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Editor(s) as Author: Huizing EH, de Groot JAM, editors. Functional reconstructive nasal surgery. Stuttgart-New York: Thieme; 2003.

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Effectiveness of Low-Level Laser Therapy in Chronic Plantar Fasciitis Conservative Treatment

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ABSTRACT

Introduction: This study aimed to evaluate the effectiveness of low-level laser treatment (LLLT) for treating chronic plantar fasciitis (PF).

Methods: The records of 60 patients with PF were retrospectively examined in this research. Thirty patients who have been applied LLLT and given exercise program constituted a treatment group. On the other side, 30 patients who have been given exercises but not applied LLLT was selected as a control group. Along with exercise, the treatment group underwent a 10-day continuous, 12-minute, 1.6 W, 808 nm wavelength diode laser treatment using galium-aluminum-arsenide. The American Orthopaedic Foot and Ankle Society (AOFAS) ankle-hindfoot scale and the Foot Function Index (FFI) were used to assess the patients' foot discomfort and functional condition while they were at rest, taking their first steps, and during activities. These assessments were all documented before, after, and after two months of treatment.

Results: In the treatment group, all VAS, FFI, and AOFAS scores except alignment score has been significantly improved both in the first and the second months compared to the initial state ($p<0.05$). The improvement in these scores was higher in the treatment group than in the control group in the first and the second months both ($p<0.05$).

Conclusion: These findings confirm that LLLT is an effective and reliable therapy choice in the conservative management of PF.

Keywords: Exercise, low-level laser therapy, pain, plantar fasciitis

Introduction

Adults who experience heel pain most frequently have plantar fasciitis (PF) (1). The degenerative condition known as PF is brought on by repeated stress to the area where the plantar fascia connects to the calcaneus (2). The etiology of PF is multifactorial; advanced age, pes planus, increased pronation, obesity, improper preference of shoe model, and decreased ankle dorsiflexion are the most common causes and result in biomechanical overload (3).

Clinical diagnosis is made substantially by anamnesis and physical examination. The typical clinical symptom is deep pain at the heel that begins after inactivity, notably with the initial steps in the morning, eases with activity, gradually worsens in response with weight-bearing toward the end of the day. The painful point with palpation is usually next to the anteromedial protrusion of the calcaneal tuberosity (4).

PF is usually a self-limiting clinical condition. Most of the patients recover conservative treatments.

Rest, adjusting activity levels, stretching exercises, resting splints, insoles, oral and topical medications, local injections, and physical therapy modalities are some of the conservative treatment choices (4-7).

Nowadays, a treatment procedure called low-level laser therapy (LLLT) is employed extensively, and new evidence has begun to emerge with the standardization of dosage recommendations according to diseases. Nowadays, LLLT is used for reducing pain and inflammation, wound healing, and increasing the speed of healing in musculoskeletal injury (8-15).

There are very few researches in the literature that examine how well LLLT works to cure PF (16). Evidence for LLLT's effectiveness in improving functional capacities in PF is still controversial. The fact that the studies were conducted with different laser devices and different treatment protocols affect these results. In this context, we need new studies that investigate different treatment protocols and dosages for finding the optimum LLLT method for PF therapy (16,17).

This study aimed to assess the effectiveness of LLLT in the management of chronic PF. Our LLLT treatment protocol in this study was distinct from previous suggested protocols that were applied in the literature. Cause no study had proved the best method for PF. For this reason, we gained to observe different kinds of treatment protocols's effects. Moreover, in our study, we use different scales that evaluate functional abilities and gait functions.

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Methods

In this retrospective investigation, the records of 60 individuals who were clinically diagnosed with PF and have been treated between May 2016 and October 2016 were included in the study. The files were retrospectively reviewed. 30 patients who have been applied LLLT and given exercise program constituted a treatment group. On the other side, 30 patients who have been given just exercises without any other therapy were selected as a control group.

The presence of chronic plantar heel pain symptoms that had persisted for at least three months and were resistant to first-step conservative treatment was the requirement for inclusion. By detecting discomfort to palpation and local pressure at the plantar fascia's origin on the medial tubercle of the calcaneus during the physical examination, the diagnosis was clinically verified. The participants who ranged in age from 18 to 75, were admitted if they had not use any anti-inflammatory medications throughout their treatment. The exclusion criteria included a history of trauma, surgery, skin lesions, malignancy, steroid injections within the preceding three months, radiculopathy, arthropathy, and pregnancy.

The University of Health Sciences Turkey, İstanbul Training and Research Hospital Ethics Committee gave its approval to the study (approval number: 2016/902). Each participant gave written consent. The research was based on a PhD thesis.

Interventions

Age, weight, height, body mass index (BMI), and daily standing time were among the demographic details of the patients that were recorded. The treatment group had 10 days continuous, once daily 12-minute LED galium-aluminium-arsenide (Ga-Al-As) 1.6 W, 808 nm wavelength diode laser treatment in addition to exercise treatment whereas control group had only exercise treatment. The plantar fascia's sensitive spots received LLLT treatment (four points), for a total dose of 4 J/cm^2 for 30 s each point periodically, with a total duration of 12 min. Figure 1 shows the locations of the LLLT applications.

The exercise regimen comprised achille tendon, gastrocnemius, plantar fascia stretching exercises, roll ball or roller exercise, toe-tap, and intrinsic muscle strengthening exercises (18,19). Achilles tendon stretching exercise is performed in a long sitting position by bringing the foot dorsiflexed and waiting for 10 seconds in this situation (20-22). Stretching the gastrocnemius muscle is done by leaning forward against the wall, keeping the legs straight, lowering the heels, and standing on the foot tip on the step (23,24). The affected side is positioned on the opposing leg in a sitting position while performing the plantar fascia stretching exercise. The foot is brought to dorsiflexion and toes to extension and held in this position for 10 seconds (25). For the rolling exercise, a cylindrical object is moved back and forth under the foot for 10 min (20). Towel curls, towel pickup, and toe-tap exercises were instructed to both groups to strengthen the intrinsic muscles of the foot. In the toe-tap exercise, all fingers are in the air while the heel is kept on the ground, and the big toe is repeatedly tapped on the ground and then the other four fingers are struck on the ground while the thumb is in the air (20,23,26). The participants were told that the exercises should be done ten times each, three times per day, for two weeks.

Outcome Measures

The patients' rest, the first step and activity pain levels were evaluated using a visual analogue scale (VAS), foot pain and functioning state was evaluated by the Foot Function Index (FFI) and American Orthopaedic Foot and Ankle Society (AOFAS) ankle-hindfoot scale. These assessments were all documented before, after, and after two months of treatment.

The level of subjective pain perception was assessed using VAS. Morning VAS, resting, and activity VAS were recorded separately. The patient selects a number describing his or her suffering levels between 0-10 (0: no pain, 10: the most severe pain). This number represents the intensity of the pain.

Functional ability was measured by AOFAS and FFI. AOFAS is a standardized evaluation of the clinical status of the ankle-hindfoot. It incorporates both subjective and objective information. Patients report their pain, and physicians assess alignment. AOFAS includes 9 items, distributed over 3 categories: pain (40 points), functional aspects (50 points), and alignment (10 points), for a total of 100 points with healthy ankles receiving 100 points (27). The FFI is a standard questionnaire used to assess foot diseases. Pain, disability, and activity restriction are among the three subscales of the FFI. The FFI consisted of 23 items. Patients take into account their foot issues from the previous week when filling out the FFI, scoring each item with a VAS. To obtain the subscales and the overall score, the scores for each item are added up (28-31).

Statistical Analysis

Descriptive information was shown using the following formats: number, percent, median, mean, ratio, frequency, and standard deviation. The Kolmogorov-Smirnov test was used to determine if the data were conformable to a normal distribution. The Independent Sample t-test and Mann-Whitney U test were used to assess quantitative independent data. Wilcoxon test results were used to assess the dependent data. The Pearson chi-square test was used to compare categorical variables. The cut-off for statistical significance was $p=0.05$. The Statistical Package for the Social Sciences program for Windows, version 22.00, was used for statistical analysis (SPSS Inc., Chicago, IL, USA).

Results

The trial involved 60 individuals in total. The baseline features and demographic data of the participants are listed in Table 1. The median age of the individuals was 45.4±12.3 years. The majority of participants were female (85%). Most individuals were overweight or obese. BMI values vary in range 19-40; the mean BMI of the participants was 28±5.7. The two groups did not substantially vary in terms of age, BMI, or daily standing time ($p>0.05$). Rest, activity, and first-step VAS scores in the treatment and control groups all significantly improved both in the first and second months compared to baseline. The improvement in these scores was better in the treatment group than in the control group in the first and the second month both ($p<0.05$) (Table 2).

In the treatment group, significant reduction has been observed in all FFI scores in the first and second months both ($p<0.05$). There has been no significant change in FFI pain subscale score in the control group

Table 1. Demographic and clinical characteristics by group

Characteristic		LLLT group (n=30)	Control group (n=30)	p	
		Mean ± SD	Mean ± SD		
Age		45.8±11.3	45.0±13.4	0.796	[m]
BMI		28.0±6.5	28.0±4.9	0.625	[m]
Standing time		6.1±1.6	6.1±1.9	0.934	[m]
		Number (%)	Number (%)		
Gender	Female	26 (86.7)	25 (83.3)	0.718	[x²]
	Male	4 (13.3)	5 (16.7)		

LLLT: Low-level laser treatment, SD: Standard deviation, n: Number, BMI body mass index

Table 2. Visual analog scale

	LLLT group (n=30)	Control group (n=30)	p	
	Mean ± SD	Mean ± SD		
VAS score resting				
Baseline	6.0±1.4	6.0±1.7	0.757	[m]
The first month after treatment	5.7±1.4	3.8±2.6	0.001	[m]
Second month after treatment	5.7±1.4	2.8±3.1	0.001	[m]
VAS score the first step in the morning				
Baseline	8.3±1.3	7.9±1.7	0.482	[m]
The first month after treatment	7.8±1.5	4.8±2.7	0.001	[m]
Second month after treatment	7.6±1.6	3.5±3.1	0.001	[m]
VAS score exercise				
Baseline	8.6±1.3	8.3±1.7	0.685	[m]
The first month after treatment	8.0±1.4	5.0±2.8	0.001	[m]
Second month after treatment	7.9±1.5	3.8±3.2	0.001	[m]

[m]Mann-Whitney U test/Wilcoxon test, LLLT: Low-level laser treatment, SD: Standard deviation, VAS: Visual analog scale

(p>0.05). Except this score, all other measurements has been improved both in the first and second months in the control group (p<0.05). The improvement in these scores was higher in the treatment group than in the control group in the first and the second months both. Just there has been no significant difference in the reduction ratio in the FFI activity limitation subscale score in the first month between the groups (Table 3).

In the treatment group, all measurements of AOFAS scores except alignment score has been significantly improved both in the first and the second months compared with to the initial state (p<0.05). The improvement in these scores was higher in the treatment group than in the control group in the first and the second months both. There has been no significant change in AOFAS pain and alignment scores compared to the initial state in the control group (p>0.05). Only the function score on the AOFAS scale in the control group showed a significant improvement (Table 4).

Discussion

For adults, PF is the most typical source of heel discomfort. Although this condition can be self-limiting, there are many conservative treatment options (32). However, their effectiveness is still uncertain, and the optimal treatment has not been defined (33).

Literature contains a insignificant number of publications examining LLLT's efficacy in the management of PF. It has been reported that there are a number of disputed cases about the LLLT treatment for PF, which may be caused by variations in the treatment protocols and kinds of LLLT. Numerous factors, including frequency, dose, and locations, are taken into account in LLLT's therapeutic use. Consequently, future research should concentrate on identifying the best treatment parameters to enhance the clinical effectiveness of the treatment (34).

The purpose of this research was to asses the efficacy of LLLT in the management of persistent PF. Our LLLT treatment protocol in this study was distinct from the other protocols described in the literature. We observed different kinds of therapy protocols's effects. Moreover, in our study, we used different scales that evaluate functional abilities and gait function.

We retrospectively examined 60 patient files diagnosed with PF. Because of our study, VAS, FFI, and AOFAS values significantly improved in both the treatment and control groups, according to our findings, which were significantly better in the treatment group compared with the control group. These results demonstrate that LLLT can be a viable therapy option for PF.

LLLT in the treatment of PF was first investigated in 1998 by Basford et al. (35). They applied LLLT at a wavelength of 830 nm at a dose of

Table 3. Foot function index

	LLLT group (n=30)	Control group (n=30)	p	
	Mean ± SD	Mean ± SD		
Pain subscale				
Baseline	7.7±1.2	7.6±1.9	0.882	[m]
The first month after treatment	7.6±1.3	4.8±2.7	**0.001**	[m]
Second month after treatment	7.4±1.3	3.5±3.0	**0.001**	[m]
Disability subscale				
Baseline	7.0±1.6	6.2±2.2	0.135	[m]
The first month after treatment	6.8±1.6	4.7±3.2	**0.006**	[m]
Second month after treatment	6.6±1.7	3.1±3.1	**0.001**	[m]
Activity limitation subscale				
Baseline	4.6±2.9	4.5±2.8	0.853	[m]
The first month after treatment	4.4±2.8	3.8±2.8	0.344	[m]
Second month after treatment	4.2±2.7	2.2±2.7	**0.002**	[m]
Total FFI score				
Baseline	6.6±1.0	6.5±1.9	0.589	[m]
The first month after treatment	6.4±0.9	4.8±2.9	**0.021**	[m]
Second month after treatment	6.3±1.0	3.3±3.0	**0.001**	[m]

[m]Mann-Whitney U test/Wilcoxon test, LLLT: Low-level laser treatment, SD: Standard deviation, FFI: Foot function index

Table 4. American orthopaedic foot and ankle society

	LLLT group (n=30)	Control group (n=30)	p	
	Mean ± SD	Mean ± SD		
Pain subscale				
Baseline	21.7±25.2	23.3±25.4	0.797	[m]
The first month after treatment	21.7±25.2	61.7±28.4	**0.001**	[m]
Second month after treatment	21.7±25.2	67.5±30.2	**0.001**	[m]
Function subscale				
Baseline	43.5±17.4	58.7±20.3	**0.001**	[m]
The first month after treatment	46.1±17.4	68.5±24.2	**0.001**	[m]
Second month after treatment	48.2±17.8	77.5±25.3	**0.001**	[m]
Alignment subscale				
Baseline	75.0±31.5	78.3±31.3	0.632	[m]
The first month after treatment	75.0±31.5	78.3±31.3	0.632	[m]
Second month after treatment	75.0±31.5	78.3±31.3	0.632	[m]
Total AOFAS				
Baseline	37.9±14.7	46.5±19.8	0.052	[m]
The first month after treatment	39.2±15.1	66.8±24.9	**0.001**	[m]
Second month after treatment	40.3±14.7	73.6±26.5	**0.001**	[m]

[m]Mann-Whitney U test/Wilcoxon test, LLLT: Low-level laser treatment, SD: Standard deviation, AOFAS: American Orthopaedic Foot and Ankle Society

1 J to the to the plantar fascia's starting point and a dose of 2 J along the medial fascial edge for 12 sessions and found no significant clinical difference with the placebo group in the first month after treatment. However, the reason for this result is likely to be due to the low dose of treatment administered. In our study, unlike this study, a higher dose of LLLT was applied to the patients. In contrast to this study, our treatment group showed a significant improvement in comparison to the control group on the VAS, FFI, and AOFAS scales for all criteria of pain, function, and activity limitation.

In their 2009 investigation, Kiritsi et al. (8) used a Ga-As laser with an infrared wavelength of 904 nm to perform LLLT. The active treatment dose was 8.4 J over the tendon insertion point, followed by 8.4 J along the medial fascial boundary. They evaluated the clinic of the patients with VAS pain scores and the plantar fascia thickness ultrasonographically.

After treatment, the LLLT group showed a substantial reduction in pain levels, although both groups also showed an increase in plantar fascia thickness. Fascia thicknesses, on the other hand, were unchanged in comparison to the placebo group.

Jastifer et al. (34) performed a total of 6 sessions of 635 nm, 17-mW dose, 10 min, 2 times a week, 3 weeks. They evaluated their patients with FFI and VAS scales before treatment, at 2 weeks, 6 months, and 12 months after treatment. They found that there was a significant difference in all evaluations compared to pretreatment values. However, in our study, we were unable to evaluate the long-term effects of treatment. Similar to this study, we also used the FFI scale and a significant change was found in the FFI scale scores in terms of both the amount of pain reduction and the improvement in functions at the 1st and 2nd months after the treatment.

Randomized placebo-controlled study in 2015, Macias et al. (36) applied LLLT at a dose of 17 mw with a wavelength of 635 nm for 10 min, twice a week, for 3 weeks. They showed that the LLLT group was significantly superior to the placebo group in both decreasing VAS pain scores and decreasing fascia thickness. They also achieved significant improvement in all FFI scores in both the LLLT and the placebo groups, but they didnot detect a difference between the groups. The limitation of our study, according to the study by Macias et al. (36) and Kiritsi et al. (8) is that the plantar fascia thickness was not evaluated by ultrasound (US) and the placebo group was excluded in our study.

In their investigation in 2017, Ulusoy et al. (16) used the AOFAS test to assess the efficacy of LLLT in PF. They applied a Ga-Al-As laser device at 830 nm, 50 mW output power, 8 j/cm^2 dose for a total of 3 weeks 5 times a week. They compared the efficacy of LLLT with extracorporeal shock wave therapy (ESWT) and therapeutic US therapy. AOFAS ratings in the LLLT group improved more than in the ESWT and US groups, according to the study.

In a randomized prospective study by Cinar et al. (37) both treatment and control groups were given insoles and a home exercise program, and LLLT was also applied to the treatment group. They used the AOFAS function scale for functional evaluation and the VAS scale for pain after the 12-minute walk test. They performed LLLT in the 5 most painful points at a dose of 5.6 j/cm^2 for 80 seconds. While both groups showed a substantial improvement in their AOFAS function scores in the third week following treatment, only the group that received LLLT in the third month showed a meaningful improvement. Although there was a significant improvement in the measurement of activity-related pain in both groups at the 3rd month, the amount of improvement was greater in the treatment group. In our study, in parallel with this study, a significant increase was observed in all groups of AOFAS scores compared with the pre-treatment scores, except the alignment score in the treatment group. This is a result consistent with previous studies. This supports that LLLT is an effective treatment. The different aspects of our study according to the study by Cinar et al. (37) is that the LLLT was applied at a lower dose and with a different application method.

The positive sides of our study; in accordance with previous studies, no adverse effects were seen in the patients throughout the study. This finding supports that LLLT is a safe treatment. The fact that the treatment responses of the patients included in our study was evaluated using the FFI and AOFAS scales also enabled us to investigate the correlation of these two scales. And the results obtained from the two scales were correlated with each other.

Study Limitations

The limitations of our study are that the evaluation process was short, retrospective, and there was no placebo group.

Conclusion

According to this study, LLLT is useful in PF conventional treatment with regard to pain, functional activities, and quality of life. It has been concluded that LLLT is a reliable and effective application in the physical treatment of PF. To investigate the effects of LLLT on PF treatment, placebo-controlled studies with longer follow-ups are needed for more patients.

Ethics Committee Approval: The University of Health Sciences Turkey, İstanbul Training and Research Hospital Ethics Committee gave its approval to the study (approval number: 2016/902).

Informed Consent: Each participant gave written consent.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions: Surgical and Medical Practices - B.G., Y.P.D., E.Y.; Concept - B.G., E.A., D.İ., E.Y.; Design - B.G., Y.P.D., D.İ., E.Y.; Data Collection or Processing - B.G., E.A., Y.P.D., D.İ., E.Y., F.U.; Analysis or Interpretation - B.G., E.A., Y.P.D., D.İ., F.U.; Literature Search - B.G., E.A., Y.P.D., F.U.; Writing - B.G., E.A., F.U.

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Comparison of Hematological Phenotypes of COPD Exacerbations in Hospitalized Patients after Emergency Department Admission

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ABSTRACT

Introduction: The aging of the communities and higher pollution levels increases chronic obstructive pulmonary disease (COPD) burden and are projected to rise in the number of the patients with COPD and its exacerbations. There is little evidence for short-term outcomes of COPD exacerbations of the biomarkers that are easily available. Biomarker-based hematological phenotype classification is useful and effective for outcome predictions. This study evaluates the relationship between the phenotypes of patients with COPD who presented in the emergency department due to COPD exacerbation and admitted to the hospital have been evaluated.

Methods: All hospitalized patients older than 18 years old who presented to the emergency department due to the COPD exacerbation between July 2018 and July 2020 were included in the study. The patient data evaluated retrospectively for vital parameters, biomarker results, and mortality rates. The primary outcome measure of the study was determined as the thirty-day mortality rates of the groups. Secondary outcome measures were determined by comparing the differences between the trophilic and eosinophilic groups.

Results: One hundred forty-three patients were included in the study. The mean age of the patients was 74.8±10.6. One hundred and two of the patients (71.3%) were male. The neutrophilic and eosinophilic groups had a statistically significant difference in body temperature and heart rate (p=0.018 and p=0.001, respectively). In contrast, no significant difference was observed for systolic blood pressure, diastolic blood pressure, and sPO_2 (p=0.400, p=0.564, p=0.248, respectively). One month mortality of the neutrophilic and eosinophilic groups were 15.9% and 3.2%, respectively. Blood neutrophil count levels have been assigned in 3 different groups for mortality and compared which had no significant difference for 1,3 and 12-month mortality (p=0.142, 0.280, 0.351 respectively).

Conclusion: The patients admitted to the hospital via the emergency department had no mortality difference between different neutrophil levels or hematologic phenotypes. Further studies are required to assess cutoff values of blood neutrophil counts as an independent biomarker.

Keywords: COPD, COPD exacerbation, blood neutrophil count, and blood eosinophil count

Introduction

Chronic obstructive pulmonary disease (COPD) is the third leading cause of death worldwide and most of these deaths occur in low and middle-income countries (1). The aging of the communities and higher pollution levels increases the COPD burden and are projected to rise the number of COPD patients and its exacerbations (2). Mostly, COPD exacerbations result in presenting to emergency departments which resulted in 2 million emergency department visits annually in the USA in 2016 (3). Furthermore, in the same year, approximately 35% of these patients were hospitalized and the in-hospital mortality rate of the patients with COPD exacerbations was reported as 17% (4). Since the mortality rate is so high, it is important to be able to predict which patients would have unfavorable progress. Spirometry is an essential method for the prediction of patients with COPD (5). However, spirometry is underused in emergency departments (6). Additionally, in the ECLIPSE study, many biomarkers predicted the one-year mortality of the patients but, none of these biomarkers can be used for anticipating the short-time prognosis. Therefore, a test that is used easily for predicting the mortality of patients with COPD is needed.

Accordingly, many biomarkers have been studied for managing COPD exacerbations. It has been reported that blood eosinophil and neutrophil counts might be the predictor of mortality for COPD exacerbations (7,8). Additionally, according to the GOLD report, blood eosinophil count cut-off values might be used to identify the treatment benefits of inhaled

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corticosteroids (5). In contrast, there have been a few research on cut-off values of blood neutrophil counts. It is uncertain what the precise value of blood neutrophil counts for the increased mortality.

We hypothesized that the different phenotypes of COPD exacerbations might be correlated with different mortality rates, and exploring the hospitalized patients' mortality rates might benefit clinicians. This study measured and compared the mortality rates between hematological COPD groups. In this retrospective study, the relationship between the phenotypes of patients with COPD who presented in the emergency department due to COPD exacerbation and were admitted to the hospital have been evaluated.

Methods

Study Design and Settings

This was a single-center, retrospective study. The participants' demographic and clinical data were extracted from electronic medical records of the hospital. The study was approved by the University of Health Sciences Turkey, Derince Training and Research Hospital Local Ethics Committee (approval number: 2020-164, date: 14.01.2021).

Selection of Participants

All hospitalized patients older than 18 years old who presented to the emergency department due to COPD exacerbation between July 2018 and July 2020 were included in the study. Pregnant women were excluded from the study.

Because of the retrospective chart review nature of the study, informed consent was exempted after acquiring appropriate institutional ethics and administrative approval.

Study Protocol

Eosinophilic COPD was defined as ≥200 cells/mL or ≥%2 of white blood cell. Neutrophilic COPD was defined as >7100 cells/mL according to our laboratory cut-off values. Blood neutrophil counts were divided into three categories between 2000-7000 cells/mL, between 7000-15000 cells/mL, and more than 15000 cells/mL. The initial blood eosinophil counts and blood neutrophil counts when the patients presented to the emergency department were recorded in predesigned data sheets. Patients' demographics, 1-month, 3-month, and 1-year mortality rates, and whether non-invasive mechanic ventilation (NIMV) or mechanic ventilation were implemented were attained from the hospital database and recorded. Patients with <7100 cells/mL defined as the neutrophilic group while patients with ≥200 cells/mL defined as the eosinophilic group.

Outcome Measures

The primary outcome measure of the study was determined as the thirty-day mortality rates of the groups. Secondary outcome measures were determined by comparing the differences between the neutrophilic and eosinophilic groups.

Statistical Analysis

SPSS 23.0 (IBM Corporation, Armonk, New York, United States) Statistical Software Package was used for data analysis. Descriptive statistics are presented with numbers and percentages for categorical variables. The Kolmogorov-Smirnov test was used to evaluate the normality of distribution. Differences between the categorical variables in the independent groups were tested with chi-square analysis. Mann-Whitney U test was used to compare variables between two independent groups. The statistical significance was accepted as $p<0.05$.

Results

One hundred forty-three patients were included in the study. The mean age of the patients was 74.8±10.6. One hundred and two of the patients (71.3%) were male. The most common comorbidity was diabetes mellitus (42%). The characteristics and comorbidities of the patient groups have been presented in Table 1.

The mean of the neutrophil count was 8.31±0.35 (10^3 x cells/mm^3), and the mean of the eosinophil count was 0.18±0.02 (10^3 x cells/mm^3). The mean of neutrophils and eosinophils of the NEU group was 11.97±3.77 and 0.19±0.18 (10^3 x cells/mm^3), respectively, while the mean of neutrophils and eosinophils of the EOU group were 5.64±1.22 and 0.35±0.24 (10^3 x cells/mm^3), respectively.

The NEU and the EOU groups had a statistically significant difference in body temperature and heart rate (p=0.018 and p=0.001, respectively). In contrast, no significant difference was observed for systolic blood pressure, diastolic blood pressure, and sPO2 (p=0.400, p=0.564,

Table 1. Characteristics of the patients

	All patients, (n=143)	Neutrophilic patients, (n=63)	Eosinophilic group, (n=31)
Age (mean ± SD)	74.8±10.6	74±10.8	74.78±10.7
Gender (male)	102 (71%)	44 (69.8%)	5 (16.1%)
Coronary artery disease	21 (14.7%)	11 (17.5%)	10 (16.4%)
Congestive heart failure	27(18.9%)	11 (17.5%)	7 (22.6%)
Chronic renal failure	21 (14.7%)	7 (11.1%)	5 (16.1%)
Hypertension	60 (42%)	25 (39.7%)	11 (35.5%)
Diabetes mellitus	52 (36.4%)	26 (41.3%)	8 (25.8%)
Home-dwelling elderly	15 (10.5%)	7 (11.1%)	2 (6.5%)
Malignity	21 (14.7%)	12 (19%)	0 (0%)

SD: Standard deviation

p=0.248, respectively). The comparison of the vital signs of the patients is summarized in Table 2.

Twenty-two (15.4%) of the patients required NIMV in the emergency department. 9 (14.3%) were in the NEU group, and 6 (19.4%) were in the EOU group. Comparison of the NEU and EOU groups, in terms of NIMV application, had no significant difference (p=0.528).

Two patients (1.4%) were intubated in the emergency department (1 patient for each group). There was no statistically significant difference between the groups in terms of intubation need (p=0.553). Patients' 1-month, 3-months, and 1-year mortality results have been summarized in Table 3.

One-month mortality rates for all patients, the NEU group and EOU groups have been determined as 16/143 (11.2%), 10/63 (15.9%), 1/31 (3.2%), respectively. Blood neutrophil count levels have been assigned in 3 different groups for mortality and compared which had no significant difference for 1,3- and 12-month mortality (p=0.142, 0.280, 0.351; respectively). Blood neutrophil count levels and mortality rates have been summarized in Table 4.

Discussion

The current study found that eosinophilic and neutrophilic exacerbations of patients with COPD had no significant difference in terms of mortality. In the study by Kandemir et al. (9), which was conducted in similar settings, the neutrophilic phenotype patients had higher mortality rates than the eosinophilic phenotypes. In their study, neutrophilic patients had 38.9% mortality rates in 3 months, whereas in our study, neutrophilic phenotype patients had 25.4% and 36.5% (3 and 12 months respectively). These mortality rates are higher than expected however both studies examine the patients presenting to the ED. This can be explained by the patient population was much more ill than outpatients, therefore had more unfavorable outcomes. In contrast, our study had higher mortality rates regarding eosinophilic exacerbations 16.1%, 25.8%, (3 and 12 months respectively). This difference might occur due to Kandemir et al. (9) have classified the exacerbations into three groups in their study. These results suggest that classifying hematologic phenotypes further might yield different mortality rates with overall deaths due to COPD remaining the same. Furthermore, their study included patients discharged and admitted to a hospital where we only included hospitalized patients, which might be the reasoning behind the difference in mortality rates for eosinophilic patients (9).

In addition, our study included important features of hematologic phenotypes. Previous studies have presented higher rates of older age, tachycardia, and higher body temperatures for neutrophilic exacerbations. In our study, we also found that tachycardia and increased body temperature and other vital signs were indifferent between the comparison of phenotypes, which was concurrent with the current literature. Furthermore, our study had similar age means in all groups.

