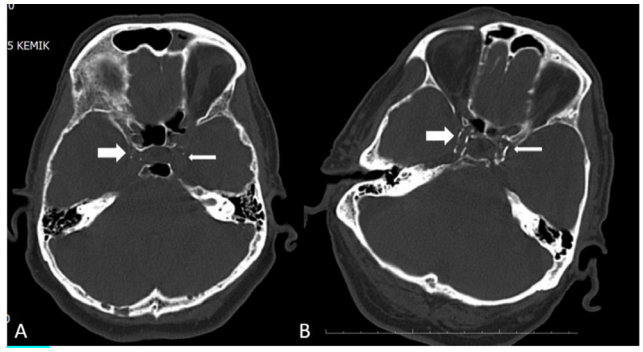


**Figure 1.** Non-contrast axial CT images with bone window setting showed A); grade 1: point calcification cavernous segment of ICA (thick arrow), cavernous sinus (thin arrow), B); grade 4: double tract calcification cavernous segment of ICA (thick arrow), cavernous sinus (thin arrow)

*CT: Computed tomography, ICA: Internal carotid artery*

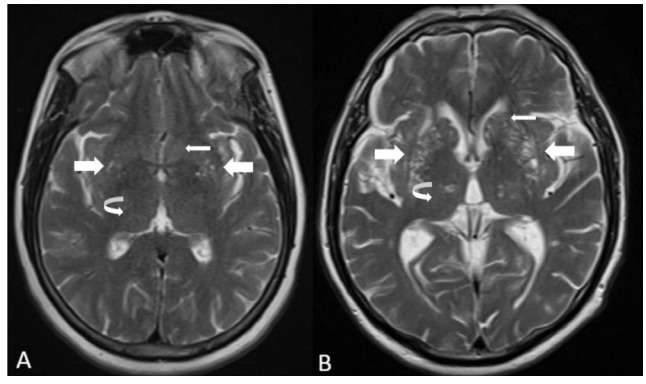


**Figure 2.** Axial T2W MR images at level of basal ganglia showed A); grade 1 BGPVS (thick arrows), head of caudate nucleus (thin arrow), thalamus (curved arrow). B); grade 4 BGPVS (thick arrows) head of caudate nucleus (thin arrow), thalamus (curved arrow)

*MR: Magnetic resonance, BGPVS: Vascular structures at the level of basal ganglia, T2W: T2-weighted*

evaluated separately for both hemispheres, and the highest score was recorded.

In GA scoring, the total brain parenchyma was evaluated in axial FLAIR sequences and the scoring method defined by Pasquier et al. (12) was used (0: no cortical atrophy; 1: mild cortical atrophy, slight enlargement of the sulci; 2: moderate atrophy, loss of volume in the gyri; 3: severe atrophy, knife blade-shaped atrophy of the sulci) (Figure 4). Scores of 2 and above were considered positive (13).

MTA scoring was performed on coronal T2-weighted (T2W) FSE images using the scoring method defined by Scheltens et al. (14) (0: no atrophy; 1: only choroidal fissure enlargement; 2: choroidal fissure and lateral ventricular temporal horn enlargement; 3: hippocampus elevation and slight volume loss; 4: severe loss of hippocampus volume). Scores of 3 and above were considered positive (13).

The Koedam scoring was performed on sagittal T1W FSE, coronal T2W FSE, and axial FLAIR FSE images, and the scoring method described by Koedam et al. (15) was used (0: no atrophy; 1: mild sulcal enlargement, without volume loss in the gyri; 2: moderate sulcal enlargement accompanied by volume loss in the gyri; 3: pronounced enlargement of the parietal sulci and knife blade-like appearance). Scores of 2 and above were considered positive (13).

Lacunar infarcts were defined as 3-15 mm in diameter T2W hyperintensities in the subcortical white matter, thalamus, or basal ganglia (16). Perivascular spaces were differentiated from lacunar infarcts by their specific locations and the absence of peripheral gliosis (16). An acute infarct was defined by hyperintensity on DWI and hypointensity on the clear diffusion coefficient map (ADC) (5). Chronic infarct was defined as hyperintensities on T2W, hypointensity on T1W, and no diffusion restriction on DWI and ADC (17). The presence and absence of lacunar, acute, and chronic infarcts were recorded on MRI.

### Statistical Analysis

Categorical variables are summarized as frequencies and numbers. Continuous variables were described as medians (interquartile range) or mean ± standard deviation. Normality was assessed using the Kolmogorov-Smirnov test. For the univariate analysis, Pearson's $\chi 2$ test was used for categorical variables, and the Mann-Whitney U test was used for calcification score. Correlations were tested with the Partial correlation analysis after controlling for age and gender. The relationship between acute, chronic, and lacunar infarcts and intracranial calcification was tested using the Mann-Whitney U test. All data was analyzed with IBM SPSS version 20 (Chicago, IL, USA). $P<0.05$ was accepted as statistically significant in all analyses.

## Results

Three hundred seventy-nine patients were included in the study. The mean age of the patients was 63.42±13.40 years (range 40-93). 42.2% of the patients were male and 57.8% were female. The MRI findings of the cases are summarized in Table 1. The distribution of MRI findings is shown in Figure 5.

The median total calcification score was 5 (min-max: 0-25). The total calcification scores of female patients were

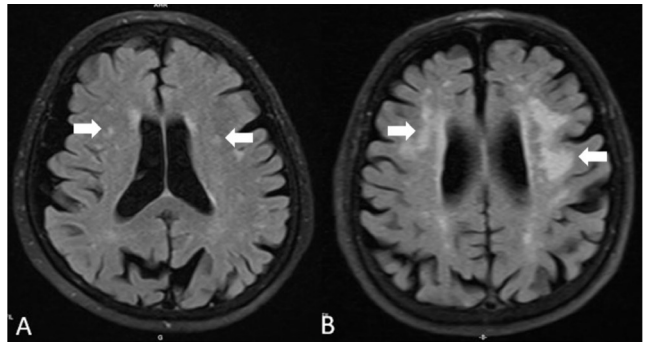


**Figure 3.** Axial FLAIR MR images showed A); Fazekas grade 1 WMHI (white arrows), grade 3, B) WMHI (white arrows)

*MR: Magnetic resonance, WMHI: White matter hyperintensities*

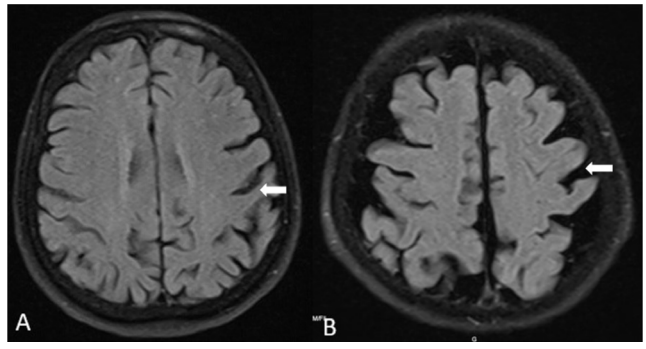


**Figure 4.** Axial FLAIR MR images at level of supraventricular showed A); global atrophy score grade 1: slight enlargement of the sulci (white arrow), B); global atrophy score grade 3: knife blade-shaped enlargement of the sulci (white arrow)