Various studies have concluded that the eosinophilic type has lower short- and long-term mortality (10-12). We have found that mortality rates did not significantly change between hematologic phenotypes. This might be the result of our work patients being studied that are admitted to the hospital and excluded discharged patients. Furthermore, our study included patients who have been admitted to the hospital from

Table 2. Comparison of the patient's vital signs

	All patients, (n=143)	Neutrophilic patients, (n=63)	Eosinophilic patients, (n=31)	p-values*
Systolic BP	123.01±24.55	124.44±24.02	121.29±25.92	0.400
Diastolic BP	71.82±12.65	72.06±11.52	71.29±14.08	0.564
Body-tempeture	37.08±0.7	37.05±0.64	36.78±0.55	0.018
Heart rate	103.16±18.1	107.16±18.06	94±13.76	0.001
Oxygen saturation	86.57±8.66	85.41±9,85	87.06±8.93	0.248

*P-values represent comparison between Neutrophilic and Eosinophilic groups, BP: Blood pressure

Table 3. Mortality rates for 1 month, 3 months, and 12 months between patient groups

Mortality	All patients (%), (n=143)	Neutrophilic patients (%), (n=63)	Eosinophilic patients (%), (n=31)	p-values*
1-month	16 (11.2%)	10 (15.9%)	1 (3.2%)	0.066
3-months	30 (%21%)	16 (25.4%)	5 (16.1%)	0.310
1-year	47 (%32.9%)	23 (36.5%)	8 (25.8%)	0.299

*P-values represent comparison between neutrophilic and eosinophilic groups.

Table 4. Neutrophil levels and mortality rates for each group

	1 month mortality, (n=16)	3 month mortality, (n=30)	12 month mortality, (n=47)
2000-7000 cell/mL	4/16	11/30	20/47
7000-15000 cell/mL	10/16	15/30	21/47
>15000 cell/mL	2/16	4/30	6/47
p-value	0.142	0.280	0.351

the emergency department. Therefore, note that patients admitted to the ED with exacerbations were more severely ill than outpatient COPDs. Similar to our findings, Bafadhel et al. (7) study also showed similar 1-year mortality between eosinophilic and non-eosinophilic exacerbations, which would suggest in-patient patients with COPD even with eosinophilic phenotypes might have similar outcomes when discharged and outpatients are excluded. Martínez-Gestoso et al. (13) study discussed blood eosinophil count is not useful in assessing outcomes after patient hospitalizations that was concurrent with our study. In contrast, ICU patient mortality rates were favorable for the eosinophilic phenotype (14).

Finally, neutrophil count levels and cut-offs have not been thoroughly studied in the literature. We have divided neutrophilic phenotypes into three groups (2000-7000, 7000-15000 and >15000 cells/mL) and found no difference between the groups. Further studies must assess blood neutrophil count cut-off values for inpatient and outpatient populations to further examine its use as an independent biomarker for mortality.

Study Limitations

Our study was a single-center study that conducted as a retrospective study; therefore, our results cannot be generalized. Furthermore, even though we included the patients hospitalized in the emergency department, which might be counted as a strength, excluding outpatients and discharged patients also provided a limited view of the population.

Conclusion

There was no mortality difference between different neutrophil levels or hematologic phenotypes for the patients admitted to the hospital via the emergency department. Further studies must assess the cutoff values of blood neutrophil counts as an independent biomarker.

Ethics Committee Approval: The study was approved by the University of Health Sciences Turkey, Derince Training and Research Hospital Local Ethics Committee (approval number: 2020-164, date: 14.01.2021).

Informed Consent: Informed consent was exempted.

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Real-Life Data of Chronic Hepatitis C Patients Treated with Direct-Acting Oral Antivirals: A Single-Center Study

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ABSTRACT

Introduction: Chronic hepatitis C virus (HCV) infection is one of the important causes of liver cancer and cirrhosis all over the worldwide.

Methods: The data of the patients diagnosed with chronic hepatitis C infection who applied to the Adult Infectious Diseases and Clinical Microbiology Outpatient Clinic of Erzincan Binali Yildirim University, Mengücek Gazi Training and Research Hospital were retrospectively analyzed. Accordingly, 51 patients treated with direct-acting oral antiviral drugs (DAAs) between January 2016 and May 2021 were included in the study. Patients whose treatment is still ongoing, whose treatment was completed but did not come to the 12th week after treatment, or whose control time has not yet come, were excluded from the study.

Results: It was observed that 58.8% of the cases participating in the study were male, 80.4% were infected with genotype 1b, and 74.5% were treatment-naive. When the treatment regimens used in the cases were examined, glecaprevir/pibrentasvir in 7.8%, sofosbuvir (SOF)/ledipasvir (LED), SOF/LED/ribavirin, and SOF/ribavirin in 15.7%, ombitasvir (OBV)/paritaprevir (P)/ritonavir (R)/dasabuvir and OBV/P/R/ribavirin in 76.5% (n=39) appears to be used. A statistically significant difference was found between the alanine aminotransferase, aspartate aminotransferase measurements, and platelet counts of the subjects participating in the study at the beginning, at the 4th week, at the end of the treatment, and at the 12th week (p=0.001). In these cases, a sustained virological response was achieved in 100%. In the follow-up of the cases, no serious side effects that required drug discontinuation were observed.

Conclusion: Our study showed that the treatment success of DAAs is 100% and their side-effect profiles are good.

Keywords: Chronic hepatitis C, DAA, SVR

Introduction

Chronic hepatitis C virus (HCV) infection is still one of the important causes of liver cancer and cirrhosis all over the worldwide. Approximately 71 million people have chronic HCV infection according to the World Health Organization's (WHO) latest data. According to the 2016 data of the WHO, approximately 399,000 people died from hepatitis C-related complications (1,2).

According to a study conducted recently, anti-HCV seropositivity was found to be around 1% in our country. Although the most common HCV genotype in the world is genotype 1, genotype 3, genotype 2, genotype 4, genotype 6, genotype 5, genotype 7, and genotype 8 infections are also seen, respectively. In our country, genotype 1 is the most common, and genotype 1b is the subtype (3-6).

Although the combination of pegylated interferon (PEG-IFN) + ribavirin was used in the treatment before, this combination has been replaced by direct-acting oral antiviral drugs (DAA) recently. A sustained virological response (SVR) of over 95% is achieved with the use of DAAs (7-11).

Our aim is to evaluate the chronic HCV patients who were treated with DAAs at our center in this study.

Methods

This study is a retrospective, cross-sectional study and was conducted with the approval of the Erzincan Binali Yıldırım University Clinical Research Ethics Committee (approval number: 08/06, date: 21.06.2021).

The files of the patients diagnosed with chronic HCV infection who applied to the Adult Infectious Diseases Outpatient Clinic of Erzincan Binali Yildirim University, Mengücek Gazi Training and Research Hospital were retrospectively analyzed. Accordingly, patients treated with DAAs between January 2016 and May 2021 were included in the study. Patients whose treatment is still ongoing, whose treatment was completed but did not come to the 12th week after treatment, or whose control time has not yet come, were excluded from the study.

Demographic, clinical, and laboratory data of the patients, whether they had received treatment before, whether they had relapsed or not were

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obtained from the outpatients clinic patient registry files. Complete blood count, biochemical tests, and HCV-RNA levels were evaluated before the treatment, at the 4th week of the treatment, at the 8th week of the treatment, and at the end of the treatment. Genotype results were obtained from the patient files. The HCV-RNA level at the 12th week after the treatment was used in the evaluation of SVR.

HCV-RNA was studied using the COBAS TaqMan real-time polymerase chain reaction (RT-PCR) (Roche, Switzerland) assay. For HCV genotyping, RT-PCR and DNA sequencing were performed for the 5'UTR region of the HCV genome. Analysis of PCR products was performed using the ABI Prism 3130xl DNA Sequencer (Thermo Fisher Scientific, USA) instrument and the HVC Databank (http://hcvdb.org). Complete blood count was measured on a Sysmex XN-1000 Hematology System (Sysmex Corporation, Kobe, Japan) automated blood count device. Biochemical tests were measured on an AU 5800 (Beckman Coulter, California, USA). Alpha fetoprotein was measured by an immunoassay (Centaur XPT, Siemens Healthcare, Germany). Coagulation tests were measured by the turbidimetric method in the Celeron® alpha (Diapharma Group, Ohio, USA) device.

Statistical Analysis

The NCSS 2007 (Kaysville, Utah, USA) program was used. Descriptive statistical methods (mean, standard deviation, median, frequency, percentage, minimum, maximum) were used in the evaluation of the research data. The Shapiro-Wilk test and graphical examinations were used to confirm the quantitative data to the normal distribution. A repeated measure of variance analysis was used for within-group comparisons of normally distributed quantitative variables. To evaluate pairwise comparisons Bonferroni-corrected pairwise assessments were used. The Friedman test was used for intragroup comparisons of quantitative variables that did not show a normal distribution, and the Wilcoxon signed-rank test with Bonferroni correction was used for evaluating pairwise comparisons. A $p<0.05$ was considered statistically significant.

Results

The study was performed between January 2016 and May 2021 at Erzincan Binali Yildirim University, Mengücek Gazi Training and Research Hospital with 51 patients, 41.2% (n=21) female and 58.8% (n=30) male. The ages of the patients ranged from 23 to 86 years, with a mean age of 59.94±14.54 years. The HCV-RNA levels of the cases ranged from 5,104 IU/mL to 4,378,000 IU/mL, with a mean of 985,576.89±1,157,972.49.

When the genotype distribution of the cases is examined, it is seen that 80.4% of them are infected with genotype 1b, 5.9% with genotype 1a, 2% with genotype 2, 9.8% with genotype 3, 2% with genotype 4.

It was observed that the treatment status of 25.5% of the cases was treatment-experienced and 74.5% of them were treatment-naive. When the treatment regimens used in the cases were examined, glecaprevir/pibrentasvir in 7.8%, sofosbuvir containing regimens in 15.7%, ombitasvir (OBV)/paritaprevir (P)/ritonavir (R)/dasabuvir in 76.5% (n=39) and OBV/P/R/ribavirin appeared to be used. It was observed that 62% of the cases had co-morbidities such as diabetes mellitus, essential hypertension, and chronic renal failure. While co-infection was not observed in 94.1% of the cases, HBV co-infection was observed in 3.9% and HIV in 2% (Table 1).

Table 1. Demographic and clinical ınformation of the patients

Age, n (%)	**Mean ± SD**	**59.94±14.54**
	Median (min.-max.)	**64 (23-86)**
Gender, n (%)	Female	21 (41.2)
	Male	30 (58.8)
HCV-RNA levels (IU/mL)	Mean ± SD	985,576.89±1,157,972.49
	Median (min.-max.)	451,200 (5104-4,378,000)
Genotype distribution, n (%)	1a	3 (5.9)
	1b	41 (80.4)
	2	1 (2)
	3	5 (9.8)
	4	1 (2)
Treatment status, n (%)	Experienced	13 (25.5)
	Naive	38 (74.5)
Treatment regimen, n (%)	Glecaprevir/pibrentasvir	4 (7.8)
	SOF/LED, SOF/LED/ribavirin ve SOF/ribavirin	8 (15.7)
	OBV/P/R/D ve OBV/P/R/ribavirin	39 (76.5)
Co-morbities, n (%)	No	19 (38)
	Yes	31 (62)
Co-infection, n (%)	No	48 (94.1)
	HBV	2 (3.9)
	HIV	1 (2)

HCV: Hepatitis C virus, SOF: Sofosbuvir, LED: Ledipasvir, OBV: Ombitasvir, P: Pariteprevir, R: Ritonavir, PROD: Ombitasvir/pariteprevir/ritonavir/dasabuvir, HIV: Human immunodeficiency virus, SD: Standard deviation, min.: Minimum, max.: Maximum

Table 2. Change in laboratory values of patients completing treatment

		Beginning	Week 4	End of treatment	Follow-up week 12	p
ALT (IU/mL)	Mean ± SD	64.65±67.64	16.25±13.41	15.09±6.83	15.22±5.72	[b]**0.001****
	Median (Min.-Max.)	45 (10-401)	13 (5-79)	14 (4-36)	14 (5-32)	
AST (IU/mL)	Mean ± SD	51.26±37.56	18.82±6.09	20.53±10.21	19.37±6.62	[b]**0.001****
	Median (Min.-Max.)	37 (13-211)	18 (7-40)	19 (6-67)	18 (7-35)	
Hemoglobin (g/dL)	Mean ± SD	14.74±2	14.59±1.91	14.32±1.94	14.45±1.93	[c]**0.062**
	Median (Min.-Max.)	15 (8.9-19.6)	15 (9.7-18.2)	14.5 (9.1-19)	14.8 (9.1-18.5)	
Absolute neutrophil count (/mm^3)	Mean ± SD	3875.29±1298.56	4280±1975.18	4112.98±1580.56	3988.24±1482.64	[b]**0.518**
	Median (Min.-Max.)	3680 (1580-8350)	4130 (2210-11770)	3800 (1440-8900)	3550 (1500-8850)	
Platelet count*10^3 (/mm^3)	Mean ± SD	211.47±85.38	235.18±90.92	229.98±74.04	225.19±84.04	[b]**0.001****
	Median (Min.-Max.)	206 (179-564)	218 (102-683)	220 (97-578)	220 (200-583)	
HCV-RNA (IU/mL)	Negative		47 (92.2)	47 (100)	51 (100)	
	Positive		4 (7.8)	0 (0)	0 (0)	

[b]Friedman's test, [c]Repeated Measures test, **p<0.01, SD: Standard deviation, Min.: Minimum, Max.: Maximum, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, HCV: Hepatitis C virus

There was a statistically significant difference between the alanine aminotransferase (ALT) measurements at the beginning, at the 4th week, at the end of the treatment, and at the 12th week of the subjects participating in the study (p=0.001). Decreases in the baseline ALT measurement at week 4, at the end of treatment, and at week 12 were significant (p=0.001; p=0.001; p=0.001).

There was a statistically significant difference between the aspartate aminotransferas (AST) measurements of the subjects at the beginning, at the 4th week, at the end of the treatment and at the 12th week of follow-up (p=0.001). Decreases at the 4th week, at the end of the treatment, and at the 12th week were significant compared with the initial AST measurement (p=0.001; p=0.001; p=0.001).

There was a statistically significant difference between the platelet count measurements at the beginning, at the 4th week, at the end of the treatment, and at the 12th week of follow-up (p=0.001). The increases in the measurement of the initial platelet count at the 4th week, at the end of the treatment, and at the 12th week were significant (p=0.001; p=0.001; p=0.001) (Table 2).

No side effects required discontinuation of treatment in patients. Itching was observed in two patient; weakness, nausea, and swelling in the legs were observed in one patient each.

Discussion

Chronic HCV infection is still one of the major causes of cirrhosis and hepatocellular carcinoma. While the combination of PEG-IFN and ribavirin was used in the treatment before, DAAs are now used today (11). When the real-life data of patients treated with DAAs are examined, different rates are reported in studies conducted in our country and in the world. In the study by Aygen et al. (8), which they analyzed the data of 55 patients infected with genotype 4, 100% SVR was found in patients without cirrhosis, while this rate was found to be 88.9% in patients with compensated cirrhosis. In another study of Aygen et al. (9), which they analyzed the data of 862 patients infected with genotype 1 or 4, SVR was found to be 99.1%. Today, pangenotypic drugs are used and Su et al. (12) evaluated the real-life data of glecaprevir/pibrentasvir in a 90-patient study and found 97.7% SVR rate. In our study, 100% SVR was detected and this rate shows that DAAs are effective.

Studies have shown that liver functions begin to improve immediately in patients with SVR. In the study of Cheng et al. (13), it was shown that ALT and AST levels returned to normal with the detection of post-treatment response and SVR. Simultaneously, histopathological improvement has been shown in patients who underwent liver biopsy before and after treatment. Similarly, in the Taiwan cohort, it was emphasized that cirrhosis and cirrhosis-related complications decreased in patients with SVR (14). Again, similar studies have shown improvement in non-invasive serum biomarkers in patients with SVR (15-18). In our study, a statistically significant decrease in ALT and AST levels at the end of the treatment; a statistically significant increase was observed in platelet counts (p<0.01). It was observed that the improvement in ALT, AST, and thrombocyte levels of the patients continued after SVR was provided. This result shows that fibrosis improves with treatment. Simultaneously, it demonstrates the importance of ensuring that patients diagnosed with chronic HCV are identified as soon as possible and access to treatment. Because if the liver reserve is good before treatment, the risk of cirrhosis and hepatocellular carcinoma will be lower after treatment. Additionally, extrahepatic findings related to HCV will be prevented (11).

Real-life data show that DAAs have a good side-effect profile compared to PEG-INF + ribavirin. Generally, it has been reported that the side effects that require discontinuation of treatment are few (8,9,12). In our study, no side effects requiring discontinuation of treatment were observed in any patient, indicating that the side-effect profile of DAAs is good.

Study Limitations

The small number of patients in our study is a limitation of the study.

Conclusion

Our study showed that the treatment success of DAAs is 100% and their side-effect profiles are good. However, the small number of patients is a limitation of our study. Multicenter studies with large numbers of patients are needed.

Ethics Committee Approval: This study is a retrospective, cross-sectional study and was conducted with the approval of the Erzincan Binali Yıldırım University Clinical Research Ethics Committee (approval number: 08/06, date: 21.06.2021).

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

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A Real-Life Turkish Experience of Ruxolitinib in Polycythemia Vera

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ABSTRACT

Introduction: Ruxolitinib is a small -molecule inhibitor of the JAK1/2 pathway. This study aimed to reveal the results and side-effect profile of the use of ruxolitinib as a treatment option in polycythemia vera (PV).

Methods: A total of 34 patients with PV from 18 different centers were included in the study. The evaluation of the response under treatment with ruxolitinib was determined as a reduction in spleen volume (splenomegaly size: ≥35%) by imaging and control of hematocrit levels (≤45%) compared to baseline.

Results: While the number of patients in which a reduction in spleen volume and hematocrit control was achieved was 19 (55.9%) at 3 months of treatment, it was 21 (61.8%) at 6 months. Additionally, while the number of side effects was negatively correlated with the reduction in spleen volume (Spearman's rho: -0.365, p=0.034), a decrease in the hematocrit level was positively correlated (Spearman's rho: 0.75, p=0.029). Those without a reduction in spleen volume experienced more constipation (chi-square: 5.988, Fisher's exact test: p=0.033).

Conclusion: This study shed light on the use of ruxolitinib in PV and the importance of splenomegaly on studies planned with larger patient groups.

Keywords: Polycythemia vera, ruxolitinib, real-life data, response, side effect

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Introduction

Polycythemia vera (PV) is a myeloproliferative disorder that is characterized by the expansion of erythroid progenitor cells, which carries the risk of developing into myelofibrosis and acute leukemia (1). It is usually diagnosed in the 6th decade or later with a high risk of thromboembolism. Ninety-five percent of patients carry the *Janus kinase 2 (JAK2)* gene V617F mutation (1).

Treatment of PV consists of intermittent phlebotomy and low-dose acetylsalicylic acid to keep the hematocrit level below 45%. In patients defined as high risk (those over 60 years of age and the presence of any thrombohemorrhagic event), cytoreductive treatment is indicated. Hydroxyurea (HU) is the first agent recommended for cytoreduction, with the most experience available for HU (1-5).

The European Leukemia Net and the International Working Group-Myeloproliferative Neoplasms Research and Treatment have defined both resistance and intolerance to HU (6). HU resistance can be defined as the presence of one of the following criteria: 1) The need for phlebotomy to maintain a hematocrit levels of <45% during treatment. 2) Uncontrolled myeloproliferation (platelet count of 400×10^9/L and white blood cell count of $>10\times10^9$/L). 3) The inability to reduce massive splenomegaly by >50%, as measured by palpation, or complete relieved symptoms related to splenomegaly. HU intolerance is defined as one of the following criteria: 1) Having an absolute neutrophil count of $<1.0\times10^9$/L or platelet count of $<100\times10^9$/L, or hemoglobin level of <10 g/dL under the lowest dose of HU was used to achieve a complete or partial hematological response. 2) The presence of mucocutaneous manifestations, gastrointestinal symptoms, pneumonitis, fever, leg ulcers, or other non-hematological toxicities related to HU at any dose of HU (7). Thus, it can be seen that different treatment options are on the agenda in these two patient groups.

Ruxolitinib is a small-molecule inhibitor of JAK1/2 that targets the Janus Kinase and signal transducer and activator of transcription pathway (8-10). Its efficacy has been proven in the Randomized study of Efficacy and Safety in PV with the JAK inhibitor ruxolitinib versus best available care (RESPONSE) 1 and RESPONSE 2 trials in the HU-intolerant or -unresponsive patient group (11,12). For post-HU patients, it appears to be a highly effective treatment option for hematocrit control, regression of the spleen size, and the elimination of PV-related symptoms. Another study, known as RELIEF (13), evaluated the efficacy and safety of ruxolitinib compared with HU in PV patients with controlled hematocrit levels, but whose symptoms did not regress. After 16 weeks, a 50% reduction in the cytokine total symptom score was reported in 43% of the ruxolitinib-treated patients and 29.6% of the HU-treated patients. Regarding pruritus and fatigue, the proportion of patients with greater than 50% reduction was 40% versus 26% in patients treated with ruxolitinib and HU, respectively (13).

This study aimed to reveal the results and side-effect profile of the use of ruxolitinib as a treatment option in PV.

Methods

A total of 34 patients with PV from 18 different centers were included in the study. In addition to the initial demographic data (age, and gender) of the patients, initial spleen and liver size, laboratory values (leukocyte, hemoglobin, platelet), starting dose of ruxolitinib, follow-up duration, and side effect profile and responses were recorded.

All the patients had received treatment with HU before being administered ruxolitinib. Ruxolitinib was discontinued due to HU intolerance, massive splenomegaly, severe and treatment-refractory constitutional symptoms, uncontrolled polycythemia, or severe pruritus. The evaluation of the response under treatment with ruxolitinib was determined as a reduction in spleen volume (splenomegaly size: ≥35%) by imaging and control of hematocrit levels (≤45%) compared to baseline. Patients with any side effects (grade 0-5) were recorded. Patients whose initial dose was increased or decreased were also recorded, and there were no patients who discontinued the treatment for any reason.

The study was approved by the University of Health Sciences Turkey, İstanbul Training and Research Hospital Ethics Committee (approval number: 2904, date: 13.8.2021).

Statistical Analysis

The IBM SPSS Statistics for Windows 26.0 (IBM Corp., Armonk, NY, USA) analysis program was used for statistical analysis. Descriptive and inferential statistics were calculated, and appropriate hypothesis tests were used. The one-sample Kolmogorov-Smirnov and Shapiro-Wilk normality tests were used for the conformity of the variables to the normal distribution. Quantitative variables were expressed as the mean ± standard deviation, minimum-maximum, median. Qualitative variables are expressed as number and percentages. The Mann-Whitney U test was used for numerical data that did not show a normal distribution, and the chi square test was used for nominal data for comparison of the groups. The Independent sample test was used for those with normal distribution. The equality of variances was tested using the Levene test for the equality of variances. The Spearman Rank correlation coefficient and logistic regression analyzes were used to correlate the data. The McNemar test was used to compare the categorical variables in the dependent groups. Statistical significance level in hypothesis tests was accepted as $p<0.05$.

Results

Of the 34 patients included in the study, 21 were female (61.8%) and 13 were male (38.2%). Initial laboratory values and liver-spleen sizes are summarized in Table 1. The median line of treatment before ruxolitinib was 1.5 (range: 1-3). The median starting dose was 30 mg (range: 20-40). The most common indication for ruxolitinib was HU intolerance (15 patients, 44.1%). The median follow-up duration was 13.5 months (range: 7-61) (Table 1).

The ruxolitinib treatment process is shown in Table 2. While the number of patients in which a reduction in spleen volume and hematocrit control was achieved was 19 (55.9%) at 3 months of treatment, it was 21 (61.8%) at 6 months. The number of patients whose initial dose was reduced for any reason was 4 (11.7%), and of these patients, 2 had anemia, 1 had thrombocytopenia, and 1 had both of them. The most common side effects were thrombocytopenia and constipation, seen in 8 patients (23.5%) (Table 2).

In the statistical analysis, which was performed for the responses and initial parameters, it was found that the group with a reduction in spleen volume at 3 months had a significantly lower number of previous treatment lines (p=0.017). No significant correlation was found between the other baseline parameters and the response criteria (Table 3).

Additionally, while the number of side effects was negatively correlated with the reduction in spleen volume (Spearman's rho -0.365, p=0.034), a decrease in the hematocrit level was positively correlated (Spearman's rho: 0.75, p=0.029) (Figure 1).

Table 1. Demographic characteristics, initial findings, and indications for ruxolitinib

		Min.-max.	Median	Mean ± SD/(n, %)
Age		47-83	65.5	65.828±9.37
Gender	Female	-	-	21 (61.8%)
	Male	-	-	13 (38.2%)
Spleen (mm)		110-400	180	196.25±61.03
Liver (mm)		120-220	165	166.91±25.45
WBC (/mm^3)		2300-28900	10000	11740.59±5884.46
Hb (gr/dL)		7.8-18.7	14.5	14.41±2.58
Platelets (/mm^3)		106000-914000	317000	374000±225421.49
Line of treatment		1-3	1.5	1.71±0.8
Ruxolitinib dosage (mg/day)		20-40	30	29.41±7.76
Indication for ruxolitinib	Massive splenomegaly	-	-	12 (35.3%)
	Uncontrolled polycythemia	-	-	5 (14.7%)
	Pruritus	-	-	1 (2.9%)
	Constitutional symptoms	-	-	1 (2.9%)
	HU intolerance	-	-	15 (44.1%)
Follow-up duration (months)		7-61	13.5	16.39±13.75

**Min.: Minimum, Max.: Maximum, SD: Standard deviation WBC: White blood cell, Hb: Hemoglobin, HU: Hydroxyurea

Table 2. Ruxolitinib results, side -effect profile

		n	%
At 3 months			
	Regression of splenomegaly	4	11.7
	Regression of polycythemia	11	32.4
	Both	19	55.9
At 6 months	Regression of splenomegaly	3	8.8
	Regression of polycythemia	10	29.4
	Both	21	61.8
Reason for dose reduction			
	Anemia	2	5.8
	Thrombocytopenia	1	2.9
	Both	1	2.9
Side effects (any of grade 0-5)			
	Weight gain	5	14.7
	Arthralgia	5	14.7
	Constipation	8	23.5
	Diarrhea	2	5.8
	Hypertension	3	8.8
	Pneumonia	6	17.6
	Anemia	7	20.6
	Thrombocytopenia	8	23.5
	Herpes zoster	1	2.9

Table 3. Statistical analysis of ruxolitinib results

			Spleen size	Liver size	Hb (gr/dL)	Leukocytes (/mm³)	Platelets (/mm³)	Follow-up duration	Age	Line of treatment
Reduction in spleen volume at 3 months	(-)	Mean	187.35	158.54	13.87	11419	389769	19	65	2.15
	(+)	Mean	201.76	172.1	14.73	11940	364238	14	66	1.43
	Mann-Whitney U	p	0.958	0.131	0.215	0.929	0.446	0.887	0.817	0.017
Decrease in hematocrit at 3 months	(-)	Mean	241.25	145	13.3	11150	258500	13	63	1.25
	(+)	Mean	190.25	169.83	14.55	11819	389400	16	66	1.77
	Mann-Whitney U	p	0.708	0.077	0.487	0.556	0.438	0.321	0.377	0.232
Reduction in spleen volume at 6 months	(-)	Mean	179.92	167.21	15.04	10814	334263	12	65	1.74
	(+)	Mean	216.93	166.53	13.61	12914	424333	21	67	1.67
	Mann-Whitney U	p	0.068	0.715	0.103	0.435	0.150	0.149	0.305	0.925
Decrease in hematocrit at 6 months	(-)	Mean	237	156	13.44	13084	304200	17	61	1.4
	(+)	Mean	189.22	168.79	14.57	11509	386034	16	67	1.76
	Mann-Whitney U	p	0.48	0.342	0.422	0.865	0.697	0.807	0.137	0.411

Hb: Hemoglobin

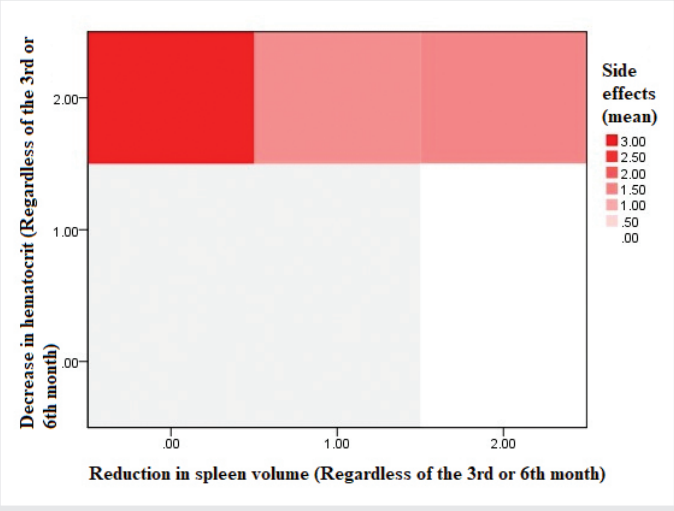

Figure 1. Responses to ruxolitinib and side -effect profile

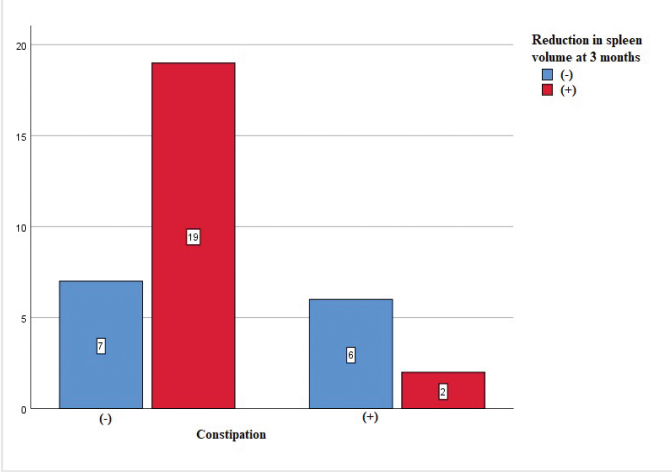

Figure 2. Reduction in spleen volume at 3 months and the presence of constipation

A positive correlation was found between the reduction in spleen volume at 3 months and constipation. In patients with a reduction in spleen volume at 3 months, the rate of constipation was also decreased. Those without a reduction in spleen volume experienced more constipation (chi-square: 5.988, Fisher' exact test: p=0.033) (Figure 2).