*MR: Magnetic resonance*

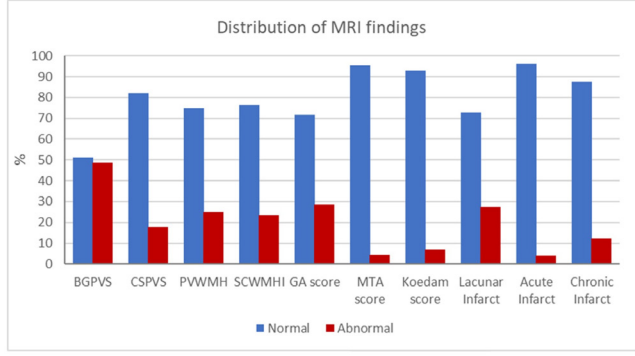


**Figure 5.** Distrubition of MRI findings

*MRI: Magnetic resonance imaging*

| Table 1. Distribution of MRI findings (abnormal/normal/%) | | |
|---|---|---|
| | n | % |
| **BGPVS** | | |
| Normal (0+1) | 194 | 51.2 |
| Abnormal (≥2) | 185 | 48.8 |
| **CSPVS** | | |
| Normal (0+1) | 311 | 82.1 |
| Abnormal (≥2) | 68 | 17.9 |
| **PVWMHI** | | |
| Normal (0+1) | 284 | 74.9 |
| Abnormal (≥2) | 95 | 25.1 |
| **SCWMHI** | | |
| Normal (0+1) | 290 | 76.5 |
| Abnormal (≥2) | 89 | 23.5 |
| **GA score** | | |
| Normal (0+1) | 271 | 71.5 |
| Positive (≥2) | 108 | 28.5 |
| **MTA score** | | |
| Normal (0+1+2) | 362 | 95.5 |
| Positive (≥3) | 17 | 4.5 |
| **Koedam score** | | |
| Normal (0+1) | 352 | 92.9 |
| Positive (≥2) | 27 | 7.1 |
| **Lacunar infarct** | | |
| No | 275 | 72.6 |
| Yes | 104 | 27.4 |
| **Acute infarct** | | |
| No | 364 | 96 |
| Yes | 15 | 4 |
| **Chronic infarct** | | |
| No | 332 | 87.6 |
| Yes | 47 | 12.4 |

MRI: Magnetic resonance imaging, BGPVS: Vascular structures at the level of basal ganglia, CSPVS: Vascular structures at the level of centrum semiovale, PVWMHI: White matter hyperintensity was scored at periventricular, SCWMHI: White matter hyperintensity was scored at subcortical, GA: Global atrophy, MTA: Medial temporal atrophy

lower compared of male patients (M/F: 6/4; p<0.05). A positive correlation was found between age and total calcification scores (r=0.659, p<0.001).

After controlling for age and gender, a positive correlation was found between calcification score and BGPVS (r=0.463 p<0.001), PVWMHI (r=0.235 p<0.001), and GA scores (r=0.368 p<0.001). A negative correlation was found between the calcification score and MTA (r=-0.112 p<0.05) and KOEDAM scores (r=-0.196 p<0.001). After controlling for age and gender, no correlation was found between calcification score and CSPVS and SCWMHI scores (p>0.05).

There was no significant relationship between the acute infarct and total calcification score (p>0.05). The total calcification scores of cases with chronic and lacunar infarcts were significantly higher (p<0.001).

## Discussion

CSVD is a disease associated with various clinical conditions ranging from acute-chronic ischemia to cognitive impairment. Although the etiology of CSVD includes pathologies such as systemic or vascular inflammation, arteriolosclerosis, cerebral amyloid angiopathy, etc., the exact cause is unclear (3,18). Recent literature showed an association between CSVD and atherosclerotic signs like arterial stiffness (19). In this study, a significant association was found between calcification of major intracranial arteries and enlarged perivascular spaces at the level of basal ganglia, PVWMHI, global, medial temporal, and parietal atrophy, and chronic and lacunar infarcts.

In this study, the relationship between perivascular spaces and ICAS was evaluated separately at the level of BGPVS and CSPVS. A significant relationship was found between BGPVS and the total calcification score. Similarly, a previous study investigating the relationship between increased PVS at the basal ganglia level with carotid siphon calcification reported a significant relationship between BGPVS and calcification grade (6). In another study evaluating the relationship between perivascular spaces and ischemic stroke, a significant relationship was found between BGPVS and lacunar stroke (10). Chen et al. (20) reported no significant correlation between the calcification score and enlarged perivascular spaces. This may be since enlarged perivascular spaces were not separated according to their localization in the study. In this study, there was no significant correlation between CSPVS and calcification score, which may be due to the different PVS etiology at the basal ganglia and CSPVS level (6).

A significant positive correlation was found between ICAS and PVWMHI score, but no correlation was found with SCWMHI. There are studies in the literature showing that WMHI are associated with extracranial carotid artery or intracranial major artery atherosclerosis (4,5,21,22). In a study investigating the relationship between ICAS and WMHI volume, a significant relationship was found between ICAS and enlarged WMHI volume (9). In the study by Babiarz et al. (23), no significant correlation was found between cavernous carotid artery calcification and WMH. Similar to the results of this study, de Leeuw et al. (21) reported a significant association between extracranial carotid artery atherosclerosis and PVWMHI, while there was no significant association with subcortical WMHI. In another study, it was shown that periventricular WMHI and deep WMHI had opposite effects on functional

decline after ischemic SVO, and this was attributed to the difference in the etiological mechanism of the two entities (24). We are also of the opinion that the opposite relationship between periventricular and subcortical WMHI and ICAS in this study is due to the difference in WMHI etiopathogenesis in the two regions.

Cerebral atrophy, one of the MRI findings of CSVD, was evaluated with a GA score, MTA score, and Koedam score. A significant positive correlation was found between the ICAS score and the GA score, while a significant negative correlation was found between ICAS and MTA and parietal atrophy (Koedam score) scores. Similarly, in a study conducted on the Japanese population (25), a significant correlation was found between the brain atrophy index and carotid plaque score. In another study, it was reported that carotid intima-media thickness was associated with sulcal enlargement in the brain (26). In a study investigating the relationship between ICAS and brain volume, a significant relationship was found between ICAS and total brain volume (27). In contrast, Erbay et al. (28) found no correlation between ICAS and cortical-volume loss. In contrast with the results of this study, Kang et al. (29) found a significant relationship between intracranial and carotid artery stenosis and hippocampal volume in patients with mild cognitive impairment. Vinke et al. (30) compared ICAS and CSVD findings and found no significant association with cerebral atrophy. There are differences between the three above-mentioned studies and this study. Visual scoring methods without software assistance were used in this study, which may have led to a difference in results. A result of this study was the negative correlation between ICAS and MTA and Koedam scores. Data on the relationship between ICAS and MTA or Koedam score are limited in the literature. Kang et al. (29), a positive correlation was shown between intracranial or carotid artery stenosis and hippocampal atrophy. However, MTA and parietal atrophy (Koedam score) are more likely to be associated with Alzheimer's disease (AD) than with vascular dementia (31,32). Studies showing that there is no relationship between AD and intracranial or carotid artery atherosclerosis (33,34) may indirectly explain the negative correlation found between ICAS and these atrophy patterns.

No significant relationship was found between acute infarct and ICAS. We believe this is due to the small number of cases with acute infarct in the study population (n=27). A significant relationship was found between lacunar infarct, chronic infarct, and ICAS. In a previous study investigating the relationship between cavernous carotid artery calcification and MCA infarct, no significant relationship was reported (35). Yilmaz et al. (36) found a significant relationship between ICAS and large vessel or cardioembolic cerebral infarct. In the study by Vinke et al. (30), a significant relationship was found between ICAS and lacunae. In these studies, the differences in both the ICAS grading systems and types of ischemic stroke (acute, chronic, TIA, etc.) included in the analyses explain the differences in the results. Additionally, a recently published study showed that intima-media localization of arterial calcification has different clinical consequences related to conditions such as collateralization and luminal stenosis (37).

### Study Limitations

There are certain limitations to the present study. First, measuring calcification manually can affect the objectivity of calcification grading. However, it was defined that there are some disadvantages to both manual and automatic measurement methods in the literature (38). Moreover, a study in the literature comparing semiautomatic and manual measurements reported a good level of concordance between the two methods (39).

Due to the retrospective design of the study, other atherosclerotic risk factors such as hypertension, diabetes, and smoking could not be included in the analyses. These risk factors may be associated with CSVD or ICAS, but the focus of our study was to demonstrate the relationship between ICAS and cerebral small vessel disease.

## Conclusions

The results of this study showed that ICAS is correlated with BGPVS, PVWMHI, GA, Koedam score, and chronic and lacunar infarcts. It was concluded that the relationship between ICAS and increased PVS at the basal ganglia and CSPVS levels was different. Similarly, the relationship between ICAS and PVWMHI was different from that of SCWMH. ICAS is a frequently encountered condition in daily practice, and the results of this study suggest that it may be associated with CSVD. Therefore, including ICAS severity in patient reports can guide CSVD risk management and treatment planning.