Discussion

This study had a multicenter patient group in which the efficacy and side -effect profile of the PV patients were demonstrated, and significant results were demonstrated. Of the patients included in the study, 44.1% switched to ruxolitinib due to HU intolerance. In the RESPONSE 1 trial, this rate was found to be 46.4% (11). In the RESPONSE 2 trial, this rate was 59% (12). The results here were similar in terms of intolerance to HU. While the median age was 65.5 years in this study, it was seen to be 62 and 63 years, respectively, in the RESPONSE 1 and 2 trials. Considering the reasons for switching to ruxolitinib, the most common reason was HU intolerance in this study, and the major reason was the same in the RESPONSE 1 and 2 trials.

Considering the responses observed, the number of patients in which hematocrit control was achieved at 3 months was 30 (88.3%). At 6 months, this number was 31 patients (91.2%). In the RESPONSE 1 trial (11), hematocrit control was achieved in 60% of patients at week 32, while in the RESPONSE 2 trial (12), the rate of patients in which hematocrit control was achieved at week 28 was 62%. In the RESPONSE 1 trial, the proportion of patients with a 35% spleen the volume reduction at week 32 was 38.2%. In this study, the number of patients with a reduction in spleen volume was 23 (67.6%) at 3 months and it was 24 (70.6%) at 6 months. In a retrospective analysis from 2020 (14), the initial rate of palpable splenomegaly in the patients treated with ruxolitinib was 48% compared to 20% at week 32. In this study, the group with a reduction in spleen volume at 3 months had significantly fewer previous lines of treatment (p=0.017). This was a first in terms of demonstrating the relationship between pre-ruxolitinib treatment burden and response. It can be considered that ruxolitinib is highly effective in treatment - naive patients, or patients with a low treatment burden. Here, especially with new risk scoring systems, the early use of ruxolitinib could be planned.

In this study, the most common side effect was constipation (seen in 8 patients, 23.5%). In the RESPONSE 1 trial (11), the most frequent non-hematologic adverse event was headache (16.4%, all grades). It was observed in 7 patients (9%) in the RESPONSE 2 trial and was the most common non-hematological side effect. Another common side effect in this study was thrombocytopenia (seen in 8 patients, 23.5%). This rate was 24.5% in the RESPONSE 2 trial (12). The most common hematological side effect was anemia, at 43.6%, in this study. Moreover, anemia that caused a dose reduction was seen in only 2 patients (5.8%). Cytopenia that caused ruxolitinib discontinuation was not observed.

Ruxolitinib-associated infections constitute an important side-effect profile. In the RESPONSE 1 trial (11), 7 patients experienced herpes zoster infections, the overall rate of infections observed was 41.8%, and the rate of grade-3 and -4 infections was 3.6% in the ruxolitinib arm. In the RESPONSE 2 trial (12), infections (influenza and bronchitis) were observed in 3% of ruxolitinib-treated patients. Only 1 patient experienced a herpes zoster infection in the ruxolitinib arm. In the patient group here, 6 patients had pneumonia (17.6%) and 1 patient had herpes zoster (2.9%).

In the statistical analysis, while the number of side effects was negatively correlated with the reduction in spleen volume (Spearman's rho: -0.365, p=0.034), a decrease in the hematocrit level was positively correlated (Spearman's rho: 0.375, p=0.029). The increase in the number of side effects may have been associated with the defect in the reduction in spleen volume. A positive correlation was found between the reduction in spleen volume and constipation at 3 months. These 2 results are quite significant in terms of revealing the role of PV treatment in the relationship between response and splenomegaly. In a study from 2019 (15), the effect of splenomegaly on overall survival and thrombosis in patients with PV patients was studied. A significant correlation was found with both the thrombosis and the poor overall survival rates. Considering the study results and literature data, splenomegaly in PV may be considered an important risk factor that is central to terms of ruxolitinib response and the side -effect profile.

Study Limitations

There were important limitations to this study. The limited number of patients was the most important limitation point. The fact that the statistically significant results obtained at 3 months could not be obtained at 6 months can be attributed to this reason. In terms of examining the reduction in spleen volume, a single center and uniform evaluation would provide more appropriate results, but the number of patients did not enable subcenter analysis.

Conclusion

The results of ruxolitinib in PV were revealed in this study with real-life data. The most common hematological side effect was thrombocytopenia, and the most common non-hematological side effect was constipation. The number of side effects was negatively correlated with the reduction in spleen volume, whereas it was positively correlated with hematocrit control. In patients with a reduction in spleen volume at 3 months, the rate of constipation was also decreased. This shed light on the use of ruxolitinib in PV and the importance of splenomegaly on studies planned with larger patient groups.

Ethics Committee Approval: The study was approved by the University of Health Sciences Turkey, İstanbul Training and Research Hospital Ethics Committee (approval number: 2904, date: 13.8.2021).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

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Evaluation of YouTube Videos Quality of Pediatric Cardiac Surgery Anesthesia

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ABSTRACT

Introduction: To evaluate the quality of YouTube videos on pediatric cardiac surgery anesthesia (PCSA).

Methods: The keywords including, "PCSA", "pediatric cardiac surgery", and "pediatric anesthesia" were browsed on YouTube between January 1st, 2023 and January 10th, 2023. Video characteristics were recorded. The modified DISCERN instrument, the Global Quality Score (GQS), and the Patient Education Materials Assessment Tool (PEMAT) were used to evaluate the quality of the videos. The videos were divided into two groups as professionals (doctor, nurse, hospital, etc.) and non-professional (patient, non-health institutions, etc.) according to the upload source.

Results: A total 82 of the videos were included in the study. Fifty-six (68.3%) videos were uploaded by professional sources and 26 (31.7%) were by non-professional sources. Statistically, the average like of the videos uploaded by professional sources were significantly higher (64.0 and 29.0, p=0.005). The average number of comments on professionally sourced videos was 46.0, and it was 30.0 for non-professional videos (p=0.015). The GQS was 3.7±1.0 for professional videos and 2.2±0.8 for non-professional videos (p=0.001). The Modified DISCERN score was found to be significantly higher in the professional videos (p=0.001). The PEMAT score was above 70% in 50 (89.3%) videos in the professional video group and 12 (46.1%) videos in the non-professional video group (p=0.001).

Conclusion: Our findings revealed that professional videos about PCSA had significantly higher "likes" number and comments rate and YouTube videos about PCSA, which were shared by professional healthcare providers had significantly higher modified DISCERN score, GQS, and PEMAT score.

Keywords: Cardiac surgery anesthesia, DISCERN, Global Quality Score, pediatric, YouTube

Introduction

Pediatric cardiac surgery anesthesia (PCSA) is performed with increasing frequency due to improvement in pediatric patients' survival with cardiovascular diseases (1). On the other side, PCSA is mostly considered a high-risk morbidity and mortality procedure, and previous studies have emphasized that pediatric patients with cardiovascular disease have a higher risk of possible anesthesia complications, including laryngospasm, bradycardia, brain ischemia, and even death (2). The presence of a chronic and serious cardiovascular pathology of the child, and complications of anesthesia and surgery can cause anxiety in parents. Thus, many parents try to obtain secondary opinions about PCSA from other doctors, other patients' experience, written sources, and social media.

Social media became an important tool for patients and patients' families to obtain knowledge about diseases due to being easily accessible, its free nature, and the presence of multiple resources (3). In addition, Freeman and Chapman (4) analyzed the effect of the source type (being written, verbal or visual) on the researcher, and the authors found that sources with visual content were significantly more preferred by the researchers (4). When it comes to obtaining this kind of information, YouTube is the most used social media application because as it is widely known, the platform has numerous videos that include many kinds of contents. Previous research stated that YouTube become an important source to obtain knowledge about disease symptoms, treatment options, and treatment outcomes. Ergul (5) analyzed the quality of YouTube videos on the surgical treatment of uterine leiomyomas, and the author stated that despite their high ratings, YouTube videos tend to have low quality. In another study, Kumar et al. (6) emphasized that YouTube videos, which consist information about hypertension had misleading data.

Although previous studies have analyzed the reliability of YouTube videos in many medical conditions and treatments, no research investigated YouTube video quality for PCSA. In this study, we evaluated the quality of YouTube videos on PCSA.

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Methods

The keywords including, "PCSA", "pediatric cardiac surgery", and "pediatric anesthesia" were browsed on YouTube between January 1st, 2023, and January 10th, 2023. The videos were sorted by relevance, and were watched by one anesthesiologist and one cardiovascular surgeon. Videos between 1 min and 30 min in length were included in the study. Only videos in the English language were evaluated, and videos in different languages were excluded. Repetitive videos, silent videos, videos in which the video title and the content did not match, and commercial videos were excluded from the study. The videos were divided into two groups as professionals (doctor, nurse, hospital, etc.) and non-professional (patient, non-health institutions, etc.) according to the upload source. URLs of videos, durations, the number of views, likes, dislikes, and comments of the videos were recorded. The target audiences of the videos were recorded as healthcare professionals or patients.

The study was planned after obtaining ethics committee approval from the Bezmialem University Faculty of Medicine Local Ethics Committee (approval number: 2022/462; date: 08.12.2022) and patient consent form was not required because patient data were not used. The modified DISCERN instrument, the Global Quality Score (GQS), and the Patient Education Materials Assessment Tool (PEMAT) were used to evaluate the quality of the videos. Scoring was done separately by the two doctors aforementioned above. If the physicians gave different scores to the videos, the average of the two values was recorded.

The modified DISCERN scale was a simplified version of the 16-question DISCERN tool that developed by Charnock and Shepperd (7), and this inquiry form consists of five questions that can be answered as 1 or 0 (yes or no). Five points indicate the highest score and quality. The GQS is a 5-question tool that evaluates video quality, video streaming, and usability. The tool gives results between 1-5 points, and a high score indicates high video quality (8). The PEMAT is a questionnaire that evaluates the understandability and applicability of the videos. It consists of a total of 17 items, 13 of which are related to intelligibility and 4 are related to applicability. Each item was scored as 1 and 0. If the total score is over 70%, it indicates high quality (9).

Statistical Analysis

The Statistical Package for the Social Sciences version 26 (SPSS IBM Corp., Armonk, NY, USA) program was used. The distribution of variables was evaluated using the Shapiro-Wilk test. Comparison of continuous variables between groups was done with the Independent Student's t-test and Mann-Whitney U test. Categorical variables were grouped and compared using the χ^2 test. A p-value less than 0.05 was considered statistically significant.

Results

A total of 119 videos were evaluated and 82 of the videos were included in the study. Thirty-seven videos were excluded due to being in other languages than English, having durations less than 1 min and more than 30 min, and consisting of inappropriate content (Figure 1).

Data on video features are summarized in Table 1. Fifty-six (68.3%) videos were uploaded by professional sources. The number of views, video lengths, and dislike rates were statistically similar between the groups (p=0.164, p=0.735, p=0.280, and p=0.272, respectively). Statistically, the average like of the videos uploaded by professional healthcare

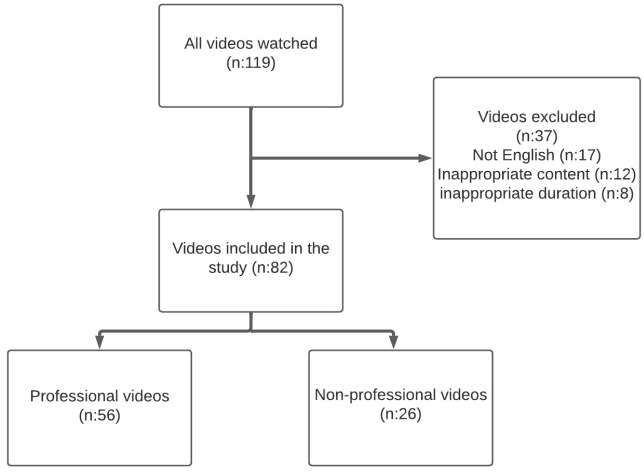

Figure 1. Flow chart

Table 1. Analysis of video features about pediatric cardiac surgery anesthesia by category

Category	Professional	Non-professional	p-value
Number of videos	56 (68.3%)	26 (31.7%)	
Audience interaction parameters*			
Number of views	4328.5 (2518.8-7020.0)	3725.0 (1214.5-5899.3)	0.164
Video length (min)	4.7 (2.5-9.0)	4.2 (2.9-7.5)	0.735
Duration on YouTube (days)	150.0 (120.0-360.0)	120.0 (90.0-240.0)	0.280
Likes	64.0 (15.0-106.8)	29.0 (9.8-59.5)	**0.005**
Dislikes	11.0 (2.3-21.0)	12.0 (1.0-13.8)	0.272
Comments	46.0 (22.3-234.0)	30.0 (12.0-58.0)	**0.015**
Target audience			0.162
For healthcare providers	14 (25.0%)	4 (11.5%)	-
For patients	42 (75.0%)	36 (88.5%)	-

*: Median (interquartile range)

Table 2. Analysis of video quality about pediatric cardiac surgery anesthesia by category

Category	Professional	Non-professional	p-value
Number of videos	56 (68.3%)	26 (31.7%)	-
Global Quality Score**	3.7±1.0	2.2±0.8	0.001
Modified DISCERN score**	3.3±0.9	1.8±1.0	0.001
PEMAT (>70%)	50 (89.3%)	12 (46.1%)	0.001

**: Mean ± standard deviation, PEMAT: Patient Education Materials Assessment Tool

providers were significantly higher than the videos uploaded by non-professional sources (64.0 and 29.0, p=0.005). The average number of comments on professionally sourced videos was 46.0, and it was 30.0 for non-professional videos (p=0.015). The target audience of the videos were patients, rather than healthcare workers in both groups (p=0.162).

A comparison of the mean scores of the video quality scales between the groups is shown in Table 2. The GQS was 3.7±1.0 for professional videos and 2.2±0.8 for non-professional videos (p=0.001). Similarly, the Modified DISCERN score was found to be significantly higher in the professional videos than in the non-professional videos (3.3±0.9 and 1.8±1.0, p=0.001). The PEMAT score was above 70% in 50 (89.3%) videos in the professional video group and 12 (46.1%) videos in the non-professional video group (p=0.001).

Discussion

Easy and free access to social media sources has dramatically modified the patients' way of obtaining information. Today, almost 19 of 20 internet users log in YouTube to watch videos. Thus, we clarified the quality and reliability of YouTube videos on PCSA. In this study, videos about PCSA, which were uploaded by professional sources had a significantly higher "likes" number and comments rate. Moreover, our findings revealed that professional videos about PCSA had significantly higher modified DISCERN core, GQS, and PEMAT score.

The DISCERN score and GQS were defined to evaluate the quality and reliability of videos as an informational tool. Yuksel and Ozgor (10) used the DISCERN score to analyze YouTube videos about pregnancy and COVID-19, and the authors stated that despite the low quality of YouTube videos about pregnancy and COVID-19, videos that were shared by professional healthcare providers had a significantly higher DISCERN score. Another study by Ferhatoglu et al. (11), which analyzed videos about bariatric surgery, found that the DISCERN score of professional videos was significantly higher than videos that were uploaded by non-professional individuals. Moreover, GQS was used by Kılınç and Sayar (12) to analyze the YouTube videos about orthodontics, and the authors found that the YouTube videos about orthodontics that were shared by professional sources had significantly better GSQ. In this research, we found significantly better DISCERN score and GSQ in professional videos, and our results emphasized that professional healthcare workers sharing more videos will lead society to obtain a more accurate information about PCSA.

The PEMAT is defined as an assessment of the applicability and understandability of education tools that are used in patient information. Ji et al. (13) used the PEMAT score to analyze the videos about overactive bladder syndrome, and the authors emphasized that videos that were shared by professional healthcare providers had a significantly higher PEMAT score. In contrast, Wong et al. (14) tried identifying the PEMAT score of YouTube videos about laryngectomy, and the authors found that the PEMAT scores were unsatisfactory for YouTube videos about laryngectomy. Moreover, Wong et al. (14) claimed that most YouTube videos included information that is too complex to be understood by the average viewer, and the authors suggested a revision of YouTube videos about laryngectomy to reach a wider spectrum of audiences. In our study, the PEMAT scores of professional videos were significantly higher.

Comment numbers and "like" numbers are critical for YouTube videos to achieve more interaction. Sevgili and Baytaroglu (15) analyzed that the "like" numbers for YouTube videos about cardiac disease, and the authors found similar "like" number between professional and non-professional videos. Accordingly, the Yuksel and Ozgor (10) study, which investigated YouTube videos about pregnancy and COVID-19, did not find a significant difference in regards of comment number and "like" number between professional and non-professional videos. However, Ergul (5) found a significantly higher comments number of non-professional videos in YouTube videos about uterine leiomyomas. In contrast, we found significantly higher comments number and "-like" number in professional videos about PCSA. This result may have been caused by the relatives of the patients wanting to ask questions to the healthcare professionals while watching the video.

Study Limitations

Our study has some limitation; we only analyzed YouTube videos in the English language. On the other side, researching in more than one language can be confusing and the results could be difficult to explain and understand. Additionally, more than half of the YouTube videos were uploaded in English. Second, we selected three words to search in YouTube, but some users may have uploaded their videos about PCSA without including these three words. Finally, the research included a certain time, but YouTube videos about PCSA are being continuously shared.

Conclusion

Our study demonstrated that the YouTube videos about PCSA are popular and easily accessible sources of information. Moreover, our findings revealed that professional videos about PCSA had significantly higher "likes" number and comments rate and YouTube videos about PCSA, which were shared by professional healthcare providers had significantly higher modified DISCERN score, GQS, and PEMAT score.

Ethics Committee Approval: The study was planned after obtaining ethics committee approval from the Bezmialem Vakıf University Faculty

of Medicine Local Ethics Committee (approval number: 2022/462; date: 08.12.2022).

Informed consent: Patient consent form was not required because patient data were not used.

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Bilateral Idiopathic Granulomatous Mastitis: Outcomes of a Tertiary Hospital

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ABSTRACT

Introduction: Bilateral granulomatous mastitis (BIGM) is a rare bilateral inflammatory pseudotumor of the breast. This study presented the clinical characteristics of BIGM and our treatment results.

Methods: Thirteen patients who met the diagnostic criteria for BIGM were included in the study. The anamnesis and the results of the physical examination, clinical radiology, histopathology, microbiology, and treatment were recorded and analyzed.

Results: The mean age of the patients was 36.23±8.98 years (range: 25 to 53 years). In the first session of the treatment, recurrence was observed in all (100%) patients. Until remission, the distribution of treatment methods in patients with BIGM (n=13) was as follows: 61.5% bilateral combined medical (BCM) treatment, 15.4% bilateral combined medical treatment plus surgery (BCMS), 23.1% unilateral combined medical treatment/unilateral combined medical treatment plus surgery (UCM/UCMS). The distribution of treatment methods in patients (n=26) in the unilateral subgroup was as follows: 73.1% UCM treatment and 26.9% UCMS. There was no significant difference (p>0.05) between the distributions of the patients' combined treatments. However, durations of remission (p=0.018) and follow-up (p=0.037) were significantly longer in young (p=0.037) patients.

Conclusion: Although there is no significant (p>0.05) difference between patients' combined (BCM, BCMS, UCM/UCMS, UCM, UCMS) treatment methods, the first choice for treating patients with BIGM is medical treatment methods. Surgery can be performed for patients who are resistant to medical treatment.

Keywords: Granulomatous mastiti, idiopathic, breast cancer, tuberculosis, disease treatment

Introduction

Non-specific or idiopathic granulomatous mastitis (IGM), which was first introduced by Kessler and Wolloch (1), is a benign chronic inflammatory disease of the breast, characterized by non-caseating granulomas. There is no epidemiological evidence in the literature; however, there are large case series reported from all over the worldwide, mostly from Eurasian countries (1,2). In the differential diagnosis, breast cancers are confused with pyogenic and granulomatous infectious or non-infectious inflammatory diseases of the breast (1,3-6). The underlying etiology is not yet known (2). Definitive diagnosis is made by histopathological evaluation and exclusion of a descriptive etiology (2-6).

IGM without a definitive etiology is theoretically considered sterile. However, empirical antibiotics and/or abscess drainage (percutaneous/incisional) are applied to patients with mastitis and/or the signs of abscess on physical examination. There are options such as conservative treatment, glucocorticoids, methotrexate, colchicine, imuran (azathioprine), non-steroidal anti-inflammatory drugs (NSAID), and surgery (local excision, mastectomy) for treating patients diagnosed with IGM histopathologically (3,4,6-10). Although there are different opinions on the management of the disease, treatment with glucocorticoids (local or systemic) and/or their combination (glucocorticoids plus methotrexate) is still the dominant treatment modality due to the autoimmune and inflammatory origin of IGM (8,9). However, despite different treatment methods available, recurrence rates range, 5% to 50% have been reported in unilateral idiopathic granulomatous mastitis (UIGM). This rate is much higher in patients with bilateral idiopathic granulomatous mastitis (BIGM) (10,11).

As far as we know, the incidence of BIGM is quite rare, except for a few case reports in the literature. This study presents the outcomes of the patients who were treated and followed up with the diagnosis of BIGM between 2010 and 2022.

Methods

This study was conducted in line with the ethical standards defined by the Institutional Research Committee and the Helsinki Declaration dated 1964. Before the study, ethics committee approval was obtained

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from the University of Health Sciences Turkey, İstanbul Training and Research Hospital Local Ethics Committee (approval number: 06, date: 13.01.2023).

Patient selection: The medical data of the patients who were approved with the preliminary diagnosis of BIGM were scanned retrospectively from the archives. Patients (n=13) with a confirmed diagnosis of BIGM were included in the study. Patients with a diagnosis of breast cancer, unilateral IGM, and specific GM were excluded from the study (Figure 1).

Diagnosis, treatment, and follow-up: Medical archives were retrospectively scanned for patients with the preliminary diagnosis of BIGM and patient data including complaints, anamnesis, and the results of the physical examination, hemogram, basic biochemistry test, serology tests, tissue biopsy (tru-cut and/or excisional and/or abscess wall), and cultures; radiological data including breast ultrasonography (USG) and/or magnetic resonance imagining (MRI) to evaluate involvement, and mammography (MMG) results for the patients aged over 40 years.

To confirm the BIGM diagnosis, we checked tissue biopsies (tru-cut and/or excisional and/or abscess wall) collected separately from each breast, lymphocytes with non-caseating granulomas, plasma cells, epithelioid histiocytes rarely accompanied by eosinophils in or around lobules, Langhans giant cells, microorganisms [Gram staining for bacteria, Periodic acid-Schiff (PAS) staining for fungi, Erlich-Ziehl-Neelsen (EZN)/polymerase chain reaction (PCR) for mycobacterium tuberculosis (TBC)] and purified protein derivative (PPD) negativity (<10 mm). Moreover, the negativity of a descriptive etiology (parasitic, fungal, bacterial) was confirmed with the culture inoculation and microscopic examinations of the biopsy samples. The results of the preoperative hemogram, basic biochemistry tests, chest X-ray to exclude sarcoidosis, and serology tests to exclude brucellosis and hepatitis were checked. The final status of the patients who had missing data in the medical archives and/or who could not come for a follow-up visit due to address change was updated by making phone calls.

Until the clinicopathological results of the patients with mastitis symptoms in the breast were obtained, these patients received empirical antibiotherapy, NSAID treatment, and drainage in the presence of an abscess (percutaneous or incisional) for 10 to 20 days. The empirical antibiotherapies of the patients were arranged by a specialist physician at the polyclinic, considering the side effects. Treatment options approved by patients with the clinicopathological diagnosis of IGM were oral systemic glucocorticoids, methotrexate, conservative treatment [antibiotherapy and drainage (incisional/percutaneous) in the presence of abscess], and surgery, respectively. Oral systemic glucocorticoids (0.5 to 1 mg/kg/day) were started in moderate/high doses (7.5 to 100 mg/day) and gradually decreased after treatment, which lasted for a minimum of 3 weeks and a maximum of 8 weeks. One patient was treated with methotrexate at a dose of 15 mg/week administered in 2 divided doses for 6 months. Due to the toxic side effects of methotrexate (hematotoxic/hepatotoxic), hemogram and biochemistry tests were performed every two months to check patients' well-being. During treatment, patients were started on calcium, vitamin D, proton pump inhibitor, and folic acid to eliminate the influence of the side effects of glucocorticoids sand methotrexate. Conservative treatment was followed by empirical antibiotherapy and drainage (percutaneous or incisional) in case of mastitis and/or breast abscess. Conservative treatment was followed by empirical antibiotherapy and drainage (percutaneous or incisional) in case of mastitis and/or breast abscess.

After the treatment, clinical regression of inflammation in the breast, closure of fistulas, regression of existing skin lesions, and/or USG findings, and no recurrence of the disease during the follow-up period were accepted as remission. Resistance to therapy during treatment and/or relapse of the disease after the treatment was considered a recurrence. The subjects whose disease recurred were informed about the treatment options and the treatment they approved was started to be administered till remission was achieved. For patients who achieved remission and who attended regular follow-up visits, follow-up visits were scheduled once every three months for 1 year and then once a year. Follow-up visits include a physical examination and USG examination of the patients. The patients who did not attend their follow-up visits due to a change in their address or restrictions due to the COVID-19 pandemic were called to obtain information about their treatment, follow-up, and final health status.

Study design: Demographic data, physical examination results, and data regarding any diagnosed diseases or concomitant chronic disorders were recorded from the medical archives of the patients. The radiologically measured size/dimensions of the masses were recorded. The treatment options approved by the patients before and after histopathological diagnosis (empirical antibiotherapy plus NSAID) were conservative therapy, glucocorticoids, glucocorticoids plus methotrexate therapy, and resection or mastectomy with intact margins. Treatment, follow-up, and remission durations of the patients were calculated based on the day the first treatment was started. All combined (1st session, 2nd session, 3 sessions, 4th session, etc.) therapies administered to patients before and after clinicopathological diagnosis (empirical antibiotherapy plus NSAID) were analyzed under the groups of bilateral combined medical (BCM), bilateral combined medical plus surgery (BCMS), unilateral combined medical/unilateral combined medical plus surgery (UCM/UCMS), UCM, and UCMS.

Statistical Analysis

We used the descriptive statistics of mean, standard deviation, median, minimum, maximum, frequency, and ratio. Quantitative parametric independent data were analyzed using the Independent samples t-test and ANOVA. Quantitative non-parametric independent data were analyzed using the Kruskal-Wallis and the Mann-Whitney U tests. Quantitative independent data were analyzed using the chi-square test, but when the conditions for the chi-square test were not met, we used the Fisher's exact test. The SPSS 26.0 program was used for the analysis.

Results

The prevalence of BIGM was 3.03% (13/428) in all granulomatous mastitis cases and 3.59% (13/362) in IGM, and the mean age of the patients was 36.23±8.98 (range: 25.0 to 53.0) years. In the bilateral and unilateral evaluations, the mean age of patients who had IGM in the right breast was 36.69±8.97 years (range: 25 to 53 years), of those who had IGM in the left breast was 36.77±9.24-year (range: 25 to 53

years) and 36.77±8.89 years (range: 25 to 53 years). All patients (100%) had a history of giving birth and breastfeeding at least once, and 84.6% of them were premenopausal. Of all patients, 15.4% had a history of tobacco use, 7.7% of trauma, 15.4% of oral contraceptive (OC) use, and 38.5% of them had a history of systemic disease. As a history of systemic disease, two patients had type 2 diabetes mellitus (DM), one patient had hypertension (HT), one patient had DM plus HT, and one patient had Hashimoto thyroiditis (HsT). The patients had no history of exposure to galactorrhea, galactocele, hyperprolactinemia, rheumatology, or tuberculous. The most common symptoms and signs (100%) were breast mass and inflammation. At the time of diagnosis, the mean size of the masses in the right breast was 4.98±2.65 cm and the mean size of the masses in the left breast was 3.38±1.25 cm. The presentation of the disease was bilateral in 46.2% of the patients, in the right breast in 23.1%, in the left breast in 30.8%, and the disorder was synchronous in 53.8% and metachronous in 46.2% (Figure 1, Table 1).

The distribution of the patients according to the radiological examinations applied was as follows: 23.1% bilateral USG, 30.8% bilateral USG and MRI, 15.5% bilateral USG plus MRI plus MMG, and the radiological distribution was different between the sides in 30.8% of the patients. The method used in the histopathological diagnosis of the patients was 30.8% bilateral abscess wall, 53.8% bilateral tru-cut

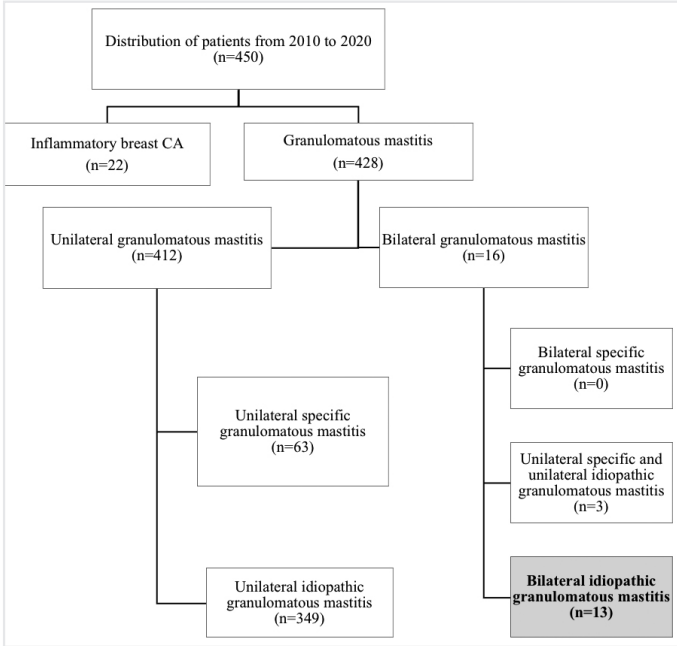

Figure 1. Distribution of patients

Table 1. Demographic and clinicopathological distributions of patients with bilateral idiopathic granulomatous mastitis

			Min.-max.	Median	Mean ± SD-% (n)
Age (year)	B		25.00-53.00	34.00	36.23±8.98
	R		25.00-53.00	35.00	36.69±8.97
	L		25.00-53.00	34.00	36.77±9.24
	U		25.00-53.00	35.00	36.77±8.89
Menopausal status	B/R/L/U	Premenopause			84.6% (11)/84.6% (11)/84.6% (11)/84.6% (22)
	B/R/L/U	Menopause			15.4% (2)/15.4% (2)/15.4% (2)/15.4% (4)
Pregnancy	B/R/L/U	+			100% (13)/100% (13)/100% (13)/100% (26)
Breastfeeding	B/R/L/U	+			100% (13)/100% (13)/100% (13)/100% (26)
Smoking	B/R/L/U	+			15.4% (2)/15.4% (2)/15.4% (2)/15.4% (4)
	B/R/L/U	-			84.6% (11)/84.6% (11)/84.6% (11)/84.6% (22)
Trauma	B/R/L/U	+			7.7% (1)/7.7% (1)/7.7% (1)/7.7% (2)
	B/R/L/U	-			92.3% (12)/92.3% (12)/92.3% (12)/92.3% (24)
OC	B/R/L/U	+			15.4% (2)/15.4% (2)/15.4% (2)/15.4% (4)
	B/R/L/U	-			84.6% (11)/84.6% (11)/84.6% (11)/84.5% (22)
TBC exposure	B/R/L/U	-			100% (13)/100% (13)/100% (13)/100% (26)
Systemic disease	B	+			38.5% (5)
	B	-			61.5% (8)
Size of mass (cm)	R		2.20-12.00	4.50	4.98±2.65
	L		1.90-6.00	3.00	3.38±1.25
	U		1.90-12.00	3.00	4.18±2.19
Mass	B/R/L/U	+			100% (13)/100% (13)/100% (13)/100% (26)
Inflammation	B/R/L/U	+			100% (13)/100% (13)/100% (13)/100% (26)
Fistula	B/R/L/U	+			23.1% (3)/38.5% (5)/53.8% (7)/46.2% (12)
	B/R/L/U	-			38.5% (5)/61.5% (8)/46.2% (6)/53.8% (14)
	B	(+/-)			38.5% (5)
Nipple retraction	B/R/L	+			7.7% (1)/15.4% (2)/23.1% (3)/19.2% (5)

biopsy, 30.8% unilateral abscess wall, or tru-cut biopsy. There was no reproduction in the cultures (aerobic, anaerobic, and fungal cultures). The methods used to confirm the TBC negativity of the patients were as follows: 30.8% bilateral TBC PCR, 46.2% bilateral EZN, 7.7% bilateral PPD, and 15.4% unilateral TBC PCR or EZN (Table 1).

Because to the synchronous/metachronous onset of the disease, there are differences between patients in terms of mean age, total treatment time, total remission time, and total follow-up time. In patients with BIGM, the mean total treatment duration was 32.04±22.00 months (range: 3.37 to 69.90 months), the mean total remission duration was

Table 1. continued

			Min.-max.	Median	Mean ± SD-% (n)
	B/R/L/U	-			69.2% (9)/84.6% (11)/76.9% (10)/80.8% (21)
	B	+/-			23.1 (3)
Erythema nodosum	B/R/L/U	+			7.7% (1)/7.7% (1)/7.7% (1)/7.7% (2)
	B/R/L/U	-			92.3% (12)/92.3% (12)/92.3% (12)/92.3% (24)
Abscess drainage	B/R/L/U	+			53.8% (7)/84.6% (11)/61.5% (8)/73.1% (19)
	B/R/L	-			7.7% (1)/15.4% (2)/38.5% (5)/26.9% (7)
	B	(+/-)			38.5% (5)
Diagnosis of tissues	B/R/L	Abscess wall			30.8% (4)/30.8% (4)/38.5% (5)
	B/R/L	Tru-cut			53.8% (7)/69.2% (9)/61.5% (8)
	B	Abscess wall/ tru-cut			15.4% (2)
TBC test	B/R/L	TBC PCR (-)			30.8% (4)/38.5% (5)/38.5% (5)
	B/R/L	EZN (-)			46.2% (6)/53.8% (7)/53.8% (7)
	B/R/L	Anergic PPD			7.7% (1)/7.7% (1)/7.7% (1)
	B	TBC PCR (-)/EZN (-)			15.4% (2)
Culture	B/R/L/U	(-)			100% (13)/100% (13)/100% (13)/100% (26)
Radiology	B/R/L/U	USG			23.1% (3)/30.8% (4)/38.5% (5)/34.6% (9)
	B/R/L/U	USG + MMG			0.0% (0)/7.7% (0)/0.0% (0)/3.8% (1)
	B/R/L/U	USG + MRI			30.8% (4)/53.8% (7)/46.2% (6)/50.0% (13)
	B/R/L/U	USG + MMG + MRI			15.4% (2)/7.7% (1)/15.4% (2)/11.5% (3)
	B	Other			30.8% (4)
The first side affected	B/R/L				46.2% (6)/23.1% (3)/30.8% (4)
Synchronous/metachronous					53.8%/46.2%
Differences between the sides in terms of duration			0.00-67.73	5.00	10.86±19.36
Total treatment duration (months)	B		3.37-69.90	29.50	32.04±22.00
	R		0.73-66.37	10.06	15.52±17.98
	L		1.00-69.90	29.50	25.87±24.21
	U		0.73-69.90	10.62	20.70±21.55
Total remission duration (months)	B		3.30-88.93	37.87	40.40±27.61
	R		3.30-170.90	50.57	58.84±47.05
	L		6.00-88.93	51.40	46.80±26.96
	U		3.30-170.90	50.98	52.82±38.07
Total follow-up duration (months)	B		9.37-115.97	76.80	76.44±34.83
	R		9.37-177.80	69.40	74.36±45.10
	L		9.37-109.07	80.90	72.67±33.73
	U		9.37-177.80	79.02	73.52±39.59

Min.-max.: Minimum-maximum, SD: Standard deviation, n: Number of patients, OC: Oral contraceptive, TBC: Mycobacterium tuberculosis, B: Bilateral, R: Right, L: Left, U: Unilateral, Positive: +, Negative: -, Unilateral positive (+/-), TBC PCR: Mycobacterium tuberculosis polymerase chain reaction, Tru-cut: Core needle biopsy, EZN: Erlich-Ziehl-Neelsen, PPD: Purified protein derivative, USG: Ultrasonography, MMG: Mammography, MRI: Magnetic resonance imaging

40.40±27.61 months (range: 3.30 to 88.93 months), and the mean total follow-up duration was 76.44±34.83 months (range: 9.37 to 177.77 months). In the unilateral evaluation, the mean total treatment duration was 20.70±21.55 months (range: 0.73 to 69.90 months), the mean total remission duration was 52.82±38.07 months (range: 3.30 to 170.90), and the mean total follow-up duration was 73.52±39.59 months (range: 9.37 to 177.80 months). For patients with IGM in the right breast, the mean total treatment duration was 15.52±17.98 months (range: 0.73 to 69.90 months), the mean total remission duration was 58.84±47.05 months (range: 3.30 to 88.93 months), and the mean total follow-up duration was 74.36±45.10 months (range: 9.37 to 177.77 months). In patients with IGM in the left breast, the mean total treatment duration was 25.87±24.21 months (range: 1.0 to 69.90 months), the mean total remission duration was 46.80±26.96 months (range: 6.0 to 88.93 months), and the mean total follow-up duration was 72.67±33.73 months (range: 9.37 to 177.77 months). In the bilateral evaluation of combined treatments administered to patients before and after clinicopathological diagnosis, recurrence rates in at least one breast were 100%, 92.3%, 30.3%, and 0%, respectively. The unilateral recurrence rate were 96.2%, 69.2%, and 19.2%, respectively. All patients achieved remission after receiving combined therapies. The incidence rate of side effects in patients receiving combined therapy was 69.2% (n=9), and all of them received glucocorticoid therapy (Table 1, 2).

After combined therapies, all patients achieved remission. The distribution of patients receiving bilateral combined therapies was as follows: 61.5% (8/13) BCM, 15.4% (2/13) BCMS, and 23.1% (3/13) BCM/BCMS. The distribution of patients receiving unilateral combined therapies was as follows: 73.1% (19/26) UCM and 26.9% (7/26) UCMS. No

Table 2. Treatment distribution, recurrence and remission

			Right	Left	Unilateral	Bilateral
			% (n)	% (n)	% (n)	% (n)
Before clinicopathological diagnosis	Treatment 1	Antibiotherapy + NSAID	100% (13)	100% (13)	-	-
	Remission		7.7% (1)	0 (0)	3.8 (1)	0 (0)
	Recurrence		92.3% (12)	100% (13)	96.2% (25)	100% (13)
After clinicopathological diagnosis	Treatment 2	Glucocorticoids	30.8% (4)	23.1% (3)	-	-
		Glucocorticoids + methotrexate	7.7% (1)	7.7% (1)	-	-
		Conservative treatment	53.8% (7)	69.2% (9)	-	-
		Surgery	7.7% (1)	0% (0)	-	-
	Remission		30.8% (4)	30.8% (4)	30.8% (8)	7.7% (1)
	Recurrence		69.2% (9)	69.2% (9)	69.2% (18)	92.3% (12)
	Treatment 3	Glucocorticoids	23.1% (3)	46.2% (6)	-	-
		Glucocorticoids + methotrexate	0% (0)	0% (0)	-	-
		Conservative treatment	30.8% (4)	15.4% (2)	-	-
		Surgery	15.4% (2)	7.7% (1)	-	-
	Remission		84% (11)	76.9% (10)	80.8% (21)	69.2% (9)
	Recurrence		15.4% (2)	23.1% (3)	19.2% (5)	30.8% (4)
	Treatment 4	Glucocorticoids	0% (0)	0% (0)	-	-
		Glucocorticoids + methotrexate	0% (0)	0% (0)	-	-
		Conservative treatment	7.7% (1)	15.4% (2)	-	-
		Surgery	7.7% (1)	7.7% (1)	-	-
	Remission		100% (13)	100% (13)	100% (26)	100% (13)
	Recurrence		0% (0)	0% (0)	0% (0)	0% (0)
Side effects	+		-	-	-	69.2% (9)
	-		-	-	-	30.8% (4)
Distribution of combined treatments		Medical treatment	69.2% (9)	76.9% (10)	73.1% (19)	61.5% (8)
		Medical treatment + surgery	30.8% (4)	23.1% (3)	26.9% (7)	15.4% (2)
		Medical/medical + surgery	-	-	-	23.1% (3)

NSAIDs: Non-steroidal anti-inflammatory drug

significant difference was observed between the total durations of the combined treatments (BCM, BCMS, UCM/UCMS, UCM, UCMS). However, in the analysis of unilateral subgroups, patients who received UCMS had significantly longer total remission time (p=0.018) and total follow-up time (p=0.037), and the patients were young (p=0.037) (Table 2-4).

Discussion

Granulomatous mastitis is divided into two main groups depending on the etiological factor: specific or non-specific (idiopathic). The term "idiopathic" is used for cases where a local or systemic etiology affecting the breast is not defined (2). IGM is a rare benign chronic disease of the breast that clinically and radiologically simulates breast carcinoma (1,2). The disease can occur in any quadrant or different quadrants of the unilateral (right or left) breast or it can develop bilaterally. The incidence of BIGM is very rare and has been reported in the literature to vary from 3% (4/152) to 7% (49/720) (6,12). In our study, the prevalence of IGM was 3.03% (13/428) in all granulomatous mastitis and 3.59% (13/362) in IGM; these results are similar to those in the literature.

Skin thickening, distortion, calcification, lymphadenomegaly, irregular focal mass, or diffuse asymmetry can be seen in MMG. However, MMG may not indicate any signs when the breasts are dense. In cases of diffuse disorder or where MMG/USG is insufficient, MRI can be preferred. IGM is frequently seen in premenopausal young patients presenting with signs of breast mass and mastitis. Therefore, the first is examined with USG rather than MMG and MRI. Radiologically, USG can detect inflammation, abscess, tunnel, sinus, and mass size. Also, USG is beneficial for guiding biopsy and during follow-up after treatment. However, none of the radiological methods can clearly distinguish the malignancy (6,13,14). Similar to the literature, USG was the first radiological method preferred in all patients (100%). The additional radiological techniques applied were MMG for patients aged 40 years and over and MRI when USG is insufficient to make a definitive diagnosis.

Table 3. Comparison of bilateral combined treatment methods

		Bilateral medical treatment		Bilateral medical treatment plus surgery		Medical treatment/surgery plus Medical		
		Min.-max.	Mean ± SD/% (n)	Min.-max.	Mean ± SD/% (n)	Min.-max.	Mean ± SD/% (n)	p
Age		27.0-53.0	38.75±10.14	25.0-29.0	27.00±2.83	33.0-39.0	35.67±3.06	0.272[A]
The first side affected	B/R/L		62.5% (5)/12.5% (1)/25% (2)		50% (1)/50% (1)/0% (0)		0% (0)/33.3% (1)/66.7% (2)	0.291χ^2
Synchronous/ metachronous			75% (6)/25% (2)		50% (1)/50% (1)		0% (0)/100% (3)	0.084χ^2
Premenopause/ menopause	+		75% (6)/25% (2)		100% (2)/0% (0)		100% (3)/0% (0)	0.478χ^2
Pregnancy	+		100% (8)		100% (2)		100% (3)	1.00χ^2
Breastfeeding	+		100% (8)		100% (2)		100% (3)	1.00χ^2
Smoking	+/-		25% (2)/75% (6)		0% (0)/100% (2)		0% (0)/100% (3)	0,478x^2
Trauma	+/-		0% (0)/100% (8)		0% (0)/100% (2)		33.3% (1)/66.7% (2)	0.164x^2
OC	+/-		12.5% (1)/87.5% (7)		0% (0)/100% (2)		33.3% (1)/66.7% (2)	0.561χ^2
TBC exposure	-		100% (8)		100% (2)		100% (3)	1.00χ^2
Mass	+		100% (8)		100% (2)		100% (3)	1.00χ^2
Inflammation	+		100% (8)		100% (2)		100% (3)	1.00χ^2
Fistula	+/-/(+/-)		25% (2)/25% (2)/50% (4)		50% (1)/50% (1)/0% (0)		0% (0)/66.7% (2)/33.3% (1)	0.483x^2
Nipple retraction	+/-/(+/-)		12.5% (1)/75% (6)/12.5% (1)		0% (0)/50% (1)/50% (1)		0% (0)/66.7% (2)/33.3% (1)	0.749χ^2
Erythema nodosum	+/-		12.5% (1)/100% (7)		0% (0)/100% (2)		0% (0)/100% (3)	0.713χ^2
Abscess drainage	+/-/(+/-)		62.5% (5)/12.5% (1)/25% (2)		0% (0)/0% (0)/100% (2)		66.7% (2)/0% (0)/33.3% (1)	0.371χ^2
Total treatment duration (months)		3.37-69.90	32.12±26.66	17.50-29.50	23.50±8.49	20.93-53.33	37.51±16.21	0.813[A]
Total remission duration (months)		3.30-63.47	26.46±23.83	51.40-88.93	70.17±26.54	23.47-77.70	49.73±27.16	0.138[A]
Total follow-up duration(months)		9.37-107.77	61.58±38.66	80.90-106.43	93.67±18.06	68.97-115.97	87.24±25.18	0.390[A]

χ^2: Pearson chi-square/Fisher's exact test, [A]: One-Way ANOVA, SD: Standard deviation, n: Number of patients, OC: Oral contraceptive, B: Bilateral, R: Right, L: Left, U: Unilateral, Positive: +, Negative: -, Unilateral positive (+/-)

Table 4. Comparison of unilateral combined treatment methods

Min.-max.		Unilateral medical treatment		Unilateral medical treatment plus surgery		p
		Mean ± SD-% (n)	Min.-max.	Mean ± SD-% (n)		
Age (year)		27.0-53.0	38.95±9.06	25.0-39.0	30.86±5.18	**0.037[t]**
Premenopause/menopause	+		78.9% (15)/21.1% (4)		100% (7)/0% (0)	0.546[x2]
Breastfeeding	+		100% (19)		100% (9)	1.000[x2]
Lactation	+		100% (19)		100% (9)	1.000[x2]
Smoking	+/-		21.1% (4)/78.9% (15)		0% (0)/100% (7)	0.546[x2]
Trauma	+/-		5.3% (1)/94.7% (18)		14.3% (1)/85.6% (6)	0.474[x2]
OC	+/-		15.8% (3)/84.2% (16)		14.3% (1)/85.7% (6)	1.000[x2]
TBC exposure	-		100% (19)		100% (19)	1.000[x2]
Right/Left			47.4% (9)/52.6% (10)		57.1% (4)/42.9% (3)	1.000[x2]
Size of mass (cm)		1.9-12.0	4.27±2.43	2.6-7.0	3.94±1.49	0.735[M]
Mass	+		100% (19)		100% (7)	1.000[x2]
Inflammation	+		100% (19)		100% (7)	1.000[x2]
Fistula	+/-		42.1% (8)/57.9% (11)		57.1% (4)/42.9% (3)	0.665[x2]
Nipple discharge	+/-		15.8% (3)/84.2% (16)		28.6% (2)/71.4% (5)	0.588[x2]
Erythema nodosum	+/-		10.5% (2)/89.5% (17)		0% (0)/100% (7)	1.000[x2]
Abscess drainage	+/-		73.7% (14)/26.3% (5)		71.4% (5)/28.6% (2)	1.000[x2]
Total treatment duration (months)		0.73-69.9	22.76±24.25	6.33-31.93	15.10±10.99	0.866[M]
Total remission duration (months)		3.3-108.0	41.09±29.54	48.03-170.9	84.66±42.45	0.018[M]
Total Follow-up Duration (months)		9.37-109.07	63.85±36.60	61.13-177.80	99.76±37.59	0.037[t]

X^2: Pearson chi-square/Fisher's exact test, [t]: Independent samples t-test, M: Mann-Whitney U test, SD: Standard deviation, n: Number of patients, OC: Oral contraceptive, B: Bilateral, R: Right, L: Left, U: Unilateral, Positive: +, Negative: -, Unilateral positive (+/-)

Due to the similarity of signs and symptoms, breast cancers, sarcoidosis, Wegener's granulomatosis, foreign body granulomas, breast infections (bacterial, fungal, parasitic), and breast tuberculosis should be considered in the differential diagnosis (1,2,6,15-17). The diagnosis of BIGM is confirmed by the presence of non-caseating sterile granulomas containing epithelioid histiocytes, giant cells, plasma cells, and eosinophils within the breast lobules on the biopsy (excisional/abscess wall/tru-cut) sample collected from the breast tissue. Tissue biopsies were evaluated with gram staining for bacteria, PAS for fungi, and hematoxylin-eosin for malignancy in the differential diagnosis. Furthermore, foreign bodies may be detected in the histopathological investigation. To exclude TBC, the presence of caseating necrosis in granulomas was tested using EZN staining, PCR, and PPD. For microbiological data, the culture tests of the additional biopsies were performed to confirm the sterility (1,5,6,14-16).

In the literature, there are many hypotheses on the pathophysiology of the disease. The first of these hypotheses is the secretion theory, which includes increased ductal permeability caused by intraductal accumulated secretions or inflammation following ductal epithelial damage. The second is the ethnic hypothesis, based on geography and ethnicity, as the disease occurs in the Mediterranean region and developing Asian countries. The third one is the autoimmune hypothesis, which is accepted due to the high T-lymphocyte count in immunohistochemical studies, its positive response to glucocorticoids or immunosuppressive treatments, and its similarity to diseases such as granulomatous thyroiditis and prostatitis. It is therefore believed that hormonal imbalance, autoimmunity, alpha-1 antitrypsin deficiency, breast trauma, smoking, ductal ectasia, hyperprolactinemia, and the use of OC play a role in the etiology of IGM. However, a definite association has not been demonstrated (2,6,7,12,17-19).

To the best of our knowledge, the incidence of BIGM is quite rare, and the last study we can make a comparison to is from 2016. In this study, patients had a history of parity (100%), lactation (100%), smoking (60%), OC use (10%), exposure to TBC (30%) (EZN negative), and systemic disease (20%), but no patient (0%) had a history of trauma. Of the patients who had a history of systemic disease, one patient had HsT and the other patient had DM. The authors state that there was an association between BIGM and giving birth, breastfeeding, and smoking. However, they did not find an association between BIGM and local trauma or OC use (11). Another study conducted by the same authors in 2021 indicated that the disease is seen in women of childbearing potential who have a history of pregnancy and breastfeeding and that it is not associated with nicotine addiction (6). In our study, the patients had a history of giving birth (100%), breastfeeding (100%), smoking (15.4%), OC use (15.4%), trauma (7.7%), and systemic disease (38.5%). The patients with a history of systemic disease had DM (n=2), HT (n=1), DM plus HT (n=1), and HsT (n=1). None of the patients had a history of hyperprolactinemia, galactorrhea, rheumatologic disease, or exposure to TBC. In this study, we also observed that the incidence of BIGM was higher in patients with a history of pregnancy and breastfeeding.

Although UIGM has been reported in a wide age range (11 to 83 years), it is most commonly seen in the third and fourth decades (2,6,14). The most common symptoms that patients had at presentation to the hospital are local or widespread inflammation accompanied by a mass and redness in the breast. In the literature, the distribution of these symptoms in UIGMs is as follows: 83% mass, 42% abscess, 6.6% erythema nodosum, and 30% fistula (12,18-20). The distribution of these symptoms in the BIGM (n=0) is as follows: 100% mass, 70% inflammation, 90% abscess, and 70% fistula. Eighty percent of the patients (n=10) were premenopausal and the mean age was 38±8.3 years (range: 29 to 52 years) (11). As can be seen, BIGMs were complicated mastitis cases with a higher rate of abscesses and fistulas (8,18). In our study, 84.6% of the patients with BIGM (n=13) were premenopausal and their mean age was 36.23±8.89 years (range: 25 to 53 years). The most common signs in all patients (100%) were breast mass (the mean size of the masses in the right breasts was 4.98±2.65 cm, in the left breasts was 3.38±1.25 cm and the mean unilateral mass size was 4.18±2.19 cm) and inflammation. Patients had in at least one breast 61.6% (bilateral: 23.1%/unilateral: 38.5%) fistula, 92.3% (bilateral: 53.8%/unilateral: 38.5) abscess, 30.8% (bilateral: 7.7%/unilateral: 23.1%) nipple retraction, 7.7% erythema nodosum. In the unilateral evaluation, these rates were lower, with 46.2% fistula, 73.1% abscess, 19.2% nipple retraction, and 7.7% erythema nodosum. However, the incidence of complicated mastitis was high in subjects with BIGM in both bilateral and unilateral analyses.

From the day it was introduced until 1980, aggressive surgical treatment methods were used for treating IGM. After 1980, aggressive surgical treatment methods were replaced by glucocorticoids, methotrexate, colchicine, Imuran(azathioprine), NSAIDs, and conservative treatment methods (2-4,6,7-10,21). Today, the first choice for treating UIGM and BIGM is medical treatment, and surgery is performed in selected resistant cases (12,22,23). Although the disease is considered sterile, drainage (incisional or percutaneous) and empirical antibiotic therapy are recommended in patients with the signs of mastitis and/or abscess, since the disease cannot be differentiated from pyogenic mastitis at the beginning (6,12). In the study, in which 93% of the patients (n=720) had UGM, the distribution of treatment methods preferred was 36% medical, 8% surgery, and 56% combination of medical and surgery. Seventeen patients had disease recurrence (12). In a study conducted in 2016, 100% of patients with BIGM (n=10) received empirical antibiotic therapy and 90% of them underwent abscess drainage. However, all of these patients had disease recurrence. After BCM therapies were administered following recurrence, 90% of the patients achieved remission for 21 months (range, 11 to 26 months). In our study, the distribution of treatment options applied for the patients (n=13) was 61.5% BCM, 15.4% BCMS, and 23.1% BCMS/BCM treatment. The distribution of patients receiving unilateral therapies was 73.1% (19/26) UCM and 26.9% (7/26.9) UCMS. While recurrence (100%) was observed in at least one breast of the patients (n=13) after the first session of treatment, the recurrence rate was 92.3% in the unilateral subgroup (n=26) analysis. After combined therapies, all patients achieved remission. There was no significant difference (p>0.05) between the groups regarding total treatment duration (BCM, BCMS, UCM/UCMS, UCM, UCMS). Since the patients who received UCMS treatment were younger patients that fallen in the baseline section (12-year cross-section) of the study, the total durations of remission (p=0.018) and follow-up (p=0.037) were significantly longer (p=0.037) in the analysis of unilateral subgroups. However, a limitation of the study was that young patients who were resistant to medical treatments preferred surgery.

Study Limitations

Our study has some other limitations. 1) Although our study could not provide strong evidence due to the rarity of BIG patients, limited sample size, and retrospective design, it is one of the most comprehensive studies to date revealing the clinical features of BIGM in the literature. 2) Etiological reasons for preferring surgical treatment in young patients who were resistant to medical treatment was the gray zone of the study.

Conclusion

The clinicoradiological diagnosis of BIGM consisting of complicated mastitis with a high recurrence rate is made as in UIGM. However, a descriptive etiology is excluded with the collection of tissue biopsies from each breast separately for histopathological and microbiological diagnosis. Although there is no significant (p>0.05) difference between the total combined (BCM, BCMS, UCM/UCMS, UCM, UCMS) treatment durations of the patients, the first choice for treating patients with BIGM is medical treatment methods. Surgery can be performed for patients who are resistant to medical treatment.

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Does Pain Following Laparoscopic Cholecystectomy Differ in Diabetics?

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ABSTRACT

Introduction: Individuals with diabetes differently respond to painful stimuli in the postoperative period than non-diabetic patients. This variation causes a scorching, tingling, numbness, or even hyperalgesic sensation due to a change in sensory perception. During routines sometimes we donot remember how patients' pain differ in some situations. Diabetes mellitus is an important disease that we must remember when we plan our postoperative pain relief plan. This study aimed to assess the pain levels and analgesic requirements of individuals with diabetes following laparoscopic cholecystectomy (LC).

Methods: Patients with symptomatic gallstones and cholecystitis underwent elective LC between April 2019 and April 2020. Patients' records were prospectively registered and retrospectively received from the patients' record system on the postoperative course. A total of 70 cases were evaluated within the scope of the study, 35 (50%) of whom were diagnosed with diabetes and 35 (50%) were control subjects.

Results: When the results were examined, it was determined that there was a difference between the two groups that were statistically significant at the 5th and 10th minutes of the bispectral index ($p<0.05$). When the two groups were compared, patients in the control group had more pain on the postoperative course and mean score of 8 ($p=0.049$), 7 ($p=0.016$), 5 ($p=0.02$), 4 ($p=0.032$), 2 ($p=0.014$) respectively 1, 2, 4, 8, 12, 24 hours on the numeric rating scale, $p<0.001$). In the multivariable analysis, the group with diabetes was shown to be strongly related with a significantly lower dosage of tramadol consumption compared to the control group.

Conclusion: According to our findings, the patient with diabetes who underwent LC experienced less postoperative discomfort than those without diabetes. In contrast to the previous studies, our findings show that patients with diabetes have less post-operative pain and require fewer analgesics.

Keywords: Diabetes mellitus, cholecystectomy, postoperative pain

Introduction

Laparoscopic cholecystectomy (LC) is the gold standard method for symptomatic patients; it has several benefits over the open approach, including reduced pain and quicker recovery (particularly in the first 24 hours), as well as a shorter length of hospital stay (1,2).

Although one of the most common surgical procedures, research on postoperative pain management for cholecystectomy is still underway (3).

When adequate postoperative pain management is not achieved, it poses a serious risk for patients (4). Inadequate pain management delays oral intake and mobilization and increases the likelihood of persistent postoperative pain (5,6).

A higher [American Society of Anesthesiologists (ASA) classification] score, younger age, preoperative discomfort, female gender, and the anatomic site of surgery are some published risk variables that indicate a higher likelihood of postoperative pain (7,8).

Individuals with diabetes differently respond to painful stimuli in the postoperative period than non-diabetic patients. This variation causes a scorching, tingling, numbness, or even hyperalgesic sensation due to a change in sensory perception. An altered perception of pain results in a longer recovery time, which typically requires multimodal and long-term pain management (9-11).

We used a numeric rating scale (NRS) to evaluate the degree of postoperative pain. NRS is a system that scores pain from 0 to 10. A tolerable pain threshold is assessed to be NRS=3, while individuals score

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NRS >4 are considered to be in moderate to severe pain and hence in need of further analgesics (12,13).

Enhanced Recovery After Surgery (ERAS) colorectal surgery guidelines recommend opioid-sparing multimodal analgesia, including paracetamol in conjunction with epidural analgesia, after open surgery (14,15).

After undergoing LC in patients with diabetes, this study aimed to assess their levels of pain and assess their need for analgesic medication.

Methods

Study Design

Patients with symptomatic gallstones and cholecystitis underwent elective LC at University of Health Sciences Turkey, İstanbul Training and Research Hospital, between April 2019 and April 2020. Patients' records were prospectively registered and retrospectively received from the patient records system in the postoperative course.

The study enrolled patients scheduled for elective LC between the ages of 23 and 69, with an ASA class of I-II. The study included 70 patients, including 35 with controlled diabetes and 35 without diabetes. The patients were excluded from the study with liver cirrhosis, concurrent common bile duct stones, acute pancreatitis, past medical history of analgesic allergy, and conversion to open cholecystectomy. Before beginning the operation, all the participants were given information on the procedure, and their written consent was obtained. Ethical committee approval was obtained from the Local Ethics Committee of University of Health Sciences Turkey, İstanbul Training and Research Hospital (approval number: 188, date: 17.06.2022). All patients were discharged from the hospital the day following the operation as part of the standard procedure, and they were followed up at an outpatient clinic one week and two months after surgery.

An intravenous patient-controlled analgesia (PCA) device (CADD-Legacy Patient Control Analgesia Device Model 6300; Ambulatory Infusion Pump Smith Medical ASD, Dublin, OH, USA) was used in all patients for postoperative pain management. All patients were informed about how to use the device and how to control the pump before and after the operation. Each pump contained 300 mg tramadol diluted in 100 mL of 0.9% saline solution. The PCA device was set to deliver a continuous infusion rate of 10 mg per hour, with a bolus dose of 10 mg and a lock-out interval of 15 minutes.

The primary outcome of the study was the cumulative dosage of tramadol, whereas the secondary outcome was the mean pain intensity 24 h after surgery. Pain intensity was assessed with the NRS by participants 0, 1, 2, 4, 8, 12, 16, and 24 h after surgery. On a scale from 0 to 10, with 0 signifying no pain at all and 10 reflecting the greatest suffering possible, patients were asked to assess their pain severity. The postoperative pain scores were assessed and recorded by the researchers. The target for postoperative analgesia management was an NRS score of 3 or less. On the day of surgery, the pain management protocol called for administrating opioids intravenously through a PCA device. During treatment with the PCA device, rescue analgesia in the form of 1 gram of paracetamol was administered when analgesia was insufficient.