### Ethics

**Ethics Committee Approval:** This retrospective study was approved by the University of Health Science Turkey Ankara Kecioren Training and Research Hospital Institutional Review Board (date: 05.10.2018, approval number: 29).

**Informed Consent:** Informed consent was not obtained because the study was retrospective.

**Peer-review:** Externally peer-reviewed.

### Authorship Contributions

Concept: C.O., O.G., Design: C.O., Data Collection or Processing: C.O., O.G., Analysis or Interpretation: C.O., O.G., Literature Search: C.O., Writing: C.O.

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

**Financial Disclosure:** The authors declared that this study received no financial support.

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Original Article

DOI: 10.4274/haseki.galenos.2022.8272
Med Bull Haseki 2022;60:483-487

# Frequency of Prodromal Symptoms in Patients Suffering from Migraines with Aura

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## Abstract

**Aim:** Prodromal findings of migraine may be overlooked when patients are not questioned well. The International Classification of Headache Disorders classifies the prodromal phase as the symptomatic phase, which may last from 2 to 48 h and manifests before the onset of pain in migraine without aura and before the aura in migraine with aura. This study aimed to evaluate the frequency and duration of prodromal symptoms and their relationship with the presence of aura in migraine patients.

**Methods:** This observational study was designed as a survey where participants took an online questionnaire between July and November 2020. The questionnaire consisted of two parts; in the first part, the diagnostic criteria for migraine were questioned. After the participants completed the migraine diagnostic criteria, they moved on to the second part, in which headache characteristics, the presence and type of the aura, and prodromal symptoms were asked.

**Results:** This study included 521 participants with migraine according to the International Classification of Headache Disorders. Two hundred seventy-one participants responded that they had auras; 169 of these experienced visual auras. Considering the frequency of prodromes, the three most common symptoms in participants with migraine with or without aura were sensitivity to light, sensitivity to sound, and mood changes. When the two groups were compared, the percentages for the prodromal symptoms except for neck pain were found to be higher in patients with migraine with aura ($p<0.05$ for each).

**Conclusion:** Our study's findings suggest that migraine patients with or without aura do not recognize the symptoms in this phase well enough. Also, the most crucial finding was that prodromal symptoms were more common in migraine patients with aura. This could be evaluated as the patients with migraine aura might have interpreted prolonged prodromal symptoms as aura. To predict the onset of attacks in migraine patients and enhance their treatment compliance, knowing and recognizing prodromal symptoms is essential.

**Keywords:** Migraine, aura, prodromal symptoms, prodrome

## Introduction

Migraine is an episodic headache that is the second cause of disability and first among women under 50 years of age, according to the Global Burden of Disease study (1). Considering the ictal disability alone, it has been ranked as the seventh most disabling disease globally (2).

Migraine's clinical presentation changes with age, and it presents in shorter durations with specific paroxysmal symptoms such as abdominal pain, vomiting, or vertigo in childhood as opposed to an absence of autonomic symptoms in the elderly (3).

Attacks often begin with prodromal and/or aura symptoms originating from the hypothalamus, brainstem, or cortex (4). Even though the headache resolves within 4 to 72 h, prodromal signs may begin up to 48 h before the headache, and the postdromal signs may persist for another 48 h after the headache passes, meaning an attack may long outlast a headache. The third edition of the International Classification of Headache Disorders (ICHD-3) classifies the prodromal phase as the symptomatic phase, which may last from 2 to 48 hours and manifests before the onset of pain in migraine without aura and before the aura in migraine with aura. As for the prodromal

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**Received:** 03.08.2022 **Accepted:** 10.09.2022

symptoms, ICHD-3 classifies them as the individual or combination of symptoms of loss of appetite, difficulty in concentrating, neck stiffness, increased sensitivity to light or sound, nausea, blurred vision, yawning, and pallor, all of which appear during the prodromal phase (5). Both the words "premonitory symptoms" and "prodromal symptoms" are frequently used in the literature. It seems that there is no consensus on this issue. This survey aimed to evaluate the frequency and duration of prodromal symptoms and their relationship with the presence of aura in migraine patients.

## Materials and Methods

### Study Design

This observational study was designed as a survey where participants took an online questionnaire due to the pandemic conditions between July and November 2020. Patients between the ages of 18 and 65 who were diagnosed with migraine and followed up on at the Haydarpasa Numune, Umraniye, and Fatih Sultan Mehmet Training and Research Hospitals neurology outpatient headache polyclinics and agreed to participate in the questionnaire study were included in the study. Patients under the age of 18 and over the age of 65 who were diagnosed with non-migraine primary headache or secondary headache and who did not agree to participate in the survey study were excluded from the study.

The questionnaire consisted of two parts, the first of which had five questions inquiring if the participants had frequent headaches, whether these headaches lasted longer than 4 h, limited their physical or mental activities, and whether they were accompanied by nausea, photophobia, or phonophobia. Having completed the diagnostic criteria for migraine, which means participants answered "yes" to at least 4 of the first 5 questions, they proceeded to the second part of the questionnaire. The second part of the survey asked 10 questions about their headache characteristics, such as frequency, duration, and severity of attacks; usage of analgesics; the presence and type of the aura; and type and duration of prodromal symptoms. Consistency among responses was evaluated by 3 neurology specialists.

### Compliance with Ethical Standards

The Clinical Research Ethics Committee of the University of Health Sciences Turkey, Istanbul Haydarpasa Numune Training and Research Hospital approved the study (approval no: HNEAH-KAEK-2020/160, date: 27.07.2020). Informed consent was obtained from the patients.

### Statistical Analysis

SPSS 20.0 package program was used for the statistical analysis. A chi-square test was used for evaluating the significance of categorical data and comparing the inter-group percentages. The p-value for statistical significance was $p<0.05$.

## Results

This study included 1095 participants reporting headaches, and then proceeded with 521 who completed the diagnostic criteria for migraine according to questions in the first part of the survey. The mean age was 37.23±7.98 years and 91% of the 521 participants were women (Table 1).

The second part of the questionnaire investigated if they had ever been diagnosed with migraine. 444 of the participants stated that they had been diagnosed with migraine before, and the mean duration of diagnosis was 141 months. The remaining 77 participants reported no previous diagnosis of migraine. The presence and type of aura were evaluated (Table 1).

While 53 of the 250 participants with migraine without aura stated that they had no prodromes, this number was six times higher for the participants with migraine with aura, which was found to be statistically significant (p=0.0001). Considering the durations of prodromal symptoms, both groups had the highest activity in the 1 to 2-hour and >2 to 4-hour periods, and they had similar percentages. The ratio of prodromes persisting for more than 12 h was statistically significant in migraine with aura compared to migraine without aura (p=0.001) p (Figure 1).

Considering the frequency of prodromes, the most common symptom in participants with migraine with aura was sensitivity to light, followed by sensitivity to sound and mood changes, respectively, and the three most common symptoms in participants with migraine without aura were the same, with mood changes being the most common, followed by sensitivity to light and sensitivity to sound. When the two groups were compared, the percentages

**Table 1. Clinical features of patients with migraine**

| | Patients with migraine (n=521) |
|---|---|
| Sex<br>Female<br>Male | <br>476 (91%)<br>45 (9%) |
| Age (years) | 37.23±7.98 |
| Diagnosed with migraine before study<br>Yes<br>No | <br>444 (91%)<br>77 (9%) |
| Presence of aura<br>Yes<br>No | <br>271 (52%)<br>250 (48%) |
| Visual aura<br>Yes<br>No | <br>169 (62.3%)<br>102 (37.7%) |

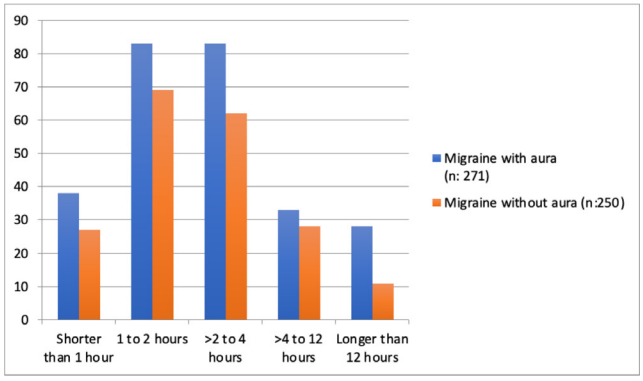


**Figure 1.** Distribution of the duration of prodromal symptoms among patients with migraine with and without aura

for the prodromal symptoms except for neck pain were found to be higher in patients with migraine with aura ($p<0.05$ for each) (Table 2).