Age, sex, body mass index (BMI), a diagnosis of diabetes mellitus (DM), and ASA class were the clinical factors that were considered to be baseline variables. The postoperative course, the preoperative treatment plan, the length of hospital stay, and any complications that arose were all recorded.

Statistical Analysis

The patient data gathered for the study were analyzed using the IBM Statistical Package for the Social Sciences (SPSS 23.0-IBM, NY, USA) for Windows 23.0 software. For categorical data, frequency and percentage were provided; for continuous data, median, minimum, and maximum descriptive values were provided. Using the Kolmogorov-Smirnov test, the compatibility of the data with the Gaussian distribution was determined. The "Mann-Whitney U test" was employed to compare groups, while the "chi-square or Fisher's exact test" was used to compare categorical variables. When the p-value was less than 0.05, the results were considered statistically significant.

Results

A total of 70 cases were evaluated within the scope of the study, 35 (50%) of whom were diagnosed with diabetes and 35 (50%) were control subjects. Table 1 shows the distribution of the demographic characteristics of the cases included in the evaluation. As shown in Table 1, there was a statistically significant difference between the age of the two groups ($p<0.05$). Patients in the diabetes group were older than the control group. There was no statistically significant difference between the two groups in terms of gender, BMI, and operation time ($p>0.05$).

Table 2 shows the distribution of the participants' bispectral index and oxygen saturation values at the start of the operation and every five minutes. When the table was examined, a statistically significant difference between the two groups was observed at the 5th and 10th minutes of the bispectral index ($p<0.05$). The bispectral index of the

Table 1. Demographic variables of patients

	Total	Diabetes group, (n=35)	Control group, (n=35)	p-value
	Median (min.-max.) or n (%)	Median (min.-max.) or n (%)	Median (min.-max.) or n (%)	
Age, year	**52 (23-69)**	**55 (35-68)**	**47 (23-69)**	**0.016**
Gender				0.332
Woman	41 (58.6)	23 (65.7)	18 (51.4)	
Man	29 (41.4)	12 (34.3)	17 (48.6)	
BMI, kg/m^2	29.3 (22.3-39.4)	29.3 (23-39.4)	29.2 (22.3-37.7)	0.888

min.: Minimum, max.: Maximum, BMI: Body mass index

control group was higher than that of the diabetes group. In terms of oxygen saturation, there was a difference between the two groups at the start and the 20-minute, with the control group having higher values than the diabetes group. There was no statistically significant difference between the two groups in the measurements of all other parameters (End-tidal CO_2, heart rate, blood pressure) every five minutes ($p>0.05$).

Table 3 shows the participants' post-operative medication dosages and pain severity distribution. The table revealed no statistically significant difference between the two groups in terms of pain or vomiting ($p>0.05$). When the two groups were compared, the control group's patients experienced more pain during the postoperative period, scoring a mean of 8 ($p=0.049$), 7 ($p=0.016$), 5 ($p=0.02$), 4 ($p=0.032$), and 2 ($p=0.014$) on the NRS, respectively, at 1, 2, 4, 8, 12, and 24 h. This difference was significant ($p<0.001$) (Table 3).

While there was a statistically significant difference in pain intensity over time and additional analgesic dosage between the two groups, the control group's pain severity was higher than the diabetes group in NRS scores ($p>0.05$).

The intensity of pain was the highest immediately following surgery and gradually decreased. In multivariable analysis, the group with diabetes was found to be strongly related to a much lower tramadol dose than the control group. In terms of additional analgesic dosage, while the control group used more than the diabetes group, the difference was not statistically significant ($p>0.05$).

In this study, the control group's age was statistically significantly lower and the NRS score was higher than the group with diabetes's. Covariance analysis was used to see if there was any difference in pain severity between the groups in terms of the effect of age and diabetes on pain severity. It was discovered that diabetics had lower NRS scores and

Table 2. Perioperative BIS and SpO_2 parameters

Characteristics (n=70)	Total	Diabetes group, (n=35)	Control group, (n=35)	p-value
	Median (min.-max.) or n (%)	Median (min.-max.) or n (%)	Median (min.-max.) or n (%)	
BIS (0. minute)	98 (90-99)	98 (90-98)	98 (92-99)	0.322
BIS (5. minute)	**47.5 (38-70)**	**44 (38-62)**	**48 (39-70)**	**0.021**
BIS (10. minute)	**46 (39-58)**	**45 (39-55)**	**48 (40-58)**	**0.044**
BIS (15. minute)	47 (39-60)	46 (40-60)	48 (39-58)	0.258
BIS (20. minute)	46 (40-61)	45 (40-61)	48 (40-60)	0.364
BIS (25. minute)	48 (40-60)	48 (40-59)	50 (40-60)	0.676
BIS (30. minute)	48 (40-60)	46 (40-59)	48 (40-60)	0.279
BIS (35. minute)	50 (40-60)	48 (40-60)	50.5 (40-56)	0.186
BIS (40. minute)	48 (40-70)	47 (41-70)	50 (40-58)	0.266
BIS (45. minute)	47 (40-67)	46 (40-67)	47.5 (40-59)	0.308
BIS (50. minute)	47 (39-55)	46 (40-55)	48 (39-55)	0.341
BIS (55. minute)	47 (40-54)	46 (41-50)	49 (40-54)	0.060
BIS (60. minute)	47.5 (40-55)	46 (41-55)	49 (40-52)	0.737
SpO_2 (0. minute)	**99 (95-100)**	**98 (95-100)**	**99 (96-100)**	**0.020**
SpO_2 (20. minute)	**99 (96-100)**	**99 (96-100)**	**99 (98-100)**	**0.021**

min.: Minimum, max.: Maximum, BIS: Bispectral index

Table 3. Postoperative pain scores and analgesic consumption amounts

Characteristics (n=70)	Total	Diabetes group (n=35)	Control group, (n=35)	p-value
	Median (min.-max.) or n (%)	Medyan (min.-max.) or n (%)	Medyan (min.-max.) or n (%)	
Total tramadol dose (mg)	**241 (135-300)**	**225 (160-300)**	**260 (135-300)**	**0.002**
Rescue analgesic consumption (n, %)				
1. hour	24 (34,3)	8 (22,9)	16 (45,7)	0.078
2. hour	10 (14,3)	2 (5,7)	8 (22,9)	0.084
8. hour	1 (1,4)	1 (2,9)	0 (0,0)	1,000
NRS 1. hour	**8 (0-10)**	**8 (0-10)**	**8 (4-10)**	**0.049**
NRS 2. hour	**6 (0-10)**	**5 (0-10)**	**7 (4-10)**	**0.016**
NRS 4. hour	**4 (0-10)**	**4 (0-9)**	**5 (0-10)**	**0.002**
NRS 8. hour	**2 (0-9)**	**2 (0-9)**	**4 (0-8)**	**0.032**
NRS 12. hour	**0 (0-7)**	**0 (0-7)**	**2 (0-6)**	**0.014**

min.: Minimum, max.: Maximum, NRS: Numeric rating scale

analgesic requirements regardless of age. Univariate analysis found no link between gender, BMI, or ASA class and postoperative pain.

Discussion

According to the findings, the patient with diabetes who underwent LC experienced less postoperative discomfort than those without diabetes. It was discovered that in both groups, the analgesic required was significant in the first 12 hours and that there was no further analgesic requirement after 12 hours.

Multimodal analgesia, particularly in the first 12 h, and then further analgesic medication as needed can be used to address post-operative pain in these patients when the ERAS protocol is used. Thus, the best balance in terms of cost-effectiveness is reached with the use of fewer analgesics, further decreasing postoperative problems and facilitating early recovery.

Despite the administration of the same analgesic regimen, there was considerable inter-individual heterogeneity in pain severity following each surgical method. Patients with diabetes' responses to painful stimuli differed from normal patients in the postoperative period. There are various findings regarding the level of postoperative pain after various surgical procedures performed in patients with diabetes. Berglund et al. (9) found that patients with diabetes had more pain (as measured by the visual analog scale for pain) and poorer functional outcomes 6 months and 1 year after arthroscopic rotator cuff surgery. Rajamäki et al. (16) identified DM as an independent predictor of persistent pain following hip or knee replacement. Another study by Reinstatler et al. (11) on patients with diabetes who had received inflatable penile prosthesis surgery due to erectile dysfunction has revealed that significant postoperative penile pain was more common in patients with hemoglobin A1c levels greater than 8% and resulted in more unplanned visits after discharge period.

Some medical conditions, such as diabetes, have been linked to increased narcotic dosage due to changes in pain perception compared to patients without such conditions.

Furthermore, up to one-fourth of patients with diabetes have co-occurring health problems such as cardiovascular disease, major depression, rheumatoid arthritis, and peripheral neuropathy (17). Neuropathy alters sensory perception and can cause sensations such as burning, tingling, numbness, and even hyperalgesia (18).

In contrast to the previous studies, our findings show that patients with diabetes have less post-operative pain and require fewer analgesics. This finding supports the hypothesis that postoperative pain levels may differ depending on the anatomical location, as stated in the literature (8). High ASA score, preoperative discomfort, young age, female gender, and anatomic site of surgery are all characteristics linked to higher postoperative pain and have been the subject of published research (7,8).

There are reports with findings consistent with our research. Lindberg et al. (19) observed, for example, that DM was related to decreased postoperative pain. Patients with diabetes experienced less postoperative pain than those without diabetes, which was linked to reduced sensation brought on by diabetic peripheral neuropathy, according to previous studies of patients undergoing heart surgery (20). Several factors, such as organ-specific surgery, may explain the variations in results. Approximately 30% of diabetics suffer from neuropathic pain (21). Nevertheless, diabetic neuropathy is associated with diminished sensory input, which may explain why our patients with diabetes experienced less postoperative pain (22).

After surgery, younger patients reported increased pain. According to a systematic review, there is a negative relationship between age and pain intensity, and postoperative analgesic use (7). Tighe et al. (8) observed that younger age was related to higher postoperative pain, on average by a half NRS unit every 10 years, when they retrospectively analyzed postoperative pain in various surgeries within the first 24 h following surgery. Lautenbacher et al. (23) discovered in a meta-analysis of the relationship between age, pain perception, and pain tolerance that mental pain perception does not change with age, but that older adults lose pain sensitivity due to an increase in pain thresholds. Opioid renal clearance reduced with age, which may lead to decreased pain in elderly people (24).

According to the current findings, there is already a need for greater analgesics to be administered to young patients on the day of surgery. Recent research indicated that older patients require a lower dosage of tramadol for postoperative pain management than younger patients do. These findings are in line with the findings of a study that showed postoperative pain ratings reduced with increasing age (25).

According to our findings, the mean age of those in the control group was significantly younger than those in the diabetes group, and mean-NRS-scores were also significantly higher, as reported in previous studies. When a statistical analysis was performed, it sufficiently said that the group with diabetes's NRS scores and analgesic requirements were lower, regardless of age.

The latest ERAS guidelines for postoperative analgesia following colorectal surgery state that the aim is to avoid opioids and use multimodal analgesia in conjunction with epidural analgesia (in open surgery) where needed (15). We would like to add to the ERAS recommendations that young patients require greater analgesia, and analgesia should be tailored because it is difficult to predict the intensity of postoperative pain..

Female sex and a high ASA class have been highlighted in various articles as reasons for postoperative pain (8,26,27).

Study Limitations

Our study had some limitations. It is single-center, and a relatively small number of patients are included in each cohort. Another limitation is that the patient's emotional states such as depression and anxiety, which may affect their pain thresholds, were not evaluated (26,27).

Conclusion

In this study, neither the presence of the ASA class nor the presence of female gender was connected with pain. As a consequence of this,

the notion that gender and ASA class affect post-LC pain levels is not supported by our data.

Ethics Committee Approval: Ethical committee approval was obtained from the Local Ethics Committee of University of Health Sciences Turkey, İstanbul Training and Research Hospital (approval number: 188, date: 17.06.2022).

Informed Consent: Their written consent was obtained.

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An Evaluation of Hepatitis A Seroprevalence and Vaccination Status in Patients with HIV/AIDS: Data from A 20-year Period

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ABSTRACT

Introduction: Hepatitis A infection, caused by the hepatitis A virus (HAV), is a non-chronic disease that can be prevented with vaccination. It is a significant cause of morbidity in adults. Homosexually active males, drug users, the homeless, and prisoners are at a greater risk of HAV infection. This study aimed to determine the hepatitis A seroprevalence and vaccination rates of people living with human immunodeficiency virus (HIV) followed up in our clinic.

Methods: A retrospective examination was made of the polyclinic files and laboratory test results in the hospital information system of 1,326 patients aged >18 years, who were diagnosed with HIV/AIDS and followed up in the Infectious Diseases Polyclinic of University of Health Sciences Turkey, Haseki Training and Research Hospital between September 30, 2002 and September 30, 2022.

Results: Anti-HAV immunoglobulin G (IgG) positivity was present in 1090 (82.2%) patients. As age increased, anti-HAV IgG positivity also increased, females were significantly more affected, no difference was determined between nationalities, and there was seen to be a significant decrease in the positivity rate over the time period of the study. The positivity rate was determined to be significantly high in heterosexual patients. The hepatitis A vaccination rate was determined to be 16.9%, and serology was examined in 60% of the patients after vaccination. The response to vaccination was determined to be 91.6% in the patients with serology examination.

Conclusion: Although improvements in sanitation and vaccination in childhood have provided a decrease in HAV seropositivity, the key populations must be informed about vaccination and vaccination adherence is ensured to prevent small outbreaks.

Keywords: Hepatitis A infection, HIV/AIDS, vaccination

Introduction

Hepatitis A infection, caused by the hepatitis A virus (HAV), is a non-chronic disease that can be prevented with vaccination (1-3). Although the main route of infection is fecal-oral, it can also be spread through the consumption of contaminated food, direct contact with an infected person, and occasionally through blood transfusion (2). The disease has been closely associated with unsafe drinking water and food, inadequate sanitation, poor personal hygiene, and oral-anal sex (1). Homosexually active males, drug users, the homeless, and prisoners are at greater risk of HAV infection (2,4).

Although HAV infection does not lead to chronic hepatitis, it is a significant cause of morbidity in adults, who experience a more severe disease course than children (3). HAV infection shows the same clinical course in patients with or without human immunodeficiency virus (HIV) infection, but higher levels of viral load and a longer period of viremia can be seen in those with HIV infection (4).

Although Turkey is accepted as an endemic region with respect to HAV infection, the frequency is decreasing. The age at which the virus is encountered has shifted from childhood to adolescence and in young adults (2,5). In 2012, the hepatitis A vaccination was included in the vaccination program in Turkey, and the vaccine started to be administered to children and individuals in high-risk groups (2).

According to the Ministry of Health data for November 2022, there are 36,630 patients with HIV/AIDS in Turkey. Despite the increase in reported cases over the years, Turkey is still among the countries with low prevalence. The cases in 2022 were reported to be 81.4% males, 16.2% of foreign nationality, and 13.8% homosexually active males (6).

This study aimed to determine the hepatitis A seroprevalence and vaccination rates of people living with HIV (PLWH) followed up in our clinic.

Methods

A retrospective examination was made of the polyclinic files and laboratory test results in the hospital information system of 1,585 patients aged >18 years, who were diagnosed with HIV/AIDS and followed up in the Infectious Diseases Polyclinic of University of Health Sciences Turkey,

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Haseki Training and Research Hospital between September 30, 2002 and September 30, 2022. The study included 1,326 patients with complete HAV serology.

The patients were evaluated with respect to demographic data, and HAV, hepatitis B virus, and hepatitis C virus (HCV) serology. Hepatitis B surface antigen (HbsAg) and anti-hepatitis B core antigen immunoglobulin G (IgG) positivity were accepted as chronic hepatitis B infection.

Approval for the study was granted by the Clinical Research Ethics Committee of University of Health Sciences Turkey, Haseki Training and Research Hospital (approval number: 145-2022, date: 27.07.2022).

Statistical Analysis

Data obtained in the study were analyzed statistically using SPSS vn. 15.0 for Windows. Descriptive statistics were stated as median, minimum, and maximum values for continuous variables, and as number (n) and percentage (%) for categorical variables. Rates between the groups were compared with the chi-square test. As the numerical variables did not conform to the normal distribution, comparisons between two independent groups were made with the Mann-Whitney U test. The level of statistical alpha significane was accepted as $p<0.05$.

Results

The evaluation was made of 1,326 patients followed up in our polyclinic, comprising 1187 (89.5%) males with a mean age of 37.8 years (range: 18-84 years). Of the 1,326 patients, 44 (3.3%) were foreign nationals, 285 (21.4%) were sexually active homosexual males, and the sexual orientation was unknown in 631 (47.5%).

Anti-HAV IgG positivity was present in 1090 (82.2%) patients. As age increased, anti-HAV IgG positivity also increased, females were significantly more affected, no difference was determined between nationalities, and there was seen to be a significant decrease in the positivity rate over the time period of the study.

Sexual orientation was determined to create a significant difference with a significantly higher anti-HAV IgG positivity rate determined in heterosexual patients.

In anti-HAV IgG-negative patients, lower CD4 (+) T-lymphocyte counts were determined, and no difference was observed in respect to HIV-RNA values, hepatitis B infection, and anti-HCV positivity. The results are shown in Table 1.

Of the 236 patients determined with anti-HAV IgG negativity, 40 (16.9%) were seen to have been vaccinated. Serology was not examined after vaccination in 16 (40%) of the vaccinated patients, and of the 24 patients with serology examined, anti-HAV IgG positivity was determined in 22. Of the 2 patients who remained anti-HAV IgG negative after vaccination, one was 23 years old and the other was 26 years old, both were male, of Turkish nationality, and both were diagnosed after 2013. One of these two patients was a sexually active homosexual, and the sexual orientation of the other was not known. CD4 (+) T-lymphocyte counts were 422 and 424, respectively, and there was no hepatitis B co-infection or anti-HCV positivity in either case.

Table 1. Prevalence of HAV immunity by baseline characteristics

	Anti-HAV IgG (+), (n=1090)	Anti-HAV IgG (-), (n=236)	p-value
Age at diagnosis			
<30 years	243 (22.3)	161 (68.5)	<0.001
30-50 years	665 (61.1)	72 (30.6)	
>50 years	181 (16.6)	2 (0.9)	
Gender			
Male	964 (88.4)	223 (94.5)	0.006
Female	126 (11.6)	13 (5.5)	
Nationality			
Turkish	1053 (96.6)	229 (97.0)	0.739
Not Turkish	37 (3.4)	7 (3.0)	
Year of diagnosis			
2003-2012	212 (19.5)	16 (6.8)	<0.001
2013-2022	877 (80.5)	220 (93.2)	
Sexual orientation			
Homosexual	209 (19.2)	76(32.2)	<0.001
Heterosexual	372 (34.1)	38 (16.1)	
Unknown	509 (46.7)	122 (51.7)	
HIV-RNA* (IU/mL)	297420 (38-1028842249)	253789 (152-46189016)	0.196
CD4 (+) T-lymphocyte count* cells/mm³	416 (1-9494)	351 (1-1714)	0.002
HBV infection	63/1088 (5.79)	11/235 (4.68)	0.502
Anti-HCV positivity	10/1077 (0.93)	3/234 (1.28)	0.713

*mean (minimum-maximum). HAV: Hepatitis A virus, HIV: Human immunodeficiency virus, HBV: Hepatitis B virus, HCV: Hepatitis C virus, IgG: Immunoglobulin G

No acute hepatitis A infection developed during the follow-up of any patient in the study who were anti-HAV IgG negative, and not vaccinated or who did respond to the vaccination.

Discussion

Although the main route of spread of HAV infection is the fecal-oral route, it can also be spread through blood transfusion or oral-anal sex. In regions where inadequate sanitation, a high prevalence is reached during childhood (1). The frequency is reduced with improvements in hygiene conditions and socioeconomic status. Vaccination is important for protection against disease (2). The USA Centre for Disease Control (CDC) has reported that since vaccination started in 1995, there has been a 95% decrease in the incidence of hepatitis A (3). In Turkey, the HAV vaccination was included in the national immunity program in 2012, but the effect on seroprevalence is not known as yet (2).

According to the Ministry of Health data for November 2022, cases were reported to be 81.4% males, 16.2% of foreign nationality, 13.8% homosexually active males, and most were in the 25-34 years age group (6). In a study by Şenoğlu and Yeşilbağ (7), 90.2% of the cases were male, 49.9% were homosexually active males, and the mean age was 35.75±11.22 years. Yemisen et al. (8) conducted a study of 829 patients and reported that 84.4% of the cases were male, 30.9% were homosexually active males, and the mean age was 37 years. In a study by Altuntas Aydin et al. (9) of 242 patients, 83% of the cases were male, 30.1% were homosexually active males, and the mean age was 38 years. In the current study, the patients were 89.5% male, 3.3% were of foreign nationality, 21.4% were homosexually active males, and the mean age was 37.8 years (range: 18-84 years). The low rate of foreign patients compared with the Ministry of Health data was thought to be due to the exclusion of cases with incomplete data. As in other studies and the Ministry of Health data, the majority of patients in the current study were male. The difference in the rate of homosexually active males was attributed to the fact that almost 50% of the current study patients did not provide information about sexual orientation.

Previous studies in Turkey have reported seroprevalence varying between 50% and 100% in the adult age group, and have reported that seroprevalence increased with increasing age, a decrease has been seen in seropositivity at younger ages recently, and there are regional differences (5). In the study by Şenoğlu and Yeşilbağ (7), the rate of anti-HAV IgG positivity was found to be 74.8%, and positive patients were determined to be significantly older than negative patients. Altuntas Aydin et al. (9) reported the positivity rate to be 91%. In the current study, the rate of anti-HAV IgG positivity was determined to be 82.2% and the positivity rate was seen to increase together with increasing age. This finding was consistent with previous data in Turkey.

In a study from Brazil, which included 581 PLWH, the anti-HAV IgG positivity rate was found to be 79.8% (10). A study in Korea of 756 PLWH reported an anti-HAV IgG positivity rate of 79.8% (11). This rate was reported to be 60.8% in a cohort of 1580 PLWH between 2004 and 2007 (12), and 21.2% in a cohort of 2860 PLWH in the period 2012-2016 (13). A study of 897 homosexually active males living with HIV reported anti-HAV IgG positivity of 35.7% (14). In the current study, the positivity rate was found to be 82.2%. When evaluated according to the World Bank data of the income levels of countries (15), it can be seen that the anti-HAV IgG positivity rate is high in low-income and low-mid-income countries (e.g., Brazil, Turkey), and the rate is low in high-income and mid-high-income countries (e.g., Taiwan, Korea, Greece). The income level of a country has an effect on sanitation.

According to the CDC data, the infection has been seen at the same rate in males and females in the general population since 2003, and after 2016, a significant increase was seen in males compared to females, which was attributed to the more widespread use of drugs by males (3). In a study of the general population by Alıcı et al. (16), no difference was determined between the sexes with respect to the distribution of HAV seropositivity. In another study that examined HAV seropositivity in PLWH according to age and years, seropositivity was found to be higher in males, which was attributed to 65% of the study population being male (10). Altuntas Aydin et al. (9) determined no difference between the sexes, whereas a study in Korea reported higher seroprevalence in females, but the reason for this was not explained (11). In the current study, HAV seropositivity in females was statistically significantly higher than the rate in males, and there can be considered as a need for a more detailed evaluation to be able to explain the reason for this.

The CDC reported that hepatitis A is seen at the same rate in all race and ethnic groups in the general population (3). In a study by Kourkounti et al. (14), 7.5% of PLWH were reported to be immigrants, the seropositivity rate of immigrants was 67.7%, and ethnicity was found to be statistically significant. In the current study, no statistically significant difference was determined with respect to ethnicity. This absence of difference was thought to be due to the high rates of seropositivity both in Turkey and in the countries from which the immigrants had come.

According to the CDC data, since the start of hepatitis A vaccination in children in 1996, the frequency of HAV infection in the general population has decreased, and small increases have been seen because of contaminated foodstuffs or intravenous drug use (3). Lee et al. (13) determined a decrease in HAV seropositivity over the years and it was reported that improvements in sanitation had contributed to this, and although the vaccination rate was very low, mathematical modeling showed that 70% of potential outbreaks had been prevented. In the current study, the patients were examined in 2 periods of 10 years, and a significant decrease was determined in the positivity rate in the second 10-year period. When it is considered that vaccinations started in 2012 in Turkey, this can be considered to be not an effect of the vaccination but of improvements in sanitation.

In a study by Şenoğlu and Yeşilbağ (7), which evaluated 788 PLWH between 2015 and 2019, HAV seronegativity was found to be statistically significantly high in homosexually active males. Altuntas Aydin et al. (9) evaluated 242 PLWH between 2006 and 2011 and found HAV seronegativity was statistically significantly high in homosexually active males. The results of the current study were similar. In a study that evaluated 581 PLWH between 1988 and 2004, Aloise et al. (10) found no significance of sexual orientation in respect to seropositivity. Similarly, Lee et al. (11) found no significance of sexual orientation in respect to seropositivity in a study of 756 PLWH between 2012 and 2021, but also

reported that there was a significant increase in seroprevalence in the group of young homosexually active males, although the reason for this was not explained. These differences can be considered as due to the years and places where the studies were conducted.

Vaccination is recommended for all PLWH with negative HAV serology, independently of the CD4 (+) T-lymphocyte count (3,4). Since 2012, the vaccine has been provided free of charge to PLWH in Turkey (2). The CDC has reported that seroconversion could sometimes occur at 6 months after HAV vaccination in PLWH, and there could be a poor response to the vaccine in those with low CD4 (+) T-lymphocyte count. If HAV serology examination is necessary after examination, it is recommended that the patient is vaccinated again (3). In a review by Lin et al. (17), it was reported that in countries with low HAV endemicity low adherence to the recommended HAV vaccination for PLWH, sensitivity to HAV infection continued because of high-risk sexual behavior and intravenous drug use, acute HAV infections were seen in children despite hepatitis A vaccinations, and it was emphasized that hepatitis A vaccination is necessary for both populations at risk and healthcare providers.

In a multicentre study by Hoover et al. (18), HAV serology was examined in 47% of 1,329 patients, with seronegativity determined in 526 (84%) of the 627 patients examined in respect to serology, and 150 (29%) were found to have been vaccinated, but no information was provided about the results of the vaccinations. In a retrospective study of 18095 PLWH by DeGroote et al. (19), of 3640 homosexually active males and/or intravenous drug addicts with HAV seronegativity, 360 (9.8%) were found to have been vaccinated, but no information was given about the response to vaccination. Kourkounti et al. (14) reported a vaccination rate of 66.3% and a response to a vaccine of 76%. In the current study, the vaccination rate was 16.9%, and the vaccine response was examined in 60% of these patients. Seropositivity developed at a rate of 91.6% after vaccination. There is a need for further more detailed studies to determine the reasons why the vaccination rates remain low despite the recommendations.

In a study by Aloise et al. (10), it was reported that of the PLWH with HAV seronegativity, acute hepatitis A infection developed in 5 (4.2%). DeGroote et al. (19) reported that anti-HAV IgG positivity developed in 27 (0.7%) unvaccinated PLWH throughout a one-year follow-up period, but no information was provided about the symptoms of the patients. In the current study, no acute HAV infection developed in the 196 PLWH who were not vaccinated and were determined with anti-HAV IgG negativity.

Study Limitations

Due to single-center design with relatively small sample size potential lack of generalizability is an important limitation of the current study.

Conclusion

Although improvements in sanitation and vaccination in childhood have provided a decrease in HAV seropositivity, the key populations must be informed about vaccination, and vaccination adherence is ensured to prevent small outbreaks.

Ethics Committee Approval: Approval for the study was granted by the Clinical Research Ethics Committee of University of Health Sciences Turkey, Haseki Training and Research Hospital (approval number: 145-2022, date: 27.07.2022).

Informed Consent: Retrospective study.

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The role of h-FABP and Myoglobin in Determining Disease Severity and Prognosis in STEMI

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ABSTRACT

Introduction: Acute coronary syndrome (ACS) remains as a single biggest cause of death worldwide. Heart-type fatty acid -binding protein (h-FABP) and myoglobin are small proteins present in the myocyte cytosol. In cases of myocardial damage, they can freely pass into the bloodstream. Thus, they might be useful in the diagnosis of ACS. The aim of this prospective study was to search the relationship between h-FABP and myoglobin levels and disease severity and mortality.

Methods: One hundred-fourty-nine male patients with ST-elevation myocardial infarction consitututed our study population. Two groups occurred according to low (<23) and high (≥23) SYNTAX score as group 1 and group 2. Blood specimens were taken for h-FABP and myoglobin analysis at hospital admission and at 12 h. Patients underwent coronary angiography for diagnosis and treatment, and the SYNTAX score was calculated. Participants were followed up for 72 months, and cardiovascular mortality rates were recorded.

Results: H-FABP at admission and h-FABP level at 12th h were lower in group 1 than in group 2 ($p<0.001$). We did not find significant differences between the myoglobin levels measured at the time of hospital entrance and at the 12th h in both groups. During 72-month follow-up, 123 patients survived and the survivors had a lower SYNTAX score, and a lower h-FABP level at admission. In the univariate analysis, h-FABP levels at admission and at 12 h were found to be independent predictors of coronary artery disease (CAD) severity. However, h-FABP levels did not predict mortality.

Conclusion: In patients with ACS, measuring h-FABP levels at admission and in the late period (12th hour) are helpful, not only in the diagnosis but also severity and seriousness of CAD.

Keywords: Myoglobin, heart-type fatty acid binding protein, myoglobin, myocardial infarction, SYNTAX score, heart-type fatty acid binding protein

Introduction

Cardiovascular disease is an important health problem worldwide, which is a chief source of death in industrialized countries and its incidence is increasing in developing countries (1). Acute coronary syndrome (ACS) is diagnosed by electrocardiogram (ECG) and biomarkers, particularly cardiac troponin (cTn). The main way to prevent major complications and deaths from ACS is early diagnosis (2).

Many biomarkers have been used and developed for early diagnosis, but nowadays it is also important to have an idea about the prognosis in the short and long term. High sensitivity markers and ECG have achieved 100% sensitivity in diagnosis and exclusion, but there is still an ongoing search for new biomarkers for prognosis.

Heart-type fatty acid -binding protein (h-FABP) has been suggested as an important predictor of early diagnosis of myocardial damage and is a potential prognostic indicator for long-term fatality (3). H-FABP presents in the cytosol and carries long -chain fatty acids (4). Myoglobin is also presents in cytosol with a molecular weight of 17.8 kd and is one of the preliminary cardiac markers delivered into the plasma when myocardial necrosis occurs. Since it is also present in the skeletal muscle, the increase in myoglobin measured in circulation is not limited to cardiac muscle damage (5). Myoglobin measurement is especially helpful at an early stage of ACS, but since it is specific for myocardium, it is not easy to decide whether elevations in myoglobin concentration is the result of myocardial or skeletal muscle damage (6). The myoglobin test may be

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useful only if it is to be used alone. It is proposed that myoglobin could be integrated with other tests to diagnose ACS (7).

The risk classification in patients with ACS is critical to determining the appropriate treatment and follow-up method (8). The most commonly used risk stratification systems are the Global Registry of Acute Coronary Events and Thrombolysis In myocardial infarction (MI) scoring systems incorporate additional points for positive cardiac markers (9). Studies have shown that the inclusion of new non-necrosis biomarkers in classical risk stratification systems may increase the sensitivity/specificity of risk estimation (10-12).

Here, we sought to question the relationship between h-FABP and myoglobin levels and ACS disease severity and long -term mortality in ST-segment elevation MI (STEMI) patients.

Methods

The study was started after the approval of the ethics committee. One hundred forty nine male patients who applied to our emergency department with chest pain and other symptoms suggestive of ACS and with STEMI findings on 12-lead ECG were included in the study. Those under 18 years of age, with active infection, malignancy, chronic diseases including musculoskeletal system, contraindications for coronary angiography, chronic renal failure, previous pulmonary thromboembolism, MI, cerebrovascular event, trauma, surgery , and cardiopulmonary resuscitation within 72 h, unconscious patients were excluded from the study.

After obtaining informed consent from the patients, in addition to routine examinations, 2 mL venous blood was taken to the EDTA tube for h-FABP and myoglobin. To measure and evaluation of h-FABP (TOYO-Turkey) and myoglobin (TOYO-Turkey), the gold absorption immunofluorescence assay method and Turklab ICA-Rapid Test Reader (Toyo, Info Rapidan Tester-Turkey) instrument were used. The patients' current diseases, cardiovascular risk factors [diabetes mellitus (DM), hypertension (HT), hyperlipidemia (HL)] were questioned and recorded. Blood was drawn again for h-FABP and myoglobin 12 h after the start of the symptoms. The diagnosis of STEMI based on cardiac symptoms, 12-lead ECG findings, and elevated cardiac enzymes underwent coronary angiography for diagnosis and treatment by a specialist cardiologist.

Coronary angiography was performed using a Judkins catheter from the femoral artery. SYNTAX score of each patient was calculated according to anatomical lesion characteristics including bifurcations, chronic total occlusions, thrombus, calcification and small diffuse disease. All of the calculations were carried out using the website program: https://syntaxscore.org. Patients were splitted into two groups according to the severity of ACS. The first group consisted of patients with a SYNTAX score of less than 23, and the second group consisted of patients with a score 23 or higher.

The follow-up period of the patients was 72 months. Patients who lost to follow-up were investigated from the state's death notification system available only to doctors and those who died were identified. Non-cardiac deaths were excluded from the 5-year mortality assessment.

Statistical Analysis

The normality assessment of the data was made by evaluating the skewnessand kurtosis of the data, and the Kolmogorov-Smirnov test. Normally, and non-normally distributed data were expressed as means ± standard deviations medians (interquartile ranges), respectively. Categorical data were expressed as percentages. Comparisons of the groups were made using of Independent sample-t test or Mann-Whitney U test for normally and non-normally distributed data, respectively. Univariate logistic regression analysis was conducted to find the predictors of coronary artery disease (CAD) severity and mortality. Variables that had significance in univariate analysis were put into multivariate analysis. The discriminatory ability of FAB and FAB12 in determining the CAD severity was analyzed using the receiving operating characteristic (ROC) curve analysis. Statistical significance was considered significant if $p<0.05$. All statistical analyses were performed using the Statistical Package for the Social Sciences version 24.0 software.

Results

The median age of the 149 male patients with STEMI was 54.65 years. DM was diagnosed in 25.5% (n=38), HT in 49.7% (n=74), and HL in 47% (n=70) of the patients. Mean age, presence of DM and HT, mortality rate, h-FABP at admission, and h-FABP level at 12th h were lower in group 1 than in group 2. The left ventricular ejection fraction (LVEF) was significantly higher in group 1 ($p<0.001$). We did not find significant differences between the myoglobin levels measured at the time of admission to the hospital and at the 12th h in both groups (Table 1).

During the 72-month follow-up, 123 patients survived and the survivors had a lower mean age, a lower prevalence of DM, a higher LVEF, a lower SYNTAX score, and a lower h-FABP level at admission. Myoglobin values were not different between the survivor and non-survivor groups (Table 2).

In the univariate analysis: in addition to age, presence of DM, presence of HT and left ventricular EF level, and h-FABP levels at admission and at 12 h were found to be independent predictors of CAD severity (Table 3). However, h-FABP level was not found to be a predictor of mortality (Table 4).

In determining the severity of CAD, in the evaluation of h-FABP level at the time of application and at the 12th h by ROC analysis, it had a discriminatory power of >16.95 at the time of admission and >21 ng/mL at the 12th h (Figure 1).

Discussion

cTns are regarded as the best laboratory test for the diagnosis of acute MI (AMI) (13). In AMI, troponins rise to a measurable level in the circulation 3 h after the onset of chest discomfort. This limits the earlier diagnosis of MI (14).

When myocyte injury occurs, h-FABP quickly passes through the interstitial spaces into the blood. Since it is much smaller than troponin, it passes into the blood faster than troponin (15). It is measurable in the blood as early as 1-3 hours after the onset of chest pain, reaches its maximum values in 6-8 h, and returns to normal concentrations within 24-30 h (16). As expected, in our study, the h-FABP level of the patients was elevated during the first admission.

Reddy et al. (17) emphasized the significance of using a pair of biomarkers (h-FABP and hs-TnT) together in the initial diagnosis of ACS. It was recommended that troponin T- and h-FABP be used together to

improve the diagnosis of ACS in the emergency room after the onset of chest pain. Furthermore, when these two biomarkers are used together, they have 100% negative predictive value (17). In this study, h-FABP was also added to routine cardiac biomarkers (cTnT, CK-MB) in patients presenting with chest pain and ST elevation on ECG, and this multiple biomarker analysis was helpful for early diagnosis. Increased h-FABP is a helpful early diagnosis of MI via facilitating early release of patients with chest pain but not MI from the hospital. The addition of h-FABP

Table 1. Demographic, clinical, and laboratory parameters of patients with low and intermediate-high anatomical SYNTAX score I

	All population, (n=149)	SxS <23, (n=105)	SxS ≥23, (n=44)	p
Age, year (median ± SD)	54.6±12.4	53.3±12	58.9±12.8	0.036
Hypertension, n (%)	74 (49.7)	46 (43.8)	28 (63.6)	0.027
Diabetes mellitus, n (%)	38 (25.5)	19 (18.1)	19 (43.2)	0.001
LVEF (%) (median ± SD)	46.7±8.7	48±7.9	43.8±9.9	0. 007
SYNTAX score, median (IQR)	13 (8.5-26)	10 (7.5-13.5)	29 (27-33.5)	0.023
Mortality, n (%)	26 (17.4)	10 (9.5)	16 (36.4)	<0.001
h-FABP (ng/mL) median (IQR)	8.5 (5-43)	5 (5-25)	36 (10-71)	<0.001
h-FABP 12th h (ng/mL) median (IQR)	11 (5-69)	5 (5-50.5)	51 (16.8-122.6)	<0.001
Myoglobin (ng/mL) median (IQR)	136 (51-285)	126 (50-240)	196 (71-323)	0.062
Myoglobin 12th h (ng/mL) median (IQR)	121 (75-253)	120 (73-206)	145 (82-298)	0.143

SxS I: Syntax score I, SD: Standard deviation, LVEF: Left ventricular ejection fraction, IQR: Interquartile range, h-FABP: Heart-type fatty acid -binding protein, PCI: Percutaneous coronary intervention

Table 2. Demographic, clinical, and laboratory parameters of survivors and non-survivors patients

	Survivor, (n=123)	Non-survivor, (n=26)	p
Age, year (median ± SD)	52.1±11.1	66.3±11.5	<0.001
Hypertension, n (%)	58 (47.2)	16 (61.5)	0.183
Diabetes mellitus, n (%)	27 (22)	11 (42.3)	0.030
LVEF (%) (median ± SD)	47.9±7.9	43.8±9.7	0. 010
SYNTAX score, median (IQR)	11 (8-17)	30.8 (19-35.5)	<0.001
h-FABP (ng/mL) median (IQR)	5 (5-39)	17.9 (5-61.7)	0.057
h-FABP 12th h (ng/mL) median (IQR)	10 (5-64)	47 (5-77)	0.381
Myoglobin (ng/mL) median (IQR)	139 (58-289)	85 (50-256)	0.650
Myoglobin 12th h (ng/mL) median (IQR)	121 (75-256)	121 (66-238)	0.975

SD: Standard deviations LVEF: Left ventricular ejection fraction, IQR: Interquartile range, h-FABP: Heart-type fatty acid -binding protein, PCI: Percutaneous coronary intervention

Table 3. Factors that were independently associated with the CAD severity

	Univariate analysis	p	Model 1 multivarite analysis	p	Model 2 multivarite analysis	p
Age	1.036 (1.010-1.063)	0.006	1.037 (1.012-1.062)	0.003	1.031 (1.006-1.056)	0.016
Hypertension	1.914 (1.036-3.537)	0.038	1.309 (0.679-2.526)	0.422	1.364 (0.715-2.603)	0.346
Diabetes	2.563 (1.411-4.655)	0.002	1.694 (0.877-3.274)	0.117	1.960 (1.045-3.675)	0.036
LVEF	0.953 (0.923-0.984)	0.003	0.960 (0.928-0.994)	0.023	0.963 (0.929-999)	0.044
h-FABP	1.009 (1.004-1.013)	<0.001	1.008 (1.003-1.013)	0.008	-	-
h-FABP 12th	1.008 (1.003-1.012)	0.001	-	-	1.005 (1.001-1.010)	0.029

CAD: Coronary artery disease, LVEF: Left ventricular ejection fraction, h-FABP: Heart-type fatty acid -binding protein

Table 4. Factors that were independently associated with the mortality

Variables	Univariate analysis	p	Multivarite analysis	p
Age	1.083 (1.047-1.120)	<0.001	1.066 (1.028-1.106)	0.001
Diabetes	2.318 (1.064-5.049)	0.034	1.595 (0.680-3.740)	0.283
LVEF	0.943 (0.904-0.984)	0.006	0.968 (0.926-1.013)	0.164
SxS I	1.132 (1.087-1.179)	<0.001	1.109 (1.062-1.159)	<0.001
h-FABP	1.006 (1.000-1.013)	0.048	0.999 (0.992-1.006)	0.750

LVEF: Left ventricular ejection fraction, SxS I: SYNTAX score I, h-FABP: Heart-type fatty acid -binding protein

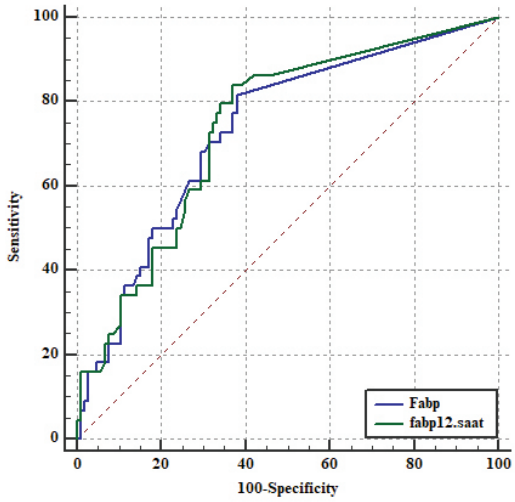

Figure 1. Discriminatory performances and diagnostic accuracies of FAB ve FAB 12th in determinig the CAD severity

AUC for FAB: 0.733, 95% CI: 0.654-0.802, p<0.001; cut-off >16.95, 70% sensitivity, 69% specificity. AUC for FAB12: 0.739, 95% CI: 0.661-0.808; cut-off >21, 73% sensitivity, 69% specificity

to Hs-cTn in patients admitted to the emergency room with chest pain without ischemic ECG findings makes easier to define it as a low risk (up to 40%) (18). Since our study included patients with STEMI , h-FABP levels in patients who had chest pain but who did not have any ECG findings were not evaluated.

Studies have shown that in patients were accepted to hospital with chest discomfort and diagnosed with ACS, the evaluation of plasma h-FABP on admission might provide added information on risk stratification. The importance of biomarkers in both the diagnosis and prognosis of ACS has been demonstrated by these studies. Prognostic guidance of biomarkers is superior to electrocardiographic guidance only (19,20).

Increased serum FABP4 levels were related to worse 30-day outcomes in patients with ACS, regardless of age, gender, renal function, and body mass index (21). The results of that study were partly alike to our study. In our study, higher SYNTAX scores were observed in patients with higher h-FABP levels and 5-year mortality of those patients was also higher. Especially h-FABP levels measured at the 12th h were remarkably higher in the group 2. In the same study, circulated FABP4 levels were found to be notably higher in females and subjects with body mass index (BMI) >25 kg/m^2 compared with men and normal weight (21). In our study, to minimize this effect, we only included male patients with BMI <25 kg/m^2.

In the early 2000s, Goto et al. (22) showed that h-FABP had positive interaction with brain natriuretic peptide (BNP) concentration in acute decompensated heart failure patients. Subsequently, Setsuta et al. (23) showed that h-FABP has a role in myocyte necrosis or apoptosis and causes worsening in heart failure status. Additionally, Hoffmann et al. (24) showed that additional h-FABP measurements in decompensated heart failure enhanced the diagnostic specificity and predictive value of NT-proBNP tests (25). In the patients with cardiac surgery, Jo et al. (26) showed that h-FABP was a more practical marker for detecting myocyte damage than CK-MB and cTnT. Another study showed that; permanently elevated h-FABP levels could have prognostic value because they can indicate progressive myocardial damage despite effective therapy and clinical progress (27). In our study, the h-FABP level at admission was found to be higher in non-survivor patients, and h-FABP levels at both admission and at the 12th h were found to be independent predictors of CAD severity. However, we cannot say that h-FABP is a predictor of mortality.

In addition to the role of myoglobin in the diagnosis of MI, it has been investigated whether it is useful for risk stratification in patients with ACS.

In patients with MI with poor prognosis and high mortality risk, skeletal muscle damage may be the cause of myoglobin elevation rather than heart muscle damage. Both hypotension and decreased renal perfusion lead to the release of myoglobin from the skeletal muscle, which may contribute to mortality after ACS (28).

There are some studies have suggesting that myoglobin adds a small amount of prognostic information to CK-MB and troponins, these studies are small sample -sized studies. There is a need for further studies on this subject (28-32).

In our study, although myoglobin levels tended to be higher in patients with a high SYNTAX score at admission to the hospital and at the 12th h, this elevation was not statistically significant (p=0.062, p=0.143).

We investigated the relationship between 5-year cardiac mortality and myoglobin. In patients who died of cardiac causes within 5 years, myoglobin levels at admission and at 12 h were not different between survivor and non-survivor patients. Our results do not support the results by Spangenthal et al. (28).

As mentioned above, many studies have been conducted on the specificity and sensitivity of h-FABP in the diagnosis of ACS. In our study, in addition to these studies, the relationship between the levels of h-FABP and myoglobulin in the first 3 h and 12 h in the diagnosis of STEMI was evaluated. SYNTAX scores were used for this evaluation. In addition to these scores, a 72-month follow-up of patients was performed, and real-life death data were included in the evaluation.

In our study, h-FABP and myoglobin values measured at admission and at the 12th h were higher in patients with higher SYNTAX scores, but only h-FABP values were found to be predictive of CAD severity. H-FABP and myoglobin are not biomarkers routinely analyzed in patients presenting to the emergency department with chest pain. After newly developed Hs-troponins, it cannot be expected to replace them in diagnosis. However, looking at the h-FABP values measured at the time of admission to the hospital or at the 12th h in selected patients, with the help of the determined cut-off values (in our study, we determined the cut-off for h-FABP as 16.95 at the time of admission and 21 ng/mL at the 12th hour) can help predict disease severity and determine the treatment strategy.

Conclusion

In patients with ACS, measuring h-FABP levels at admission and in the late period (12th hour) are helpful, not only in the diagnosis but also severity and prognosis of CAD. However, it is necessary to develop a

precise test that allows quick and economical measurements of h-FABP. Additionally, an internationally consistent standardization should be made, and a consensus on the h-FABP threshold should be reached. To achieve this, further prospective randomized clinical trials are needed.

Ethics Committee Approval: University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinical Research Ethics Committee (date: 05.08.2019/decision no: 2019-15).

Informed Consent: After obtaining informed consent from the patients, in addition to routine examinations.

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The Relationship Between Cochlear Nerve and Cochlear Nerve Canal Dimensions in Incomplete Partition Types

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ABSTRACT

Introduction: Incomplete partition (IP) type and accompanying cochlear nerve (CN) anomalies affect the patient's management. We revealed the cochlear nerve area (CNA), cochlear nerve canal width (CNCW), and inner auditory canal width (IACW) of IP types.

Methods: We retrospectively scanned patients with IP. There were 88 IP ears (26 IP type 1, 54 IP type 2, 8 IP type 3) and 54 controls. The CNCW and IACW were measured in axial temporal computed tomography sections. The CNA and facial nerve area (FNA) were measured in the distal IAC on the sagittal-oblique plane of 3D constructive interference steady-state T2-weighted magnetic resonance images.

Results: CNA and CNA/FNA values for each IP type differed significantly compared with the control group. However, the CNCW and IACW values did not differ significantly. The CNA was the least in IP 1 cases. Five CN aplasia were detected, and all were associated with IP type 1 anomaly (3.5% of all, 5.6% of IP types, and 19.2% of IP type 1 cases). CN hypoplasia was observed in 10 IP type 1 (38.5% of IP 1), 6 IP type 2 (6.8% of IP type 2), and 1 IP type 3 (12.5% of IP type 3) ears. None of the CN hypoplasia had a CNC hypoplasia.

Conclusion: CN aplasia and hypoplasia most frequently accompanied with IP type 1 in our study. Therefore, they need an extra interest in CN evaluation. CNCW and IACW are not very useful in predicting CN dysplasia in IP cases.

Keywords: Incomplete partition, cochlear nerve, cochlear nerve canal width, inner auditory canal width

Introduction

One-fourth of sensorineural hearing loss (SNHL) cases have an anomaly that computed tomography (CT) or magnetic resonance imaging (MRI) can detect, and the detection rate with CT (25%) was higher than with MR (18%) (p=0.0001) (1,2). While the most common anomalies detected by CT were cochlear or semicircular canal anomalies, the most common anomalies detected by MRI were cochlear nerve (CN) abnormalities and semicircular canal anomalies (2). Incomplete partition (IP) disorders describe the cochlea anomalies that comprise approximately 40% of the inner ear anomalies and are divided into three groups. Types of IP are distinguished by the presence or absence of the cochlea's partition to varying degrees (3). Some patients with IP may not have a chance for a cochlear implant (CI) due to the possibility of CN aplasia (1). Patients with normal CNs had better post-CI outcomes rather than patients with CN dysplasia. Patients with a narrower bony cochlear nerve canal (CNC) showed less favorable results, even if the CN was intact (4).

The CNC, also called the cochlear aperture, is the central bony passage at the base of the modiolus that allows the course of the CN from the Cochlea to the internal acoustic canal (IAC). When the CNC is not visible, it is considered aplasia; when the cochlear nerve canal width (CNCW) is narrow, it is regarded as hypoplasia (5). In a study in SNHL cases with normal cochlea and CN abnormalities, the CNC diameter was smaller than 1.5 mm in 90.6% of patients with CN aplasia and 31.7% of patients with CN hypoplasia (6). Narrowing of the IAC maybe seen with CNC abnormalities. Different cut-off values have been used for the inner auditory canal's width (IACW) in different studies (7-9). The CN should be evaluated in narrow IAC, CNC hypoplasia, or CNC aplasia. While CN hypoplasia or aplasia might be expected to attend CNC hypoplasia, both can also be seen with a normal CNC.

However, CNC aplasia accompanies CN aplasia (10,11). It is considered hypoplastic if the diameter of the CN is smaller than the normal CN on the contralateral side or the normal facial nerve (FN) on the same side (12). Evaluation of the CNC and IACW is possible with high-resolution CT of the temporal bone. However, thin-section T2-weighted MR sequences should be used for CN evaluation (13).

In the literature, numerous studies have evaluated the relationship between CNCW and CN hypoplasia-aplasia. However, these studies assessed independently of the normal-abnormal configuration of the

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cochlea (5,10,12). It is essential to reveal the form of the CN (aplasia, hypoplasia, or normal) for planning the management approach. The relationship between cochlear nerve area (CNA) and CNCW in IP types have not yet been studied yet. This study revealed the CNA, CNCW, and IACW and their relationship with CN dysplasia in IP patients.

Methods

This study was conducted at our hospital in accordance with the principles of the Declaration of Helsinki Ethics Committee Approval was taken from University of Health Sciences Turkey, İstanbul Training and Research Hospital Clinical Research Ethics Committee (approval number: 326, date: 27.10.2022).

Subjects

For this study, we retrospectively scanned our hospital's Picture Archive Communication System for patients diagnosed with IP based on the classification of Sennaroğlu and Bajin (1) from January 2017 to October 2022 from January 2017 to January 2022. We reached 97 ears diagnosed with IP who underwent temporal CT and MRI. Seven ears were excluded because they had CT or MR images unsuitable for measurement, previous skull base or temporal surgery, skull base or facial trauma with fracture, history of head and neck malignancy, and calvaria abnormalities or deformities. Of the remaining 88 ears, 26 had IP type 1, 54 had IP type 2, and 8 had IP type 3. In the same period, 54 patients under 18 with CT and MRI scans for mastoiditis and cholesteatoma, who had no inner ear anomalies, were randomly selected for the control group.

Imaging and Analysis

All CT and MRIs of the SNHL and control patients were performed in our radiology department for routine medical treatment. The CT images were performed with a 64-slice CT (MSCT; Brilliance 64, Philips Medical System, Best, the Netherlands). All the scans were obtained as routine HRCT of temporal bone imaging in the supine position with the scanning baseline parallel to the orbitomeatal line (kVp=120, mAs=100, FOV=240 mm, slice thickness=0.5 mm). The MR images were performed with a 1.5-T scanner (Siemens Healthcare, Aera Magnetom, Erlangen, Germany) equipped with an 8-channel head coil. The imaging protocol included axial 3D constructive interference steady-state (CISS) T2 (TR/TE: 5.39/2.40 ms, matrix: 384x211, NSA: 1, slice thickness: 0.72 mm) images as a part of the standard protocol for temporal MRI at our institution.

Each cochlea's CT and MRI scan were transferred to the Syngo Via® workstation (Siemens Medical Solutions) for precise measurements. All images were examined separately by a radiologist experienced in temporal bone imaging. The CNCW was measured on axial CT images at the mid-modiolar plan (Figure 1A). The IACW was measured at the mid-point in axial CT sections (Figure 1B). Sagittal-oblique images of 3D CISS T2-weighted MRI were performed perpendicular to the nerve's long axis by multiplanar reconstructions. The cochlear and FN cross-sectional areas were measured separately in the distal IAC on the sagittal-oblique plane of the CISS images (Figure 2). The CN was defined as aplasia if the CN could not be seen in any reconstructed image, and the area was recorded as 0 mm^2 (Figure 3A). The ratio was calculated by dividing the ipsilateral CN by the facial nerve areas (CNA/FNA) (14). CN is considered hypoplastic if the area of the CN is smaller than the normal CN on the contralateral side or the normal FN on the same side (Figure 3B) (12). In cases where the CNC measurement was not made because the canal opening was not chosen, the CNC was noted as atretic and recorded as 0 mm. It was defined as stenotic when the CNCW was <1.5 mm (6). We evaluated the incidence of CN aplasia and hypoplasia in each case group when we separated the CNC width as aplasia, stenotic, and normal (6). If the IACW was below 4 mm, it was considered abnormal, and its relationship with CN hypoplasia and aplasia was evaluated (15).

Statistical Analysis

In the descriptive statistics of the data, mean, standard deviation, median, minimum, maximum, frequency, and ratio values were used.

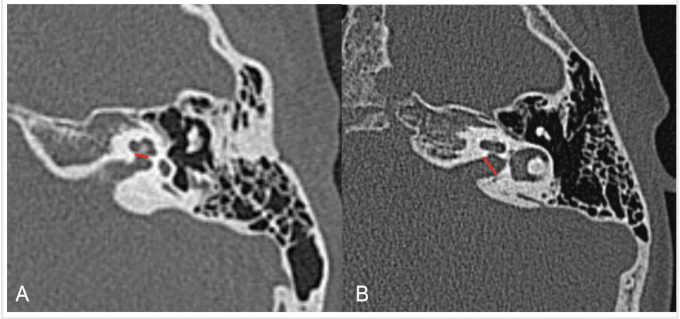

Figure 1. (A) CNCW measurement at the mid-modiolar plan on axial CT images. (B) IACW measurement at the mid-point in axial CT sections

CNCW: Cochlear nerve canal width, CT: Computed tomography, IACW: Inner auditory canal width

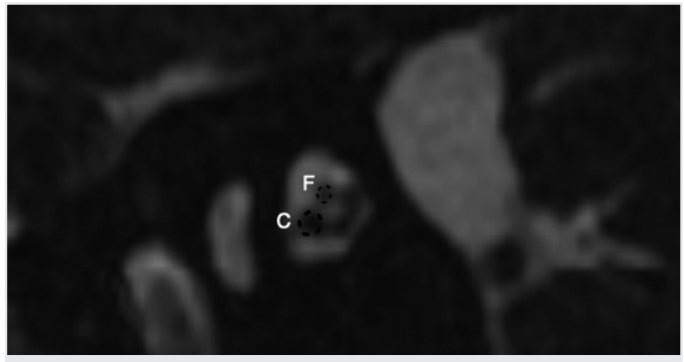

Figure 2. Cochlear and facial nerve cross-sectional area measurement

F: Facial nerve, C: Cochlear nerve

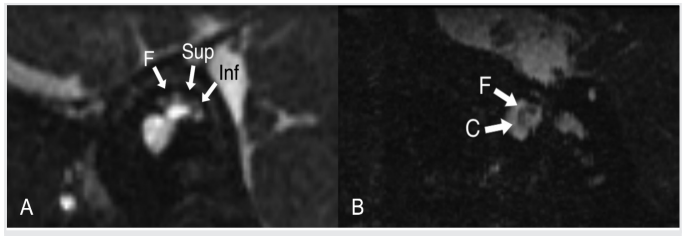

Figure 3. 3D CISS T2-weighted MRI images of (A) cochlear aplasia and (B) cochlear hypoplasia

CISS: Constructive interference steady-state, MRI: Magnetic resonance imaging, F: Facial nerve; C: Cochlear nerve; inf: Inferior colliculus Sup: Superior colliculus

The distribution of variables was measured using the Kolmogorov-Smirnov test. Kruskal-Wallis, Mann-Whitney U test was used to analyse independent quantitative data. The Wilcoxon test was used in the analysis of dependent quantitative data. SPSS 28.0 program was used in the analysis.

Results

The mean age of the cases included in the study was 61.4±46.6 months in control, 46.2±55.4 months in IP type 1, 67.5±53.2 months in IP type 2, and 163.3±57.6 months in IP type 3. The mean values of CNA, FNA, and CNA/FNA for each group are summarized in Table 1.

Both CNA and CNA/FNA values for each IP type differed significantly compared with the Control group (Table 1, Figure 4).

Additionally, no significant difference was found between all groups for FNA. CNCW and IACW values are also summarized in Table 1 for each group. Both did not differ significantly between the control and IP types.

CN dysplasia was not detected in any case in the control group. In our case group, five CN aplasia was detected, and all were associated with IP type 1 anomaly (3.5% of all, 5.6% of IP type, and 19.2% of IP type 1 cases). CNC stenosis was found in 4 patients with CN aplasia, and CNC hypoplasia was found in 1 patient. CN hypoplasia was seen in 10 IP type 1 (38.5% of IP 1), 6 IP type 2 (6.8% of IP type 2), and 1 IP type 3 (12.5% of IP type 3) ears. None of these ears with CN hypoplasia had a CNC hypoplasia.

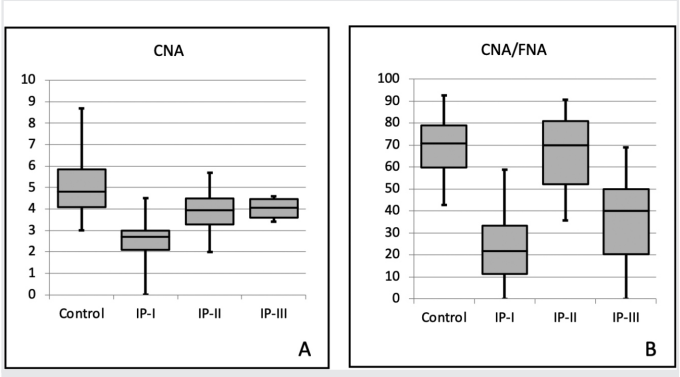

Figure 4. Box plot of the mean values for CNA and CNA/FNA
CNA: Cranial nerve area, FNA: Facial nerve area

The CNC was hypoplastic in 2 ears of the control group and one ear of the IP type 1, and the CN diameter was within the normal limits in these cases.

There is no significant difference in IACW between the control and the IP types. IACW was measured below 4 mm in 4 cases in the control group, 4 cases in the IP type 1 group, and 6 cases in the IP type 2 group. CN diameter in all these control and IP type 2 cases was within normal limits. In 4 cases with IP type 1 and IACW were measured below 4 mm; two have CN aplasia, one has CN hypoplasia, and the other has normal CN diameter. The IAC diameter was greater than 4 mm in all IP type 3 cases.