## Discussion

The properties and durations of prodromal symptoms in patients who were divided into two groups, namely, migraine with aura and migraine without aura, were evaluated. The number of participants who reported a previous diagnosis of migraine was 444, and 271 of them reported auras. Considering the durations of prodromal symptoms in the migraine with the aura group, only the category with a duration of prodromal symptoms longer than 12 h had significantly higher values compared with the migraine without the aura group. The durations of prodromal symptoms were similar in both groups for the other durations. It was found that only the neck pain among the prodromal symptoms was more common in the migraine without the aura group, while all other symptoms were significantly more common in the migraine with the aura group. Considering the frequency of prodromal symptoms, the most common one was sensitivity to light, followed by sensitivity to sound and mood changes in the migraine with the aura group, whereas the most common symptom was mood changes followed by sensitivity to light and sensitivity to sound in the migraine without the aura group.

In migraine, the headache phase characterized by nausea, vomiting, photophobia, and phonophobia accompanying a moderate-to-severe headache is the best-known phase (6). The fatigue and concentration problems that may develop after the headache are considered the accompanying symptoms (7,8). The phenotype and prevalence of prodromal symptoms have recently been better understood (9,10). Among the typical prodromal symptoms are extreme tiredness, increased yawning, changes in taste, craving for certain foods, attention deficit, and mood changes. The literature has an insufficient number of prospective studies and is often based on retrospective studies. The prevalence of prodromal symptoms in migraine patients ranges from 30 to 90% (11,12). In this study, 88.7% of the patients were reported to have had at least one prodromal symptom, and this ratio was higher in the migraine with aura group compared to the migraine without aura group.

**Table 2. Distribution of the frequency of prodromal symptoms among patients with migraine with and without aura**

| Prodromal symptom | Migraine with aura (n=271) | | Migraine without aura (n=250) | | p-value |
|---|---|---|---|---|---|
| | Number | % | Number | % | |
| Loss of appetite | 39 | 14.7 | 16 | 8.1 | 0.004 |
| Nausea | 144 | 54.3 | 85 | 43.1 | 0.0001 |
| Sensitivity to light | 194 | 73.2 | 113 | 57.3 | 0.0001 |
| Difficulty in concentrating | 165 | 62.2 | 78 | 39.5 | 0.0001 |
| Anxiety | 142 | 53.5 | 85 | 43.1 | 0.0001 |
| Sleep disorder | 102 | 38.4 | 55 | 27.9 | 0.0001 |
| Yawning | 50 | 18.8 | 33 | 16.7 | 0.073 |
| Facial change | 56 | 21.1 | 12 | 6 | 0.0001 |
| Irritability | 119 | 44.9 | 61 | 30.9 | 0.0001 |
| Neck pain | 138 | 52 | 105 | 53.2 | 0.043 |
| Sensitivity to sound | 192 | 72.4 | 113 | 57.3 | 0.0001 |
| Mood changes | 189 | 71.3 | 126 | 63.9 | 0.0001 |
| Hyperactivity | 16 | 6 | 1 | 0.5 | 0.0003 |
| Osmophobia | 36 | 13.5 | 10 | 5 | 0.0002 |
| Craving for certain foods | 56 | 21.1 | 26 | 13.1 | 0.0016 |

*Chi-square test was used

The greatest clinical significance of prodromes is that they allow an early diagnosis and thus an efficient treatment of migraine (13). Prodromal symptoms may not be thought to be associated with migraine attacks, so patients should know them quite well. The study by Atalar et al. (14) showed that, migraine affects daily life and causes limitations in all headache phases; prodromal (34%), headache (62%), and postdrome (31%). Patients may mistake these symptoms for migraine triggers, just like in the case of the idea that eating chocolate triggers migraine attacks, while in fact it results from the craving for sweets developing as a prodromal symptom (12). In the study by Karsan et al. (15), it has been shown that situations such as light exposure, sound, or consumption of certain foods, which can be considered triggers by patients, may be associated with prodromal findings.

The durations of prodromal symptoms vary as well. In both groups, symptoms most frequently lasted for 1-2 h, followed by more than 2-4 h. The durations were similar between the migraine with aura and migraine without aura groups, with only the symptoms persisting longer than 12 h being more frequent in the aura group than in the migraine without the aura group (Figure 1). This could be evaluated as the patients with migraine aura might have interpreted prolonged prodromal symptoms as aura.

The most reported prodromal symptoms in the literature are fatigue, mood changes, and yawning (16). In a prospective study where the attacks were triggered with nitroglycerin, the most common complaint was photophobia, with mood changes being less common (17). Consistently with those findings, our study reported sensitivity to light and sensitivity to sound as the most common symptoms in the migraine with aura group. In the migraine without the aura group, the most common complaint was the mood changes (Table 2). The fact that 32.4% of our patients described visual aura suggested that some patients might have evaluated the prodromal symptoms of photic hypersensitivity as aura.

A study by Laurell et al. (16) included 2,223 migraine patients and found prodromal symptoms in 77% of them, with yawning being the most common one, followed by mood changes. It was the first time a study showed that the number and frequency of prodromal symptoms were higher in patients with migraine with aura than in patients with migraine without aura (16). Consistent with this study, our study found that the prodromal symptoms except for neck pain were more common in the migraine with the aura group than in the migraine without the aura group (Table 2). Neck pain is a common finding in patients with migraine (18), and no clear interpretation has been made as to why neck pain is more common in patients with migraine without aura. Similar to our study's findings, sensory hypersensitivity-induced phonophobia and photophobia were the most frequently co-occurring symptoms (16).

### Study Limitations

The most important limitation of this study is that it is a survey. As the patients were not examined by doctors, their migraine diagnoses could only be determined based solely on their responses to the questionnaire. The prevalence of migraine with aura was found to be higher than migraine without aura, suggesting that patients might have interpreted the prodromal symptoms as aura. It is assumed that the frequency of prodromal symptoms was found to be high because of memory illusions in patients. Electronic migraine diaries may ensure more reliable results (19).

The frequency and number of prodromal symptoms are higher in women. Furthermore, there is a positive correlation between the duration, number, and severity of migraine attacks and the number of early signs (16). Another important limitation is that this study does not evaluate the prevalence of prodromal symptoms according to sex and migraine attacks.

The strongest aspect of the study was the high number of patients. This allows for better identification of the type and frequency of prodromal symptoms. Additionally, the detailed evaluation of migraine patients with and without aura presents the most comprehensive approach in the literature in this regard.

## Conclusion

The most important finding of our study was that prodromal symptoms were more common in migraine patients with aura than in the migraine without aura group. The high frequency and duration of prodromal symptoms in our large patient group suggests that migraine patients with or without aura do not recognize the symptoms in this phase well enough. Prodromal symptoms, which reduce the quality of life and precede the migraine attacks, may contribute to an increased loss of workforce and limitations in daily life. Thus, knowing and recognizing prodromal symptoms better may act as an important factor in predicting the onset of attacks in patients and enhancing their treatment compliance and adherence. Comprehensive studies where patients are interviewed in person are important in that they can provide more precise information on this matter.

**Acknowledgment:** We thank Abdullah Karaakin from Beykent University for translating this study from Turkish into English.

### Ethics

**Ethics Committee Approval:** The Clinical Research Ethics Committee of the University of Health Sciences

Turkey, Istanbul Haydarpasa Numune Training and Research Hospital approved the study (approval no: HNEAH-KAEK-2020/160, date: 27.07.2020).

**Informed Consent:** Informed consent was obtained from the patients.

**Peer-review:** Externally peer-reviewed.

**Authorship Contributions**

Concept: B.R.H.B., Design: B.R.H.B., Data Collection or Processing: B.R.H.B., G.G., M.F.P., Analysis or Interpretation: B.R.H.B., G.G., M.F.P., Literature Search: B.R.H.B., G.G., M.F.P., Writing: B.R.H.B., G.G.

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

**Financial Disclosure:** The authors declared that this study received no financial support.

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Original Article

DOI: 10.4274/haseki.galenos.2022.8177
Med Bull Haseki 2022;60:488-493

# Association Between Thyroid Antibodies and Ultrasonic Imaging in Patients with Hashimoto's Thyroiditis

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## Abstract

**Aim:** The association between high levels of anti-thyroid antibodies and the extent of destruction of thyroid tissue is well documented. The aim of the present study was to analyze the relationship between anti-thyroid antibodies, thyroid hormones, and sonographic parenchymal changes.

**Methods:** The study was designed as a case-control study. Four hundred and seventy-five patients with HT and 98 healthy subjects were included in the study. Serum levels of free thyroxine (fT4), free triiodothyronine (fT3), thyroid-stimulating hormone, and anti-thyroid antibodies (anti-thyroid peroxidase antibodies and anti-thyroglobulin antibodies) were measured. The ultrasonographic results of the patients were also recorded.

**Results:** Serum levels of anti-TPO and anti-Tg were significantly associated with hypoechogenicity, heterogeneity, and pseudonodulation ($p<0.001$). There was no significant difference between the two groups in terms of cyst and nodule formation, however, a significant difference was found in terms of thyroid volume ($p<0.001$). Thyroid volumes were higher in the HT group. As serum anti-TPO levels increased in the HT group, parenchymal hypoechogenicity increased ($p<0.001$).

**Conclusion:** Ultrasonography is a non-invasive method that provides information about the inflammatory activity of the thyroid gland. Significantly reduced echogenicity, heterogeneity, and multifocal pseudonodular infiltration were indicators of inflammatory activity and were associated with higher anti-TPO levels. Anti-TPO and ultrasonographical changes may be useful in the follow-up of Hashimoto's thyroiditis.

**Keywords:** Hashimoto thyroiditis, ultrasonic diagnosis, autoantibodies

## Introduction

Hashimoto's thyroiditis (HT) is an organ- specific autoimmune disease that occurs due to immune defects caused by genetic predisposition and environmental factors. The disease is characterized by lymphocytic infiltration that causes progressive loss of thyroid function (1-3). The reported overall incidence is more than 2% in the general population and is 10 times more common in women than in men (4). The diagnosis of HT is based on clinical evaluation, laboratory results and ultrasound findings. Anti-thyroid antibodies (TPO-Ab, Tg-Ab) are widely used in the diagnosis of autoimmune thyroid diseases and are closely associated with lymphocytic infiltration and thyroiditis. Anti-thyroid antibody positivity

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**Received:** 09.02.2022 **Accepted:** 30.10.2022

is found in 83.3% of clinically hypothyroid patients (5). However, this positivity is also found in10-13% of the normal population without thyroid disease (6,7). Anti-TPO reflects current activity, stage of lymphocyte infiltration and thyroid destruction via T-cell mediated cytotoxicity (8).

Ultrasonography (US), which has been used clinically in the diagnosis and follow-up of HT since the 1990s, provides valuable information about the size and structure of the thyroid gland as well as the ability to detect possible thyroid nodules (9).

Classic US findings in HT are reduced echogenity, heterogeneous parenchyma, increased volume, hypervascularity, and micronodulations that may reflect the lymphocyte infiltration (10-12). While micronodulation was reported in 43% of patients, nodules were detected in 10% of patients with HT (13).

HT is a chronic, high-incidence autoimmune thyroid disorder that is a common cause of hypothyroidism. It is mainly manifested by positive thyroid-specific antibodies in the peripheral blood with thyroid lymphocytic infiltration and fibrosis. The best imaging modality for diagnosing thyroid diseases is US, which provides the exact dimensions of the thyroid goiters (14). Ultrasound echo intensity reflects the internal pathological basis of HT. Lymphocyte and plasma cell infiltration, for example, reduces echo intensity, whereas fibrosis causes heterogeneous echo intensity. Therefore, ultrasound has become the most important imaging method for evaluating and monitoring HT (15).

In this study, we evaluated the relationship between US findings and antibodies in patients with HT.

## Materials and Methods

### Compliance with Ethical Standards

Ethics committee approval was received for this study from the ethics committee of Ankara Numune Training and Research Hospital (approval number: 865, date: 21.07.2014).

### Study Population

This retrospective study included 475 patients (group 1) previously diagnosed with HT (clinical signs and symptoms for thyroid disease, elevated thyroid antibodies, and US findings were used for diagnosis) and 98 control subjects (group 2) (subjects with no signs or symptoms and/or history of thyroid disease) who were admitted to the endocrinology clinic (Table 1). The demographic, laboratory, and ultrasonographic characteristics of the cases and controls who applied to the endocrinology outpatient clinic were recorded from the clinical database. HT patients were divided into two groups, hypothyroid and euthyroid, according to their thyroid functions.

The exclusion criteria were as follows: age <18 and >65 years; pregnancy, postpartum, or lactating periods; smoking; hormone replacement therapy, or medication that may affect thyroid hormone levels (such as amiodorane, interferone, litium, gonodotropine releasing hormone analogs, rifampicine, and anticonvulsants).

### Laboratory

Thyrotropin, free T4, and free T3 levels were determined using chemiluminescence methods with the Access Hypersensitivite human TSH, Access FT3 kit, and Access FT4 kit. The normal range of TSH was 0.34-4.25 μIU/mL, FT4 level was 0.61-1.2 pg/mL, and the FT3 level was 2.5-3.9 pg/mL.

Anti-TPO and anti-TG were measured using an Elecsys Anti-TG (Roche Diagnostics, Germany) kit and an electrochemiluminescence (ECLIA) kit. The normal range of the anti-TPO level was 0-34 IU/mL, and the anti-Tg level was 0–40 IU/mL. The intra- and inter-assay coefficients of variation were all <5%.

### Thyroid Ultrasonography

Thyroid US was performed in an out-patient clinic by the same experienced endocrinologist using a high-resolution ultrasound machine with a 13 megahertz high-frequency linear transducer (Hitachi EUB 7000 HV, Japan) while the patients lay supine with slightly hyperextended necks. Right and left thyroid lobes were visualized in longitudinal and transverse planes. Anteroposterior, transverse, and longitudinal measurements of both thyroid lobes were evaluated. Thyroid volume was calculated using a previously reported formula (13):

Thyroid volumes (mL) = Length (cm)x width (cm)x Depth (cm) x π /6

Besides volume, all US findings (echogenity, parenchymal structure, presence of pseudonodulation, nodules, or cysts) were recorded in detail.

### Statistical Analysis

Statistical analyses were performed using SPSS 19.0 software (SPSS Inc., Chicago, IL, USA). The distribution of data was determined by the Shapiro-Wilk test. Continuous variables were expressed as mean±standard deviation and categorical variables as frequency and percentage. Continuous variables were compared with the Mann-Whitney U test, and categorical variables were compared using Pearson's chi-square test or the Fisher's exact test. The linear relationship between two continuous variables was evaluated by Spearman correlation analysis. A p-value less than 0.05 was considered statistically significant for all tests.