Discussion

The CN condition affects the CI results in IP and other SNHL cases (1). Therefore, in this study, we revealed whether the CN dimensions of IP cases differ from those of normal subjects and which IP types are more accompanied by CN dysplasia. We also investigated whether CNC and IAC widths may be associated with CN dysplasia and whether they differ from normal cases. The mean CNA value was 5±1.2 mm in the control group compared to the IP types, and there was a statistically significant difference. The lowest CNA was found in IP type 1 cases than in the other IP types and the control in our results. We did not find a significant difference in FNA between the IP types and the control. Naguib et al. (14) also found no significant difference in the FNA between patients with SNHL patients and control. They stated that the FN could be used as a reference in evaluating CN dimensions (14). Therefore, FNs can be used as a reference in IP cases too. CNA/FNA values differ between control and IP types, similar to CNA values in our results.

Carner et al. (16), in their study on 36 patients with CN aplasia, found that IP type 1 anomaly was accompanied in 5 cases and IP type 2 anomaly in 4 cases. In the study of Sorge et al. (17) found middle and inner ear anomalies in 10 of 32 cases with CN defects. Among these, IP type 2 was accompanied in 3 ears, and IP type 1 was in two ears (17). Tahir et al. (18) found 3 IP type 1 cases in 41 patients with CN aplasia.

Table 1. Statistical analysis of MRI and CT measurements

		Control	IP-1	IP-2	IP-3
CNA	Mean ± SD	5.0±1.2	2.3±1.3	3.9±0.8	4.0±0.4
	p		**0.001**	**0.001**	**0.029**
FNA	Mean ± SD	3.2±0.9	3.1±0.7	3.1±0.6	3.3±0.5
	p		0.750	0.963	0.388
CNA/FNA	Mean ± SD	1.6±0.3	0.8±0.5	1.3±0.3	1.3±0.2
	p		**0.001**	**0.001**	**0.002**
CNCW	Mean ± SD	2.2±0.4	2.0±1.0	2.1±0.3	2.2±0.4
	p		0.930	0.691	0.817
IACW	Mean ± SD	5.2±1.0	4.8±0.9	5.3±1.1	5.4±1.1
	p		0.058	0.866	0.674

Statistically significant data with p<0.05 are bolded. MRI: Magnetic resonance imaging, CT: Computed tomography, CNA: Cochlear nerve area, FNA: Facial nerve area, CNCW: Cochlear nerve canal width, IACW: Inner auditory canal width, SD: Standard deviation

CN aplasia was detected in only five cases among our entire patient and control group, and all of them were associated with IP type 1 anomaly. Suk et al. (19), in their study evaluating the surgical results in IP type 1 cases, found hypoplasia in 9 (53%) of 17 cases in which the CN was assessed. In an MRI examination of the IP type 1 cases, hypoplasia of the CN was found in 16.2% and aplasia of the CN in 6.3% (20). In our study, we examined 26 IP type 1 cases, and 38.5% (n=10) of them had CN hypoplasia, and 19.2% (n=5) had CN aplasia. CN hypoplasia was also seen in 6 IP type 2 (6.8% of IP type 2) and 1 IP type 3 (12.5% of IP type 3) ears. None of these ears with CN hypoplasia had a CNC stenosis.

It is an expected finding that the CNC is narrower in patients with SNHL than in patients with normal hearing (5,11). However, our results found no significant difference between the CNCW in the normal cases and IP types (Table 1). The addition of CNC stenosis to the inner ear abnormalities may accompany more severe SNHL (5). Zainol Abidin et al. (21) reported in their research that the most common cochlear anomaly accompanying CNC stenosis was IP type 2 (23%). However, 37 of the 48 cochlear anomalies in their study were IP type 2 cases. Of 38 patients with a stenotic CNC in a study, 6 had IP type 1, and 1 had IP type 2 (18). The CNCW was measured below 1.5 mm in just three ears in our study. Two of these CNC stenoses were in the control group, and one was in the IP type 1. There were no significant Accompaniment of CNC stenosis to IP cases. Stenosis of the CNC often accompanies CN hypoplasia or aplasia, and the severity of hearing loss and canal narrowing has been associated with each other (5; 11). However, concomitant CN dysplasia was not found in all three of our cases with CNC stenosis.

Because of the high incidence of CN abnormalities, IAC stenosis has been considered a Contraindication for CI application in previous studies (22). Although CN evaluation with MRI is routinely performed today, narrow IAC retains its ability to predict low CI success because it indicates CN abnormalities. In addition, in cases where CNC dimensions are within normal limits, CN dysplasia may not be predicted without MRI (10). In a study conducted in cases with normal cochlear configuration, IAC diameter was less than 3 mm in 50% of cases with CN aplasia and 40% with CN hypoplasia (6). Giesemann et al. (23) found that 92% of 25 cases with IAC malformation were present with VCN aplasia in their study on a case group with different inner ear anomalies. Glastonbury CM accepted 4 mm as the limit for IAC abnormality evaluated on 3D T2W MR images and showed that IAC abnormality was accompanied in 16 of 18 ears with CN abnormality (15). Monsanto et al. (24) evaluated 38 temporal bone specimens inner ear anomalies in their study. The vestibulocochlear nerve, CNC, and IAC were markedly hypoplastic in a single IP type 1 case. IAC and CNC were normal in the two IP type 2 cases, but nerve fibers were significantly lost (24). In a study evaluating the IAC width (at the level of porus acusticus internus), there were 8 cases of IP type 1, 16 cases of IP type 2, and 8 cases of IP type 3. The IAC width was approximately 5.5 mm in the control group, and there was no significant difference between the IP types and the control group (25). We found a mean IACW of 5.2±1.0 mm in the control group and did not find a significant difference with IP types. IACW was measured below 4 mm in 4 cases in the control group, 4 cases in the IP type 1 group, and 6 cases in the IP type 2 group. IAC diameter was greater than 4 mm in all IP type 3 cases. CN diameter in all these control and IP type 2 cases was within normal limits. In 4 cases with IP type 1 and IACMW were measured below 4 m; two have CN aplasia, one has CN hypoplasia, and the other has a normal CN diameter.

Study Limitations

The limitations arising from the study's retrospective nature, with the fact that the patient population excludes other inner ear anomalies, causes us to be unable to make a comprehensive comparison. A single author made measurements, and inter-observer variability was not checked. All measurements were made manually. Difficulties and differences may arise from the complex anatomical structure. Especially, in anatomical variations and advanced abnormalities, measuring and standardizing measurements becomes difficult. MRI may not provide sufficient resolution to detect nerve thickness in cases with extremely thin nerve fibers.

Conclusion

Because IP type and accompanying CN anomalies may affect post-implantation performance, their preoperative determination will affect the patient's management. CNA was the highest in the control group and least in IP type 1 cases. There was a significant difference between control and IP types in CNA and CNA/FNA. Therefore, the CN status of IP cases should be carefully evaluated. CN dysplasia was the most frequently accompanying the IP type 1 cases (CN hypoplasia 38.5%, CN aplasia 19.2%) among the IP types, so they need an extra interest in CN evaluation. There was no significant difference in CNCW and IACW between the control and IP cases. It could not be said that CNC and IAC widths are very useful in predicting CN dysplasia in IP cases.

Ethics Committee Approval: This study was conducted at our hospital in accordance with the principles of the Declaration of Helsinki Ethics Committee Approval was taken from University of Health Sciences Turkey, İstanbul Training and Research Hospital Clinical Research Ethics Committee (approval number: 326, date: 27.10.2022).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Surgical and Medical Practices - D.Ö.A.; Concept - D.Ö.A., Y.K., A.S.M.; Design - D.Ö.A., K.F.K., M.B.U.; Data Collection or Processing - D.Ö.A., K.F.K.; Analysis or Interpretation - D.Ö.A., Y.K.; Literature Search - D.Ö.A., M.B.U.; Writing - D.Ö.A.

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Incidence and Risk Factors of Venous Thromboembolism in Patients Undergoing Surgery for Gynecologic Malignancies

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ABSTRACT

Introduction: A potentially fatal complication of gynecological cancer surgery is venous thromboembolism (VTE). Low-molecular-weight heparin prophylaxis does not reduce the risk of VTE. This research determined the incidence of VTE and to identify the risk factors in patients having surgery for gynecological malignancy with extended dual prophylaxis.

Methods: In this retrospective cohort study, all patients with gynecological cancer undergone surgery at the Division of Gynecologic Oncology of İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine were identified between January 2008 and April 2018. Age, body mass index (BMI), menopausal status, comorbidities, the primary site of the neoplasm in gynecology, surgical details, and operative time, the need for intensive care unit admission, perioperative complications, the patient's smoking habits, the diagnosis of VTE, and follow-up assessments up to one month after surgery were among the data collected.

Results: With a 2.4% incidence rate, 29 of 1,201 analyzed patients experienced postoperative VTE events. BMI >30, operation duration >180 min, paraaortic and/or pelvic lymphadenectomy, neoadjuvant chemotherapy, smoking, and chronic renal failure were revealed to be significant variables [odds ratio (OR): 5.357; 95% confidence interval (CI): 1.833-15.654; p=0.002; OR: 5.698; 95% CI: 1.971-16.474; p=0.001; OR: 0.252; 95% CI: 0.068-0.933; p=0.039; OR: 0.002; 95% CI: 0.001-0.025; p=0.001; OR: 0.217; 95% CI: 0.082-0.577; p=0.002; OR: 0.033; 95% CI: 0.003-0.379; p=0.006, respectively].

Conclusion: We suggest that every patient undergoing gynecological oncology surgery should have preoperative pharmacological and postoperative extended dual prophylaxis to achieve the lowest incidence of VTE in this group.

Keywords: Pulmonary embolism, venous thromboembolism, gynecological cancer, postoperative care, deep vein thrombosis

Introduction

The incidence of malignant tumors has risen dramatically recently. Gynecological cancers are common and frequently necessitate radical surgery; in 2020, it is estimated to be 604,127 new cases of cervical cancer, 417,359 new cases of endometrial cancer, and 313,959 new cases of ovarian cancer (1).

Gynecological cancer operations can result in a deadly complication called venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (PE) (2). In patients with gynecologic malignancy, the incidence of postoperative DVT was as high as 37.9% without VTE prophylaxis (2-5). Within 30 days of diagnosis, approximately 12% of VTE patients die (6). Consequently, perioperative VTE prophylaxis is of utmost importance.

There was no universal standard for VTE thromboprophylaxis. There are various therapies and procedures for reducing the risk of postoperative VTE: Mechanical prophylaxis, preoperative or postoperative pharmacologic prophylaxis, and dual pharmacologic and mechanical prophylaxis for an extended duration (7,8). After gynecological cancer surgery, there is an exceptionally high risk of VT, this is true even when low-molecular-weight heparin (LMWH) prophylaxis is used (9,10). Guidelines recommend dual prophylaxis for patients with a high risk of getting postoperative VTE (7, 8). There was a need for further studies regarding

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the selection of cancer patients for thromboprophylaxis. Several studies comparing prophylaxis techniques for VTE incidence have concluded that extended dual prophylaxis is effective (2-4,6,9,11-12). To the best of our knowledge, no research on VTE in gynecological cancer patients getting extended dual prophylaxis has yet been conducted in Turkey.

This current research estimated the incidence of VT and identify risk factors for VTE in patients undergoing surgery for gynecological cancer and receiving extended dual prophylaxis.

Methods

This retrospective cohort analysis included all consecutive patients who had undergone gynecological cancer surgery at Division of Gynecologic Oncology of İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine between January 2008 and April 2018. The clinical Research Ethics Committee of İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine approved the study in accordance with the Declaration of Helsinki (approval number: A-51, date: 08.05.2018). The collected data consisted of age, body mass index (BMI), menopausal status, comorbidities, the primary gynecologic site of the tumor, surgical details (open/laparoscopy, upper abdominal surgery, pelvic and paraaortic lymphadenectomy, inguinal lymphadenectomy), the need for intensive care unit, and postoperative complications (surgical site infection, wound dehiscence, fistula formation, sepsis, acute renal failure, cardiac arrest, DVT and PE, smoking, and follow-up evaluations until one month after surgery. Since 2008, our division has been used extended dual prophylaxis. All patients received combined thromboprophylaxis with compression anti-embolic stock, initiated at the induction of anesthesia, and LMWH (1 mg/kg/day, maximum: 100 mg), which began 12 h before surgery and 8 h after surgery and continued until hospital discharge. All surgical patients received 28 days of extended prophylaxis consisting of stocks and LMWH. All patients provided their written informed consent.

The inclusion criteria included patients who had gynecologic cancer surgery. Patients lacking data and those who did not receive extended double thromboprophylaxis were excluded, as were pregnant patients and those receiving preoperative prophylaxis and anticoagulation therapies.

The primary objective of the study was the occurrence of VTE, defined as DVT or PE or both, confirmed by imaging [a positive duplex ultrasound, venogram, or computed tomography (CT) scan for DVT, and a positive CT examination, pulmonary arteriogram, or CT angiogram for PE] within 30 days of surgery.

The paper was created under the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) standard (10).

Statistical Analysis

SPSS 18.0 for Windows was used to make a statistical study (SPSS Inc., Chicago, IL, USA). The descriptive statistics of the data used mean, standard deviation (SD), median, minimum, maximum, frequency, and ratio values. Using the Kolmogorov-Smirnov test, the distribution of the factors was assessed. The chi-square test was used for categorical variables, and regularly distributed continuous variables, and the Student's t-test was applied. The link between VTE and variables was analyzed using the Sperman correlation method. Additionally, logistic regression analyses were carried out to find the potential predictors of VTE onset. We evaluated the model's structure with and without each factor to avoid multi-collinearity. To control for any confounding effects, we used correlation tests with regression variables. The results were presented as odds ratios (ORs) with 95% confidence intervals (95% CI). The p-value of all tests was calculated as two-tailed with a 95% CI and significance at <0.05.

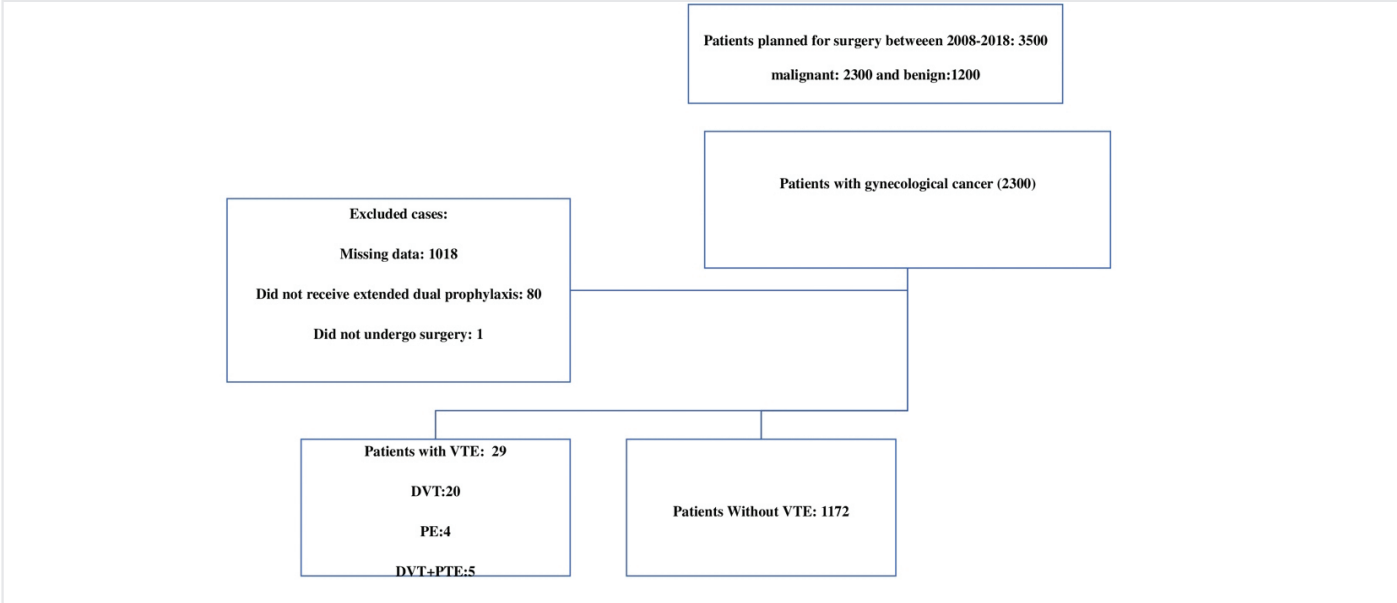

Figure 1. Flowchart diagram of the study
VTE: Venous thromboembolism, DVT: Deep venous thromboembolism, PE: Pulmonary embolism

Table 1. Patient demographic features

Variable	VTE group, (n=29) (DVT: 20.69.0%, PTE: 413.8%)	Non-VTE group, (n=1172)	Total, (n=1201)	p
Age, years	56.76±12.29	54.20±13.92	54.26±13.88 (13-92)	0.327
BMI, kg/m^2	**38.02±20.12**	28.85±7.62	29.04±8.25 (15.22-132.33)	0.021*
>25	**25 (86.2%)**	744 (63.5%)	769 (64.0%)	0.011*
>30	**19 (65.5%)**	424 (36.2%)	443(36.9%)	0.001*
Smoking	**16 (55.2%)**	224 (19.1 %)	240 (20.0%)	0.001*
Prior VTE history	**2 (6.9%)**	3 (0.3%)	5 (0.4%)	0.001*
Neoadjuvant chemotherapy	**7 (20.1%)**	1 (0.1%)	7	0.001*
The type of gynecological cancer	1 (3.4%)	28 (2.4%)	29 (2.4%)	0.848
Vulvar	3 (10.3%)	191 (16.3%)	194 (16.2 %)	
Cervix/vagina uterine	11 (37.9%)	479 (40.9%)	490 (40.8%)	
The ovary gestational	14 (48.3%)	470 (40.1%)	484 (40.3 %)	
Trophoblastic neoplasm	0	4 (0.3%)	4 (0.3%)	
Type of surgery laparoscopic open	6 (20.7%) 23 (79.3%)	179 (15.3%) 993(84.7%)	185 (15.4%) 1016 (84.6 %)	0.425
Duration of surgery, min	171.38±68.63	116.48±48.77	117.81±50.02 (30-420)	0.001*
Hospitalization duration, days	10.93±5.33	9.29±6.74	9.33±6.72 (1-95)	0.194

VTE: Venous thromboembolism, DVT: Deep venous thromboembolism, PE: Pulmonary embolism

Results

Postoperatively, 29 (DVT=20, PE=4, DVT + PE=5) of the 1,201 patients analyzed experienced VTE (DVT: 20, PTE: 4, DVT + PE: 5), for an incidence rate of 2.4%. Figure 1 shows a flowchart for the study. We divided the patients who underwent analysis into two groups: Group 1 is the VTE group, and Group 2 does not have VTE. The patients were evaluated in Tables 1, 2. The population characteristics are outlined in Table 1. The mean age was 54.26 (SD:13.8), and the mean BMI was 29.04 (SD: 15.22). We found no significant differences between the groups concerning age and type of gynecological cancer (vulvar: 2.4%, cervix-vagina: 16.2%, uterine=40.8%, ovary: 40.3%, gestational trophoblastic neoplasm: 0.3%), type of surgery (open: 84.6%, laparoscopic: 15.4%); but BMI (38.02+20.12, P= 0.021), smoking (55.2%, p=0.001), prior VTE (6.9%, p=0.001), neoadjuvant chemotherapy (NACT) (20.1%, p=0.001), and operation duration (171.38+68.63, p=0.001) differed in the VTE group statistically significant.

In Table 2, the characteristics of patients with VTE are summarized. 27 of 29 patients had VTE in the first week and 2 in the third week. In Table 3, comorbidities and surgery modalities between the groups were analyzed. Atrial fibrillation (17.2%, p=0.001), congestive heart failure (13.8%, p=0.003), prior VTE history (6.9%, p=0.001), and chronic renal failure (10.3%, p=0.001) were higher in the VTE group. Operation duration >180 min (44.8%, p=0.001), paraaortic lymphadenectomy (44.8%, p=0.042), and total lymphadenectomy (79.3%, p=0.019), postoperative intensive care unit monitorization (27.6%, p=0.001), sepsis (20.7%, p=0.001), postoperative wound infection (20.7%, p=0.001), and postoperative renal failure (13.8%, p=0.001) were found high in the VTE group.

We conducted a logistic regression analysis to determine the variables that might be potential risk factors for VTE (Table 4). The variables found to be significant included BMI >30 (OR: 5,357; 95% CI: 1,833 to 15,654; p=0.002), operation period >180-minute (OR: 5,698; 95% CI: 1,971 to 16,474; p=0.001), Paraaortic and pelvic lymphadenectomy (OR: 0.252; 95% CI: 0.068 to 0.933; p=0.039), NACT (OR: 0.002; 95% CI:0.001 to 0.025; p=0.001), smoking (OR: 0.217; 95% CI: 0.082 to 0.577; p=0.002), and chronic renal failure (OR: 0.033; 95% CI: 0.003 to 0.379; p=0.006).

Discussion

VTE is the second major factor for mortality in women with gynecologic cancer who received surgery. DVT risk and PE prevalence were calculated to be 17-40% and 1-26%, respectively, in this population of women. International guidelines, including those from the ACCP5 and ASCO, recommend combined mechanical and pharmacological thromboprophylaxis for most cancer patients undergoing abdominal and pelvic surgery (7,8). In a study, Corr et al. (9) used the Caprini Risk Assessment Model to give each patient a Caprini score to clarify the operation's complexity. Seventy-six percent of benign and 96.3% of malignant patients were categorized as high risk and were administered extended dual prophylaxis. Their investigation showed that extended dual prophylaxis significantly decreased the VTE rate from 6.7% to 2.7% (9). Additionally, a meta-analysis of 16 trials demonstrated that preoperative pharmacologic thromboprophylaxis reduces the risk of VTE in the perioperative phase for major gynecologic oncology surgery by about 40% when combined with mechanical prophylaxis (intra-operative and postoperative sequential compression devices) (11). In this study, independently of the Caprini Risk Assessment Model, all cancer patients

Table 2. Patient with VTE characteristics

Patients	Age	Weight	BMI (kg/m²)	Primary malignancy site	Open/ laparoscopic	Operation duration (minute)	Lymphadenectomy	Neoadjuvant chemotherapy	Other primary malignancy	Smoking	Chronic renal failure	Hospitalization (day)	Postoperative diagnosis time of the VTE event (day)
1	63	138	52	The ovary	Open	210	No	No	No	No	No	12	1st day
2	49	74	29	Uterus	Open	110	Yes	No	No	No	No	6	2nd day
3	38	120	41	Uterus	Laparoscopy	155	Yes	No	No	No	No	15	1st day
4	59	100	40	Uterus	Laparoscopy	120	Yes	No	No	No	No	7	2nd day
5	60	94	39	Uterus	Laparoscopy	120	Yes	No	No	No	No	8	2nd day
6	49	93	33	The ovary	Open	120	Yes	No	No	No	No	3	5th day
7	51	102	35	Cervix	Open	300	No	No	No	No	No	15	2nd day
8	53	63	26	The ovary	Open	180	No	Yes	No	No	No	18	3rd day
9	49	78	34	Uterus	Open	55	Yes	No	No	No	No	10	2nd day
10	49	90	35	Cervix	Open	120	Yes	No	No	No	Yes	5	1st day
11	56	170	80	Uterus	Laparoscopy	170	Yes	No	No	No	No	13	1st day
12	63	85	30	The ovary	Open	180	Yes	Yes	No	No	No	20	3rd day
13	61	65	27	The ovary	Open	280	Yes	Yes	No	No	No	12	2nd day
14	75	60	23	The ovary	Laparoscopy	170	Yes	Yes	No	Yes	No	7	1st day
15	85	51	20	The ovary	Open	180	No	No	No	Yes	No	7	1st day
16	70	104	39	Uterus	Open	180	Yes	No	No	Yes	No	8	1st day
17	51	107	44	Uterus	Open	120	Yes	No	No	Yes	No	6	2nd day
18	28	80	30	The ovary	Open	240	Yes	No	No	Yes	No	6	14th day
19	42	98	45	Cervix	Open	200	Yes	No	No	Yes	No	8	3rd day
20	63	55	21	The ovary	Open	160	Yes	Yes	No	Yes	No	12	2nd day
21	58	56	20	Uterus	Open	160	Yes	No	Yes	Yes	No	6	1st day
22	38	74	28	The ovary	Open	160	Yes	No	No	Yes	No	13	2nd day
23	63	119	52	The ovary	Open	240	Yes	Yes	No	Yes	No	7	1st day
24	73	64	26	The ovary	Open	120	No	Yes	No	Yes	Yes	8	1st day
25	73	89	35	Uterus	Open	250	Yes	No	No	Yes	No	7	18th day
26	66	65	25	The vulva	Open	360	No	No	Yes	Yes	Yes	21	2nd day
27	52	85	31	The ovary	Open	180	Yes	No	No	Yes	No	17	3rd day
28	57	160	62	The ovary	Open	120	Yes	Yes	No	Yes	No	22	5th day
29	52	98	39	Uterus	Laparoscopy	90	Yes	No	Yes	Yes	No	18	1st day

VTE: Venous thromboembolism, BMI: Body mass index

Table 3. Comorbidities and surgery modalities

Variable	VTE group, (n=29)	Non-VTE group, (n=1172)	Total	p
Comorbidities				
None	15 (51.7%)	649 (55.4%)	664 (55.3%)	0.919
1	9 (31.0%)	328 (28.0%)	337 (28.1%)	
≥2	5 (17.2%)	195 (16.6%)	200 (16.7%)	
Hypertension	10 (34.5%)	367 (31.3%)	377 (31.4%)	0.690
Diabetes	4 (13.8%)	129 (11.0%)	133 (11.1%)	0.553
Coronary artery disease	8 (27.6%)	92 (7.8%)	100 (8.3%)	0.002*
Atrial fibrillation	5 (17.2%)	16 (1.4%)	21 (1.7%)	0.001*
Congestive heart failure	4 (13.8%)	23 (2.0%)	27 (2.2%)	0.003*
Hipothroidism	2 (6.9 %)	64 (5.5%)	66 (5.5%)	0.481
Prior VTE history	2 (6.9%)	3 (0.3%)	5 (0.4%)	0.001*
Chronic renal failure	3 (10.3%)	3 (0.3%)	6 (0.5%)	0.001*
Operation duration, >180 minutes	13 (44.8%)	156 (13.3%)	169 (14.1%)	0.001*
Pelvic lymphadenectomy	15 (51.7%)	668 (57.0%)	683 (56.9%)	0.571
Paraaortic lymphadenectomy	13 (44.8%)	329 (28.1%)	339 (28.2%)	0.042*
Pelvic + paraaortic lymphadenectomy	23(79.3%)	674 (57.5%)	697 (58.0%)	0.019*
Type of surgery				
Laparoscopic	6 (20.7%)	179 (15.3%)	185 (15.45%)	0.425
Open	23 (79.3%)	993 (84.7%)	1,016 (84.6%)	
Intensive care unit yes	8 (27.6%)	58 (4.9%)	66 (5.5 %)	0.001*
Sepsis yes	6 (20.7%)	9 (0.8%)	15 (1.2%)	0.001*
Postoperative wound infection	6 (20.7%)	14 (1.2%)	20 (1.7 %)	0.001*
Postoperative renal failure	4 (13.8 %)	6 (0.5 %)	10 (0.8 %)	0.001*

VTE: Venous thromboembolism

Table 4. Logistic regression analysis of predictive factors of VTE

Risk factors for VTE	Sperman's correlations (r;p)	Logistic regression analysis	
		OR (95% CI)	p-value
BMI >30	0.001; 0.093	5,357 (1,833-15,654)	0.002*
Operation duration, >180 minutes	0.001; 0.139	5,698 (1,971-16,474)	0.001*
Lymphadenectomy	0.019; 0.068	0.252 (0.068-0.933)	0.039*
Neoadjuvant chemotherapy	0.001; 0.415	0.002 (0.001-0.025)	0.001*
Intensive care unit	0.001; 0.152	0.851 (0.851-0.168)	0.845
Smoking	0.001; 0.138	0.217 (0.082- 0.577)	0.002*
Chronic renal failure	0.001; 0.220	0.033 (0.003-0.379)	0.006*
Prior VTE	0.001; 0.158	0.086 (0.002-3.261)	0.186
Coronary artery disease	0.001; 0.110	0.479 (0.118-1.947)	0.304
Atrial fibrillation	0.001; 0.186	0.119 (0.011-1.258)	0.077
Chronic heart failure	0.001; 0.123	0.873 (0.058-13.230)	0.922

VTE: Venous thromboembolism, BMI: Body mass index

received preoperative LMWH and extended dual thromboprophylaxis, and the incidence of VTE was 2.4%.

Race, age, BMI, ascites, comorbidities, major complications, operating hours, upper abdominal surgery, NACT, ovarian cancer, and lymphadenectomy were all recently found to be risk factors for VTE in patients undergoing laparotomy for gynecological cancers with extended prophylaxis (4). The duration of an operation, disseminated disease, and ovarian cancer were found to be independent risk factors (4). Similarly, we found that chronic renal failure, smoking, lymphadenectomy, NACT, a BMI greater than 30, and operations lasting more than 180 min are all predictors of VTE. Smoking and other primary cancers were among the different risk variables we identified.

The incidence of VTE in gynecologic cancer patients undergoing laparoscopy ranges from 0.5% to 1.2% on average (13). According to Bouchard-Fortier et al. study, only two of 352 individuals receiving laparoscopy for gynecologic cancer without VTE prophylaxis (anticoagulation or compression devices) experienced VTE (14). However, a recent retrospective study found that 11.55% of 355 patients who received gynecological laparoscopic surgery experienced postoperative DVT. This research identified age, hypertension, D-dimer level, surgery duration, intraoperative pneumoperitoneum, and length of hospital stay as significant risk variables (15). We were unable to establish a link between the form of surgery (open versus laparoscopic) and VTE. In this study, 185 patients received dual extended prophylaxis and underwent laparoscopic surgery at a rate of 15.4%. Six (3.2%) were diagnosed with VTE. Five of the six individuals had a BMI greater than 39. Each patient should be evaluated individually because, despite having undergone a laparoscopy, they may still be at risk for VTE for other reasons.

Study Limitations

The study's strengths include its big sample size from a single center where the same gynecologic oncology surgeons worked throughout the research and surgical procedures were standardized. A hospital-based retrospective cohort from a prominent referral hospital in the most populous city is a limitation of this study.