## Results

Sonography revealed an increase in heterogeneity, a decrease in echogenicity, and an increase in

| Table 1. Compassion of two groups for demographic, laboratory and ultrasound features | | | |
|---|---|---|---|
| **Variable** | **Group 1 (n=475)** | **Group 2 (n=98) (control)** | **p-value** |
| Age (year) | 44.12±12.80 (26-77) | 42.03±12.21 (19-67) | 0.056 |
| Gender (F/M) (%) | 420 (88.4%)/55 (11.6%) | 92 (93.9%)/6 (6.1%) | 0.157 |
| FT3 | 2.92±0.52 (0.28-4.86) | 2.98±0.40 (2.26-3.84) | 0.315 |
| FT4 | 0.84±0.23 (0.15-1.92) | 0.85±0.31 (0.29-3.37) | 0892 |
| TSH | 10.45±15.46 (0.42-100) | 7.31± 9.73 (0.86-100) | 0.914 |
| Anti-TPO | 385.65±346.21 (45-1149) | 2.73±4.67 (0.10-38.4) | **<0.001** |
| Anti-Tg | 278.59±649.98 (0.0-4000) | 1.49±1.05 (0.10-6.3) | **<0.001** |
| Thyroid volume ($mm^3$) | 50.93±33.34 (20-202) | 34.12±24.13 (21-159) | **<0.001** |
| Echogenity (n, %)<br>Isoechoic<br>Mild hypoechoic<br>Overt hypoechoic | <br>84 (17.7%)<br>182 (38.3%)<br>209 (44%) | <br>56 (57.1%)<br>31 (31.6)<br>11 (11.2%) | **<0.001** |
| Texture (n, %)<br>Homogen<br>Heterogen | <br>94 (19.8%)<br>381 (80.2) | <br>72 (73.5%)<br>26 (26.5%) | **<0.001** |
| Pseudonodulation<br>Absent<br>Present | <br>117 (24.6%)<br>358 (75.4%) | <br>91 (92.9%)<br>7 (7.1%) | **<0.001** |
| Nodule (n, %)<br>Absent<br>Present | <br>319 (67.2%)<br>156 (32.8%) | <br>65 (66.3%)<br>33 (33.7) | **0.871** |

FT3: Free triiodothyronine, FT4: Tetraiodothyronine, also called free thyroxine, TSH: Thyroid stimulating hormone, Anti-TPO: Anti-thyroid peroxidase antibody, Anti-Tg: Antithyroglobulin antibody, F/M: Female/male

pseudonodulation (micronodulation) in group 1 (p<0.001). Pseudonodulation was found in 75% of group 1 and in only 7% of the control group. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of echogenicity were 82.3%, 57.1%, 90.3%, and 40%, respectively, for TPO-positive HT patients. The sensitivity, specificity, PPV, and NPV of heterogenicity were 81.3%; 73.4 , 93.6%, and 43.3% for TPO-positive HT patients, respectively. The sensitivity, specificity, PPV, and NPV of pseudonodulation were 24.7%; 92.8; 94.4%; and 20.2% for TPO-positive HT patients, respectively. The sensitivity, specificity, PPV, and NPV of thyroid volume (>25 mL) were 82.9%; 34.6%; 86%; 29.5% for TPO-positive HT patients, respectively.

Increased antibody levels were negatively correlated with the echogenicity of the thyroid gland, but there was no difference between the two groups according to the presence of nodules. Nodule frequency was found in 32.8% of HT patients and 33.7% of controls (p=0.871). In patients with positive antibodies, anti-TPO was positively correlated with both TSH and thyroid volumes (p<0.001). There was a positive correlation between anti-Tg and TSH levels (p<0.001), but not with thyroid volume (p=0.341) (Table 2).

Group 1 was divided into two categories according to thyroid status: euthyroid and hypothyroid. The hypothyroid group had higher thyroid antibodies and more heterogeneous and hypoechoic thyroid parenchyma compared to the euthyroid group. However, no significant difference was found between the two groups in terms of thyroid volume or the presence of pseudonodulation (Figure 1).

## Discussion

In this study, we documented a higher incidence of decreased echogenicity, increased heterogeneity, increased thyroid volume, and pseudodulation in the HT group compared to healthy individuals (p<0.001), and there was no difference in terms of the presence of nodules and cysts between the two groups. Both anti-tpo and anti-Tg levels were found to be positively correlated with TSH; however, only the anti-level was correlated with thyroid volume.

The most accurate method for the diagnosis of HT is histological diagnosis, but this method is rarely used because of its invasive nature. Physical examination, laboratory testing, and US examination are used to

| Table 2. Relationship between TSH levels and thyroid antibodies of thyroid volumes | | | | |
|---|---|---|---|---|
| | **TSH** | | **Thyroid volume** | |
| | r | p | r | p |
| Anti-TPO | 0.235 | <0.001 | 0.272 | <0.001 |
| Anti-Tg | 0.231 | <0.001 | 0.047 | 0.341 |

TSH: Thyroid stimulating hormone, Anti-TPO: Anti-thyroid peroxidase antibody, Anti-Tg: Antithyroglobulin antibody

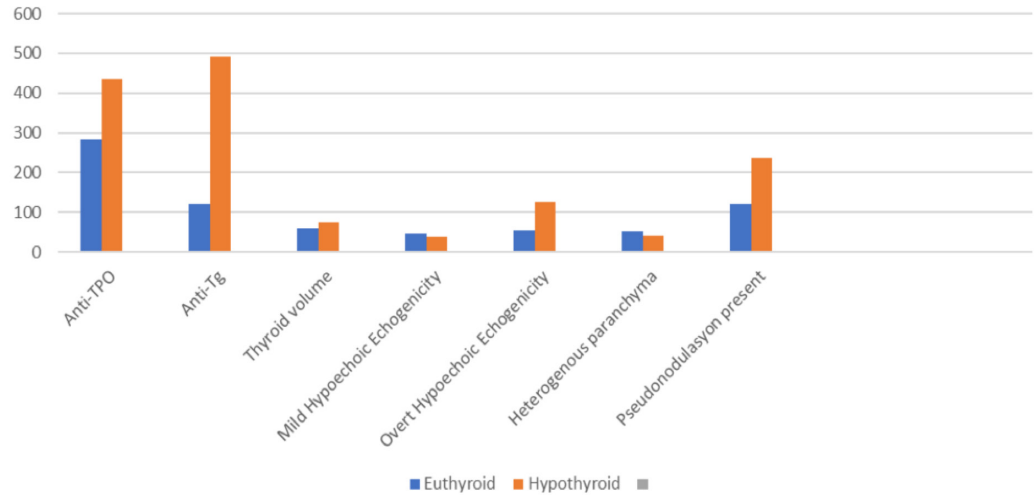


**Figure 1.** Comparison of thyroid antibodies and USG feature between patients with euthyroid and hypothyroid patients

*Anti-TPO: Anti-thyroid peroxidase antibody, Anti-Tg: Antithyroglobulin antibody, USG: Ultrasonography*

diagnose and monitor HT patients. The ease of use and non-invasiveness make the US a key procedure in the diagnosis and follow-up of HT (10).

If the diagnosis of HT was based only on physical examination and laboratory results, at least half of the patients with HT would be overlooked. The clinical and laboratory features of HT may vary. Sometimes HT can be totally asymptomatic (16). The US may be a very practical diagnostic tool for thyroid disease (17). Previous studies have shown that 13% of HT may have normal thyroid antibodies. Moreover, thyroid antibodies may be found in 10% of people who have no thyroid disease (6,7,9). US can provide additional information in the gray zone of HT. The use of US with clinical and laboratory findings significantly increases the sensitivity and specificity of an accurate diagnosis because of its easy accessibility and non-invasive nature (7,9,16).

High-resolution US is a quick, reliable, inexpensive, and highly sensitive tool for both diagnosis and guidance in the therapeutic intervention of thyroid disease and nodules (18,19). During the course of HT, US findings vary significantly, which defines the stage of histopathological progress. Moreover, Marcocci et al. (20) reported that the US is more predictive in detecting patients who are prone to hypothyroidism and reflects different stages of HT.

The normal thyroid parenchyma has a unique hyperechogenic and homogenous structure due to its follicular structure and colloid. However; in HT patients, thyroid parenchyma echogenicity is reduced because of the disruption of normal tissue and lymphocyte infiltration (21).

The PPV of reduced echogenicity for HT was 88.3%, and the NPV was found to be 93% (2,5). In accordance with previous studies, we found PPV as 30.3%. However, NPV was found to be lower than literature with 40%. Willms et al. (10) reported isoechogenicity in 21.5%, mild hypoechogenicity in 32.7% and overt hypoechogenicity in 45.7% of patients with HT. In accordance with their results, isoechogenity, mild hypoechogenity, and overt hypoechogenicity were found in 17.7, 38.3%, and 44% in our series, respectively. Autoimmune diseases exclude 95% with an isoechoic pattern in the US (22).

In a recent study, thyroid volume was higher in patients with thyroid antibodies than in patients without thyroid antibodies. But thyroid volume did not differ between the hypothyroid group and controls (3). Similarly, we found that thyroid volume was higher in HT than controls. However, there was no difference in the thyroid volume between the euthyroid and hypothyroid groups. We also found that thyroid volume was correlated with anti-TPO. Similar to our results, Anderson et al. reported that elevation of TSH and thyroid volume was correlated with thyroid antibodies (23). In contrast to our results, Willms et al. (10) did not find any correlation between thyroid volumes and thyroid antibodies.

The presence of multiple discrete hypoechoic micronodules (1-6 mm in size) is strongly suggestive of chronic thyroiditis. Thin echogenic fibrous septae may produce a pseudolobulated appearance in the parenchyma. Micronodulation was more common in the group with thyroid antibodies than in the controls (10,11). Similar to previous studies, we found pseudonodulation was more common in HT patients than in controls. The micronodular pattern has been found to have a 95% predictive value for the diagnosis of HT (23,24). Alidrisi et al. (25) found that hypoechogenicity and pseudonodulation were significantly

associated with high anti-TPO for diagnostic. Another study suggested that pseudonodulation and hypoechogenity reflect high inflammatory activity (26). Acar et al. (11) reported that micronodulation was not observed in control; 43% in euthyroid HT and 26% in hypothyroid HT. Like their results; in our study, micronodulation was found to be higher in HT patients than in controls. We did not observe any differences between euthyroid and hypothyroid patients.

This study demonstrated that thyroid antibodies in the parenchymal heterogeneous group were higher than those in the homogeneous group ($p<0.001$). These findings were consistent with the literature (10,27,28). Willms et al. (10) reported that nodules were found 21.9% in HT patients. In our study, nodules were found in 32.8% of HT patients; there were no significant differences between the two groups in terms of the presence of nodules. Conversely, Anderson reported that nodules were found in 4% of HT (23).

### Study Limitations

An important limitation of our study is that no fine needle aspiration biopsy was performed, which is the gold standard examination for diagnosing HT. However, ultrasound evaluation using the same endocrinology specialist and the inclusion of 475 patients in the study are the study strengths.

## Conclusion

US is a simple, non-invasive, and useful method. The USG provides helpful information about the HT stage. Heterogeneous thyroid parenchyme, hypoechogenicity, and pseudonodulation predict the diagnosis and follow-up of HT and are risk factors for elevated concentrations of thyroid antibodies. Also, it is an ideal tool to detect complications such as malignant nodules.

### Ethics

**Ethics Committee Approval:** Ethics committee approval was received for this study from the Ethics Committee of Ankara Numune Training and Research Hospital (approval number: 865, date: 21.07.2014).

**Informed Consent:** Retrospective study.

**Peer-review:** Internally peer-reviewed.

### Authorship Contributions

Concept: I.D.D., Design: M.U., Data Collection or Processing: E.K., Analysis or Interpretation: M.N.B., Literature Search: S.G., Writing: M.U.

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

**Financial Disclosure:** The authors declared that this study received no financial support.

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Case Report

DOI: 10.4274/haseki.galenos.2022.8612
Med Bull Haseki 2022;60:494-497

# Diffuse Miliaria Cristalina due to Severe Hypernatremic Dehydration: A Neonatal Case Report with a Current Literature Review

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## Abstract

Miliaria is a common, transient cutaneous disease caused by obstruction of the eccrine sweat duct. A female patient who was admitted with the complaint of decreased sucking on the postnatal 15th day learned that after the postnatal 10th day, the sucking reflex decreased, the amount of urine decreased, and the number of stools per day decreased. We observed that the patient's general condition was poor and that his weight loss was 31%. Fluid therapy was adjusted for the patient, whose serum sodium level was 192 mEq/L. On the 5th day, while the serum sodium level was 156 mEq/L and the body temperature was within normal limits, vesicles and bullae were detected in the body, especially in the trunk, and relatively few in the extremities. Although miliaria crystallina is a common skin problem in newborns, our case is the second documented case of miliaria crystallina due to hypernatremia in the literature. Physicians; It should be kept in mind that miliaria crystallina may be seen in the newborn during the treatment of severe hypernatremic dehydration.

**Keywords:** Miliaria cristalina, severe dehydration, neonatal

## Introduction

Miliaria is a common, transient cutaneous disease caused by obstruction of the eccrine sweat duct. There are three main types of miliaria: miliaria crystallina, miliaria rubra, and miliaria profunda, which are distinguished by their clinical appearance and histological findings. Miliaria rubra is the most common type, observed in 4% of newborns (1). Miliaria crystallina, also known as Sudamina, is very common in newborns; it peaks at approximately one week of age, and its frequency has been reported to be between 4.5 and 9% (2).

The reason for this is that bacteria such as *Staphylococcus epidermidis* form cutaneous residues or biofilm formation (3). This blockage causes sweat to leak into the epidermis or dermis, resulting in cellular overhydration, swelling, and further blockage of the ducts. The reason for the frequent occurrence of miliaria crystallina in newborns is the underdevelopment of the eccrine sweat duct. It is usually seen as 1-2 mm superficial vesicles in newborns younger than 2 weeks of age (4).

Here, a newborn case who was treated for severe hypernatremic dehydration and who developed widespread and extensive miliaria crystallina during treatment is presented.

## Case Report

From the history of the girl who was brought in with the complaint of decreased sucking on the postnatal 15th day, it was determined that the 1st and 5th minute APGAR 8/9 of the patient, who was born by cesarean section at 39 weeks and 3200 g from a 30-year-old mother. It was learned that the sucking reflex of the patient decreased after the postnatal 10th day, and there was a decrease in the amount of urine and the number of daily stools. The patient was admitted to the neonatal intensive care unit (NICU) with the diagnosis of severe dehydration.

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**Received:** 15.07.2022 **Accepted:** 13.11.2022

On arrival, the general condition was poor during the physical examination: body weight of 2200 grams, body temperature of 38 °C, respiratory rate of 56 beats per minute, heart rate of 145 beats per minute, saturation of 98%, arterial blood pressure of 100/71 (mean: 82 mmHg), and weight loss observed in 31% of the patient. The patient had severely decreased skin turgor, dry skin, was conscious and hyperalert, had increased muscle tone, threw his head back, and had strabismus. Peripheral vascular access was established for the patient. Due to the lack of urine output, a saline loading of 10 cc/kg was used once more. The blood gas pH was 7.32, the $pO_2$ was 35, the $pCO_2$ was 31.5, the BE was 8.4 and the HCO3 was 16.1. C-reactive protein: 0.27 mg/L, phosphorous: 5.13 mg/dL, creatinine: 1.42 mg/dL, blood urea nitrogen (BUN): 124.39 mg/dL, sodium: 192 mEq/L, potassium: 4.82 mEq/L, chlorine: 150.9 mEq/L, calcium: 11 mg/dL, hematocrit: 52.7%, platelet count: 179.00/$mm^3$, leukocyte count: 10.530/$mm^3$. The patient's fluid was given at a rate of 180 cc/kg/day (130 cc/kg maintenance, 150 cc/kg deficit, divided by 3). In the control blood tests taken at the second hour of the fluid treatment, BUN was 104.67 mg/dL, creatinine was 0.99 mg/dL, sodium was 192 mEq/L, and potassium was 4.8 mEq/L. On the 4th day, the sodium value of the patient was 156 mEq/L, and the sodium decrease in 72 hours was 36 mEq/L (12 mEq/day), and the fluid was continued in the same way. On the 5th day, while the serum sodium level was 156 mEq/L and the body temperature was within normal limits, vesicles and bullae were detected in the body, especially in the trunk, and relatively few in the extremities (Figure 1).

The patient's viral serology and varicella immunoglobulins were negative. A moisturizing cream was recommended to a patient who was evaluated by a pediatric dermatologist. On the 6th day, the bullae began to erode (Figure 2).

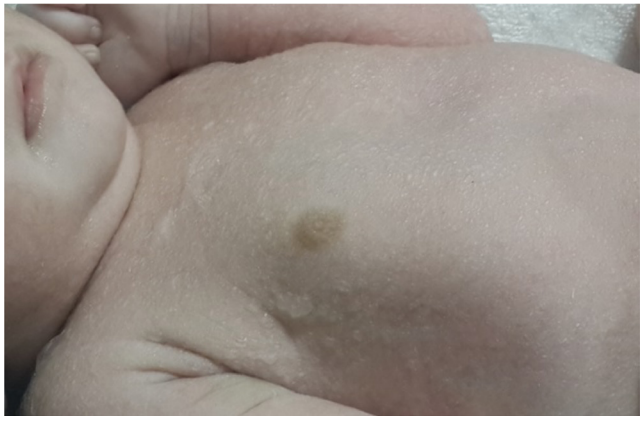

**Figure 1.** Diffuse vesicles and bullae on the trunk and upper extremities on the 5th day of hospitalization

On the 7th day, the patient's sodium levels returned to normal, kidney functions and urine output were good, the patient's fluid was stopped, and full oral nutrition was started. A daily bath was taken for the skin lesions, then she was laid on a sterile cover, and the whole body was treated with a moisturizing cream containing avocado perseose. In the follow-ups, the skin lesions completely resolved (Figure 3).

On the 12th day of his hospitalization, the patient, whose body weight was 3330 grams, was fed orally by his mother, and weight gain was regular. The patient was discharged with no further recommendations.

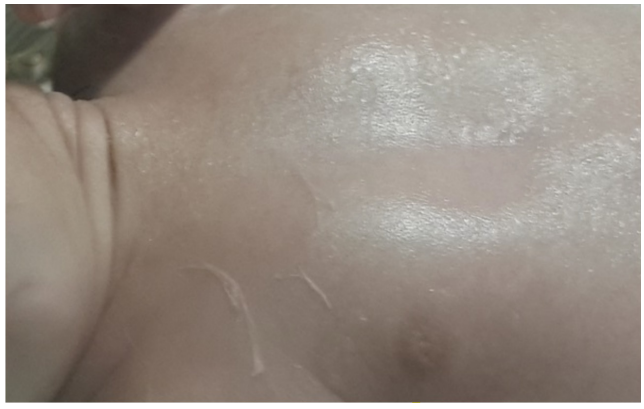

**Figure 2.** Eroded vesicles and bullae in the trunk area on the 6th day of hospitalization

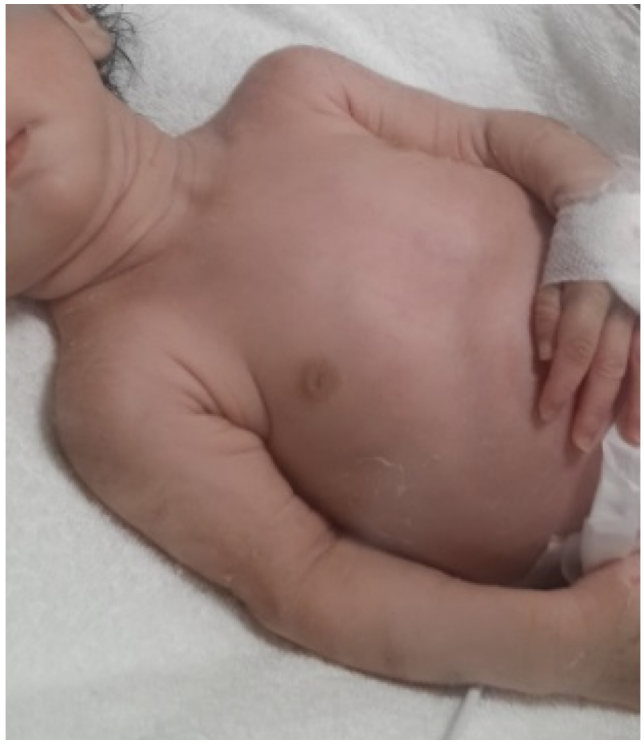

**Figure 3.** The patient is healed of all lesions

## Discussion

Anything that causes sweating can cause miliaria crystallina in infants, children, and adults. The common causes are hot and humid environments, strenuous physical activity, febrile illness, occlusion of the skin by non-porous clothing or bandage dressings, and transdermal drugs (5).

Miliaria crystallina is widely considered in the differential diagnosis of bullous diseases in newborns. Miliaria is caused by sweat retention in clogged eccrine ducts because of keratin plugs. Retrograde pressure causes the duct to rupture and leak sweat into the epidermis and/or dermis. In Miliaria crystallina, the occlusion of the eccrine duct is very superficial, i.e., in the stratum corneum, and may contain neutrophils (6). The upper body, neck, and head are the most commonly affected areas. The rash usually appears a few days after exposure to risk factors and resolves within a day after the superficial layer of skin is removed (7).

The differential diagnosis of miliaria crystalina includes herpes simplex, chickenpox, erythema toxicum neonatorum, staphylococcal scalded syndrome, neonatal pustular melanosis, and neonatal acropustulosis. In Miliaria crystallina, the vesicle content is as clear as water. Therefore, the color and shape of the blisters allow for a definitive clinical diagnosis (7). In this study, the location of the lesions and content of the lesions clinically suggested miliaria crystallina. However, its difference from the classical miliaria crystallina is that it is more common and takes the form of rather large bullae.

Miliaria crystalina is quite common in newborns and children. Studies report an incidence of 1.3% in newborns who develop skin lesions within the first 48 hours of life. In a retrospective study involving 5387 infants in Japan, it was reported that miliaria crystallina peaked on the postnatal 6$^{th}$ and 7$^{th}$ days, and its frequency was 4.5% (8). Although it usually does not occur at birth and the main cause is canal disruption, a few congenital miliaria crystalina cases have been reported (7).

Skin lesions, mostly in the form of vesicles in the miliaria crystallina, were observed as bullous lesions in this study. It has been reported that disorders associated with increased salt in sweat may cause miliaria crystallina. To the best of our knowledge, there are two cases of hypernatremia in the literature. Chao (9) reported miliaria crystallina in a hypernatremic adult patient without fever, and they suggested that this situation may have arisen because of direct drying of the corneocytes with excessive sodium. Engür et al. (10) detected diffuse miliaria crystalline a few days after admission to the NICU in a 16-day-old term newborn with a serum sodium level of 186 mEq/L who was followed up for hypernatremic dehydration, and they suggested that this is related to high serum sodium levels in sweat (11). In this study, as in the cases of Engür et al. (10), there was no history of fever, thick clothing, or any previous medication. In this study, while there were no skin findings on admission to the NICU, lesions began to appear on the 5$^{th}$ day of fluid therapy, which is the process in which the serum sodium level is in the decline phase. The increase in the amount of sodium excreted in sweat while serum sodium decreased may have caused diffuse miliaria crystallina in this study.

The general approach to treating miliaria is to reduce sweating and eccrine duct obstruction. Miliaria crystallina is usually untreated as it is self-limited and usually resolves within 24 hours (6). In this study, a daily bath was taken for the skin lesions, then he was laid on a sterile cover, and the whole body was treated with a moisturizing cream containing avocado perseose. In the follow-ups, the skin lesions resolved completely.

In conclusion, although miliaria crystallina is a common skin problem in newborns, our case is the second documented case of miliaria crystallina due to hypernatremia in the literature. It should be kept in mind that miliaria crystallina may be observed during severe hypernatremic dehydration treatment.

### Ethics

**Informed Consent:** Consent information was obtained from the patient's family.

**Peer-review:** Externally and internally peer-reviewed.

**Authorship Contributions**

Concept: B.A., Data Collection or Processing: B.A., E.B., Analysis or Interpretation: E.B., Funding Acquisition: B.A., Methodology: B.A., E.B., Project Administration: B.A., Visualization: B.A., E.B., Writing - Review & Editing: E.B., B.A.

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

**Financial Disclosure:** The authors declared that this study received no financial support.

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