Conclusion

Morbid obesity, prolonged surgery duration, lymphadenectomy, neoadjuvant chemotherapy, smoking, and chronic renal failure were independently associated with the risk of postoperative VTE in patients getting extended dual thromboprophylaxis for gynecological cancer surgery. To obtain the lowest possible incidence of VTE in this population, we propose that all patients undergoing gynecological oncology surgery receive preoperative pharmacologic and postoperative extended dual prophylaxis.

Ethics Committee Approval: The Clinical Research Ethics Committee of İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine approved the study in accordance with the Declaration of Helsinki (approval number: A-51, date: 08.05.2018).

Informed Consent: Written informed consent was obtained from all the subjects.

Peer-review: Externally peer-reviewed.

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The Role of Three-dimensional Printer Modeling in Preoperative Planning of Brain Tumor and Aneurysm Surgery

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ABSTRACT

Introduction: The three-dimensional (3D) modeling technique, which is one of the latest technologies, has been applied in neurosurgical practice. The surgeon's knowledge and experience are crucial for the success of the surgical treatment of brain tumors and brain aneurysms. This study emphasizes that the contribution to successful surgery is by ensuring that the surgeon is fully oriented before and during the operation.

Methods: The study included five patients with brain tumors and five patients with hemorrhagic aneurysm, which were diagnosed between May 2021 and November 2022. Both patient groups were evaluated retrospectively, and all operations were performed by the same experienced surgeon. 3D models of the patients were prepared using a computer program. These models were examined by the operating surgeon during the preoperative period and were sterilized and used as a guide during the operation.

Results: The patients were divided into two groups, one composed of five patients undergoing surgery with the diagnosis of a tumor and the other composed of five patients undergoing surgery due to a ruptured aneurysm. All operations were performed by the same experienced surgeon. Successful clipping was performed in all patients with ruptured aneurysms.

Conclusion: Surgeons have been analyzing complex neuroanatomy data using the 3D modeling technique before surgery. The preoperative simulation improved the surgeon's command of the field and orientation to the surgery. These findings suggest that 3D modeling will positively affect a successful surgical operation and the management of complications that may occur. More prospective randomized studies are needed to confirm these findings.

Keywords: Three-dimensional printing, aneurysm, intracranial tumor

Introduction

Since its introduction in the 1980s, three-dimensional (3D) printing has birthed a new era of rapid prototyping (1). Realistic 3D modeling has been used in preoperative planning, resident education, and the testing and development of new technologies for endovascular and open surgery for cerebrovascular diseases (2,3).

The use of 3D printing in neurosurgery has led to significant developments. Since the importance of complex surgical anatomy affects surgical success, 3D printing has been applied in clinical practice as an advanced neuroimaging method. This technology has enabled a noninvasive visualization of the patient's pathology and complex neuroanatomical structures for both diagnostic and therapeutic purposes (4).

Owing to this technology, complex anatomical structures can be reconstructed from 3D volumes. The physical models created as a simulator can be used for surgical planning by the attending surgeon and for the assistance in education (5).

It is critical to have the necessary anatomical knowledge in surgical planning and to develop a strategy for a successful surgery. Until today, these strategies were made on the basis of cadaver studies and information in neuroanatomy textbooks. The development of 3D modeling technology has created an identical simulation and provided the opportunity to present the surgical anatomy knowledge to the neurosurgeon perfectly. We think that the 3D modeling technique will increase the success of the surgery in the near future and will be used as an important tool in the training of neurosurgeons.

In our clinic, we used 3D printing modeling technique in our patients who underwent surgical procedures for cranial tumors or aneurysms. This study explains in detail the 3D models we used in the preoperative planning phase and our intraoperative experiences for treating these patients.

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Methods

Ten patients who underwent surgery in our clinic with the diagnosis of brain tumor and intracranial aneurysm between May 2021 and November 2022 were included in this study. The contribution of the use of preoperative 3D models during surgery was analyzed retrospectively.

In the neuroanatomy laboratory of our clinic, 3D modeling studies started before May 2021. Developing the modeling technique, optimizing the printing time and low cost targets have emerged because of many years of work and this technology has been put into the service of our patients. Today, this method has been further developed in our clinic and it has started to be applied in complex spine stabilization and spine tumors surgeries. It is aimed to contribute to the literature by sharing our experience in this technology, which we have been working on and developed for many years. This technique continues to be routinely used and developed by the same surgeon who performed these surgeries.

All patients reviewed and signed the informed consent forms in detail. Approval from the İzmir Katip Çelebi University Ethical Committee was granted (approval number: 0598, date: 22.12.2022). Data regarding the demographics of the patients, location of the tumor, symptoms upon admission, pathology results, the duration of the operation, duration of stay, presence of complications, and Karnofsky performance score (KPS) were evaluated.

3D Model Creation

The computed tomography (CT) and magnetic resonance imaging (MRI) data were obtained in Digital Images and Communications in Medicine (DICOM) format, enabling the formation of an interface between devices in favor of creating a solid model. The RadiAnt DICOM Viewer (Medixant, Poznan) application was used to differentiate between the tumoral tissue, skull base, and vascular neuroanatomy. The data of the tumoral tissue, skull base, and vascular structures were converted into a 3D model and exported as ".stl" files. 3D STL models were obtained from the Radiant DICOM Viewer and meshed again using the Meshmixer™ (Autodesk, San Rafael, U.S.A.) software. The models prepared for 3D printing were exported and sliced using the Cura (Ultimaker, Geldermalsen, The Netherlands) software and then the Gcodes were created (Figure 1) (6).

The PLA filament of 2.85 millimeters was used during the printing process in accordance with the manufacturer's recommendations. The process settings were standardized as follows: extruder temperature at 215 °C, room temperature at 24 °C, primary layer height of 0.1 mm, and filling rate of 20%. The 3D models were printed on a 1:1 scale (7).

The skull base model and 3D tumor model were created separately in different sessions. Thin section (0.3 mm) brain tomography data were used for modeling the skull base, whereas the thin section (0.5 mm) cranial MRI data were used to print the tumor tissue. The 3D tumor model was adhered to the skull base model using a special model glue and the tumor model was colored with special model paints.

Brain aneurysm 3D models were prepared in a single session using thin section (0.3 mm) cranial CT angiography data, and then the vascular structures were colored using special model paints.

A professional photography studio was created to obtain high-quality 3D images of each 3D model by combining multiple focus images using Canon EOS 2000D (Tokyo, Japan).

Thin section tomography data are used in the printing of bone tissue and vascular structures while creating the 3D model. Thin section t2 flair MRI sequence data are used for printing tissues such as tumors. The required print quality could not be achieved in non-thin section tomography and t2 flair MRI sequence data. It is technically possible to model every patient whose necessary data can be obtained. The main difficulty is that the entire modeling cannot be done in a single print. The necessary data must be printed separately and then joined with suitable adhesives. The aim of all this 3D modeling technique is to increase the surgical neuroanatomical orientation of the neurosurgeon and to reduce the complications that may develop.

Preoperative planning was performed based on the patient's history and imaging, individualized 3D printed tumor, skull base, and vascular neuroanatomy models. The models were sterilized and taken to the operation theater for intraoperative navigational purposes. After the operations were performed, the material quality, potential benefits on the preoperative planning, impact on the prediction of complications, and usefulness for the educational purposes of the 3D printed models were evaluated.

Statistical Analysis

The Statistical Package for Social Sciences Version 22.0 (SPSS, Chicago, IL, USA) software was used for statistical analysis. The mean, median, and standard deviation values were also obtained.

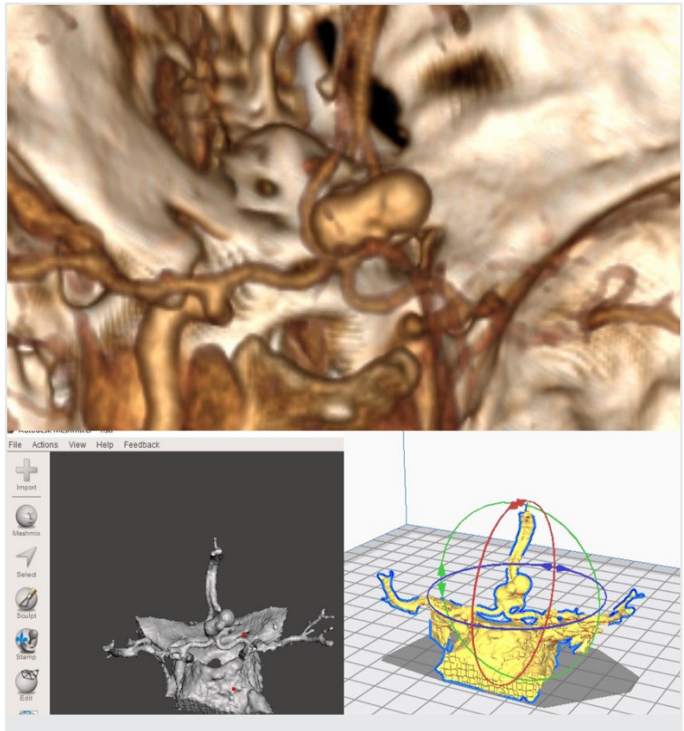

Figure 1. Screen images from computer programs used for 3D aneurysm modeling of a patient with acom aneurysm

Results

Five patients with a diagnosis of brain tumor and five patients with a bleeding aneurysm were included in our study. 3D models of all patients were prepared in the preoperative period, and the surgeon had the opportunity to work on 3D models in the neuroanatomy laboratory before surgery (Figures 2-4). Both patient groups were evaluated within themselves.

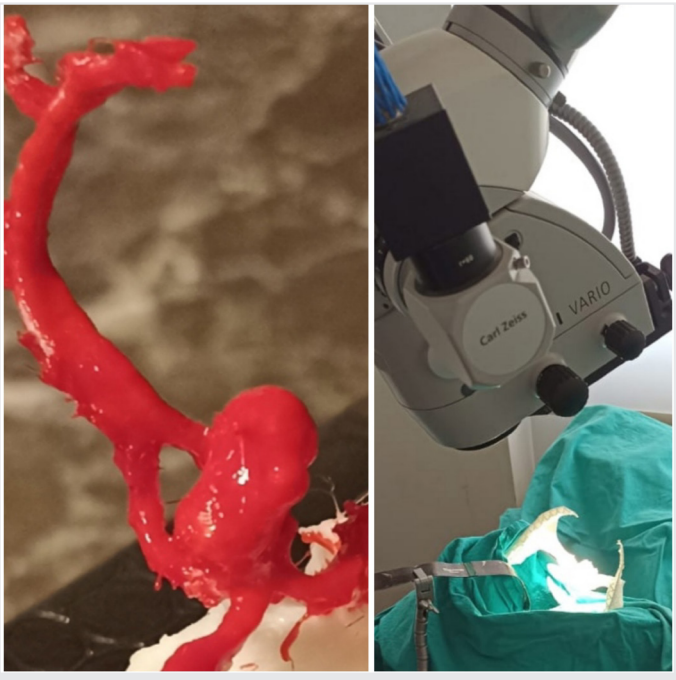

Figure 2. Aneurysm 3D model and training under a surgical microscope in a neuroanatomy laboratory

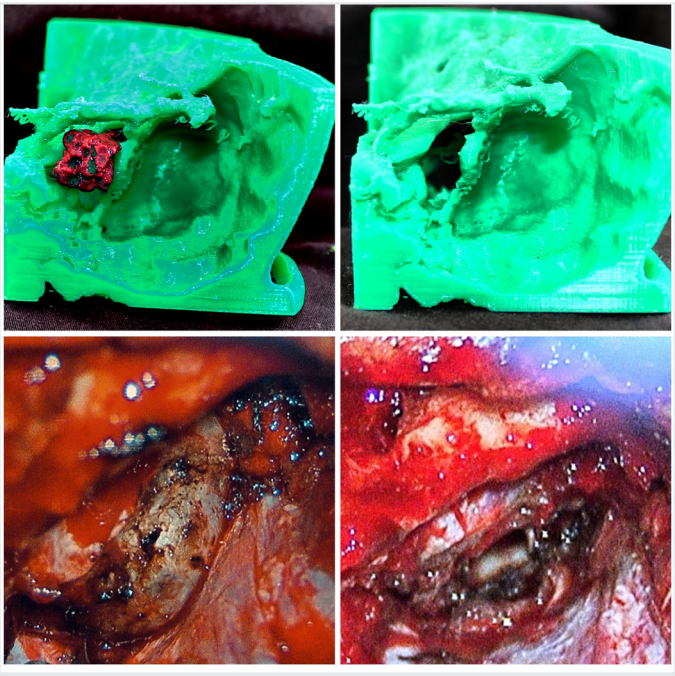

Figure 3. Presentation of the created 3D model of the patient with a retro-orbital tumor with intraoperative image

Tumor Group (Table 1)

The mean age of five patients was 57.2±24.47 (range 22-84), in which 40 % (n=2) of the patients were female and 60% (n=3) male. The mean duration of hospital stay was 7.8±0.83 days. The presenting symptoms were headache (40%), dizziness (20%), hearing loss (20%), and vomiting (20%). Three patients had tumors in the posterior fossa. The other patients' tumors were located on the anterior skull base. Three patients (60%) underwent total resection, one patient gross total resection (20%), and one patient (20%) subtotal resection. The mean duration of operation was 202±35.63 minutes. The pathology results were as follows: two (40%) meningiomas, one (20%) hemangioblastoma, one (20%) neuroendocrine metastasis, and one (20%) schwannoma. One patient experienced temporary oculomotor paralysis and was treated with I.V. steroids for 7 days. The patient also received additional oral steroid treatment after discharge. The mean postoperative KPS was 88±16.43. The KPS of the patients at the time of discharge was as follows: 100 (40%, n=2), 90 (40%, n=2), and 60 (20%, n=1).

Ruptured Aneurysm Group (Table 2)

The mean age of five patients was 46±15.08. 40% (n=2) of the patients were female and 60% (n=3) male. All patients had high bleeding stages and were in a severe coma, and their Glasgow Coma scale (GCS) were below 8. The mean GCS was 6.2±1.48. Four patients (80%) had Fisher grade 4/Yasargil grade 4, whereas one patient (20%) had Fisher grade 3/Yasargil grade 5. While the aneurysm localization of three patients (60%) was in the middle cerebral artery, two patients (40%) were in the anterior communicating artery. The mean size of the aneurysm was 11.9±5.89 mm, and 4 patients (80%) had intraparenchymal hematomas opening into the ventricle. The mean hematoma volumes were 28.59±18.4 cc. The mean midline shift in the patient' brain tomography was 7.66±4.49

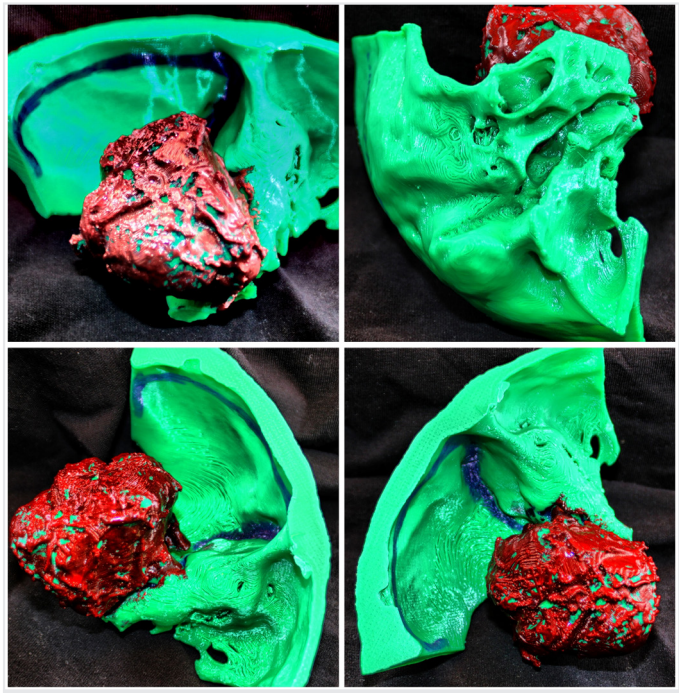

Figure 4. Preoperative 3D model of a patient with vestibular Schwannoma who underwent cerebellopontine angle tumor surgery

mm. Decompressive craniotomy, external ventricular drainage, and clipping were successfully performed in all patients. The mean duration of operation was 188±19.23 minutes. One patient was discharged with a KPS of 90. Severe vasospasm developed in four patients postoperatively. While three patients died, one patient was discharged with a KPS of 20 in a vegetative state. In the high-stage ruptured aneurysm group, the mean hospital stay was 20.6±14.94 days.

Discussion

Okonogi et al. (8) created 3D-printed anterior clinoidectomy models in patients with sphenoid wing meningiomas and giant ophthalmic segment aneurysms. They performed anterior clinoid drilling on the model preoperatively and considered it beneficial for surgical training (8). We also performed drilling studies on the models we created in our study and observed the benefits of these drills for resident training. Particularly in the 3D model of our patient with a retro-orbital mass lesion, the relationship of the tumor with the superior orbital fissure positively affected the planning of our surgical strategy.

Oishi et al. (9) simulated deep intracranial tumors (meningioma, schwannoma, epidermoid tumor, etc.) in 12 patients in a 3D virtual environment. They then decided on surgical strategies by creating 3D

Table 1. Demographic data, as well as location and pathology of the tumors and complications are shown on the table

No	1	2	3	4	5
Age	84	22	48	76	56
Gender	Male	Female	Female	Male	Male
Radiology	Cerebellum	Cerebellopontine	Retro-orbital	Cerebellum	Olfactory groove
Size (mm)	55*56*44	40*35*30	20*12*15	40*41*35	25*30*19
Symptom	Dizziness	Hearing loss	Headache	Vomitting	Headache
Sign	Neurological deficit	Neurological deficit	Exophthalmus	Neurological deficit	None
Surgery	Total resection	Subtotal resection	Total resection	Gross total resection	Total resection
Surgery time (min)	230	210	170	240	160
Pathology	Meningioma	Schwannoma	Hemangioblastoma	Neuroendocrine metastasis	Meningioma
Complication	None	None	Temporary oculomotor paralysis	None	None
Hospital stay (day)	7	9	8	8	7
Preoperative KPS	100	90	100	70	100
KPS on discharge	100	90	90	60	100

KPS: Karnofsky performance score; min: Minimum

Table 2. Demographic and morphological data, as well as complications of the aneurysm surgery are shown on the table

No	1	2	3	4	5
Age	54	51	23	62	40
Gender	Male	Male	Female	Female	Male
Aneurysm	MCA	Acom	Acom	MCA	MCA
Size (mm)	15	12	6,5	6	20
Parenchymal hemorrhage size (mm)	20*20*25	40*45*29	none	42*60*39	49*41*34
Shift (mm)	3,5	8,6	2,5	12,5	11,2
Intraventricular hemorrhage	+	+	-	+	+
SAH	Fischer grade 4 Yaşargil grade 4	Fischer grade 4 Yaşargil grade 4	Fischer grade 3 Yaşargil grade 5	Fischer grade 4 Yaşargil grade 4	Fischer grade 4 Yaşargil grade 4
GCS	6	7	4	8	6
Surgery	Decompressive craniotomy + succesfully clipping	Decompressive craniotomy + succesfully clipping	Decompressive craniotomy + succesfully clipping	Decompressive craniotomy + succesfully clipping	Decompressive craniotomy + succesfully clipping
Surgery time (min)	200	180	190	210	160
Complication	Vasospasm	None	Vasospasm	Vasospasm	Vasospasm
Hospital stay (day)	16	15	10	15	47
Outcome	Exitus	Dischargered	Exitus	Exitus	Dischargered
KPS on discharge	-	90	-	-	20

MCA: Middle cerebral artery; KPS: Karnofsky performance score; GCS: Glasgow Coma scale; SAH: Subarachnoid haemorrhage

anatomical models. In our study, we created surgical strategies based on such models.

Lan et al. (10) created preoperative 3D models for aneurysms and highly vascular tumors. They discussed the optimal preoperative surgical approach and the relationship of the aneurysm or tumor with the calvarium. They emphasized that young neurosurgeons would benefit from models, especially in cases with complex anatomy (10). In our study, 3D models of the aneurysms positively affected the surgical strategy. Aneurysm clipping was successful in all our aneurysm patients. It was observed that working on the 3D model contributed to the success of the surgery.

Van de Belt et al. (11) used 3D-printed models of glial tumors to provide sufficient information to the patients. They stated that the patients had a better understanding of their diseases with the help of 3D printed models. It was also noted that the patients were more confident in deciding on the treatment options offered to them (11). In our study, the 3D printed models were presented to patients and their relatives and were used to guide them while explaining the treatment of the disease.

Lin et al. (12) created a 3D model of two patients with a sellar tumor and one patient with acoustic neurinoma and compared the shape of the tumors intraoperatively. The relationship of the tumor with the sphenoid sinus, hypophyseal fossa, cerebellopontine angle, and main arteries is presented in 3D printed models. They emphasized the potential benefits of 3D modeling in neurosurgery education, while stating that cranial nerves would not be suitable for modeling (12). In our study, the nerve modeling of a patient with a corner tumor could not be performed clearly in 3D modeling, but the complex anatomy of the tumor in brainstem localization was clearly demonstrated. The 3D model has clearly made a positive contribution to the surgical treatment of the patient's surgery and resident education.

Damon explained in detail the 3D modeling of tumors and the printing technique (13). We successfully applied this technique in our study.

Thawani et al. (14) showed a relationship between low-grade glial tumors and white matter fibers on a 3D model. However, we did not perform white matter modeling in this study.

In another study, Thawani et al. (3) modeled arteriovenous malformations (AVM), feeding arteries, and drainage veins by printing them separately preoperatively. However, only aneurysm models were created in our study.

Weinstock et al. (15) produced monochrome models for patient and resident education. Uzunoglu et al. (7) emphasized the positive contribution of preoperative 3D models for successful surgery in 15 patients operated for an AVM.

Anderson et al. (16) created 3D models of ten aneurysms and compared the aneurysm diameter measurements with those measured by digital subtraction angiography (DSA), indicating no significant difference. Kondo et al. (17) analyzed the length, thickness, and diameter of the aneurysm on 22 aneurysm models and found no significant difference. Mashiko et al. (18) evaluated DSA and intraoperative appearance on 3D models of 20 aneurysms. They reported that the modeling was realistic and consistent. Namba et al. (19) compared 3D models of ten aneurysms with DSA and reported no inconsistencies. Furthermore, Wurm et al. (20) compared 13 aneurysm models intraoperatively and reported no inconsistencies.

It will take time for new technologies and developed techniques to be accepted in the medical field. New materials and different techniques continue to be introduced about the 3D modeling technique. As limits continue to be exceeded, 3D modeling may become routine in clinical use. To now, experience needs to be accumulated and developed to meet the high expectations in the field of neurosurgery (21).

All these studies suggest that 3D modeling is a safe technique and is anatomically consistent with reality. When we evaluated the radiologic measurements and intraoperative observations of our patients in our study, we observed that the 3D models we created were exactly compatible with actual pathology and showed no inconsistencies.

Study Limitations

Desired quality could not be achieved in the modeling of patients with CT and MRI sections over 1 cm. Therefore, these patients were excluded from the study.

Conclusion

Surgeons have been analyzing complex neuroanatomy data in detail with the use of 3D modeling before surgery. The preoperative simulation improved the surgeon's command of the field and their orientation to the surgery. Particularly in brain stem localization and during operations, in which the surgeon encounters technical challenges, such as clipping of a bleeding aneurysm, the benefit of 3D models has been confirmed. The difficulty in clipping a ruptured aneurysm accompanied by increased intracranial pressure, hematoma, and extensive subarachnoid hemorrhage, termed as angry brain, was overcome with improved orientation to the surgical field conferred by 3D models. Successful clipping was achieved in all patients. All these findings suggest that the use of preoperatively designed 3D models can result in a successful surgical operation and facilitate the management of complications that may occur.

Ethics Committee Approval: Approval from the İzmir Katip Çelebi University Ethical Committee was granted (approval number: 0598, date: 22.12.2022).

Informed Consent: All patients reviewed and signed the informed consent forms in detail.

Peer-review: Externally peer reviewed.

Authorship Contributions

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

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

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Factors Affecting Surgical Outcomes in Cervical Spondylotic Myelopathy: A Retrospective Study

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ABSTRACT

Introduction: To determine the factors that may affect surgical outcomes in patients with cervical spondylotic myelopathy (CSM) by evaluating consecutive patients at our institution.

Methods: Medical charts of the patients were reviewed retrospectively between 2012 and 2019. The modified Japanese Orthopedic Association scale and the postoperative functional recovery (PFR) rate were used to assess the clinical outcomes and benefits of surgical intervention. Demographics, clinical presentations, radiological variables, and surgical techniques were evaluated.

Results: A total of 98 patients with CSM with a mean age of 55.4±10.7 years were included. Fifty (51.0%) patients were male. A good preoperative functional status ($p=0.001$, $R_2=0.22$), female sex ($p=0.008$, $R_2=0.07$), short preoperative period ($p=0.007$, $R_2=0.074$), and dynamic compression on more than one dynamic magnetic resonance imaging phase ($p=0.001$, $R_2=0.115$) were associated with good surgical outcomes and a higher PFR rate. No significant differences were found in the PFR rate and the complications among all surgical approaches ($p>0.05$).

Conclusion: Demographic, clinical, and radiological factors, such as sex, preoperative functional status, preoperative clinical course, and number of dynamic compression phases, can impact surgical outcomes in CSM. Early diagnosis is very critical and extremely important in reducing persistent neurological deficits associated with CSM. We recommend early surgical intervention for patients with CSM to obtain good surgical outcomes.

Keywords: Cervical spine, myelopathy, spondylosis, corpectomy, stabilization

Introduction

Cervical spondylotic myelopathy (CSM) is the most common cause of spinal cord injury in the advanced age population that leads to spinal cord dysfunction (1). Joint-related spinal cord compression develops later, as ligament hypertrophy often happens gradually. Patients who present with severe myelopathy are indicated for surgical intervention to prevent clinical worsening (2). Spinal cord deformations caused by CSM are treated either anteriorly or posteriorly or by two-stage combined surgery. The anterior approach includes discectomy and/or corpectomy with fusion, which can be performed more easily to relieve compression on the spinal cord caused by herniations, osteophytes, and hypertrophic ligaments. The posterior approach typically includes foraminotomy, laminectomy, fusion with laminectomy, and laminoplasty.

Although some evidence indicates that most patients with CSM recover after surgery, the basic clinical and imaging factors that predict surgical outcome have not been established (3). Pre-surgical magnetic resonance imaging (MRI) may predict postoperative functional recovery levels in CSM. Age, duration of symptoms, and baseline score for the modified Japanese Orthopedic Association (mJOA) scale appear to correlate with postoperative functional scores. A recent systematic analysis identified important limitations in the current medical literature that prevent formal recommendations regarding the use of prognostic factors in treatment algorithms (4). The main limitations were that the mJOA scale is not used and the disregard of factors that confuse the functional status when evaluating patients prospectively.

In this retrospective study, we determined the factors that may affect the surgical outcomes of patients with CSM by evaluating 98 patients consecutively operated at our institution.

Methods

The medical charts of patients with CSM operated consecutively at our institution between 2012 and 2019 were reviewed retrospectively. Demographics, clinical presentations, radiological variables, and surgical techniques were evaluated. Our study was approved by the Clinical

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Research Ethics Committee of University of Health Sciences Turkey, Fatih Sultan Mehmet Training and Research Hospital under a decision number (approval number: 2020/3).

Verbal and written consent were obtained from all patients who agreed to participate in this study.

Study Population and Criteria

The inclusion criteria of the study were age 18 years or older, symptomatic CSM with at least one clinical sign of myelopathy, imaging compatible with cervical cord compression, and no previous cervical spine surgery. The exclusion criteria were being asymptomatic, having an active infection, neoplastic disease, rheumatoid arthritis, ankylosing spondylitis, and concomitant symptomatic lumbar stenosis. In addition, patients lost to follow-up were excluded from the study. The surgical criteria were persistent or recurrent radiculopathy, progressive neurological deficit, and static neurological deficit with severe radicular pain (5).

Out of 107 patients screened, 9 were excluded. Of these 9 patients, 2 were asymptomatic, 2 had symptomatic lumbar spinal stenosis, and 5 were lost to follow-up. The final analysis evaluated the data of 98 patients.

Clinical Evaluation

Clinical evaluation was conducted for patients suffering various symptoms, such as gait disturbance, bilateral upper extremity paresthesia, Lhermitte phenomenon, pyramidal motor deficits, hand muscle atrophy, positive Hoffman's sign, stable basal skin reflex plantar responses, lower extremity spasticity, and broad-based unsteady gait that were supported by radiological evidence of compression on the spinal cord in the cervical region.

Clinical variables that were investigated for prognosis included age, sex, symptom duration (preoperative clinical course), and initial functional status (preop mJOA). The mJOA scale and postoperative functional recovery (PFR) rate were used to evaluate the clinical outcomes and the benefits of surgical intervention (6).

Imaging Analysis

Imaging analysis was performed by two neuroradiologists with standard 300% magnification Sante DICOM Viewer Pro v. made using 11.7.3 64-bit software. After a reasonable interval, the two neuroradiologists repeated the measurements, following the same protocol and using the same computer unit and software.

MRIs were analyzed based on three parameters: 1) the cross-sectional area at the maximum compression level of the spinal cord; 2) the spinal cord signal intensity on the T1- and T2-weighted MRI sequences; and 3) the number of compression levels.

Sagittal plane alignment was calculated using the Harisson posterior tangent method on standing scoliosis (whole spine) radiographs that were taken from 3 feet (~90 cm) distance. The alignment was measured by finding the angulation created by intersecting the tangents drawn between the posterior edges of both C2 and C7 bodies (7) (Figure 1). The patients were divided into two groups according to the spinal cord cross-sectional area on the axial sequences based on cut-off values reported previously (0.76 cm^2) (8-10). The surface measurement at the narrowest level of the spinal cord at the maximum compression level (in cm^2) was obtained on axial T2-weighted sequences (Figure 2).

Functional Evaluation

The preoperative and 12th postoperative month evaluations were performed using the mJOA functional disability scale. The PFR rate was calculated using the pre- and postoperative mJOA scores via the formula by Hirabayashi et al. (11):

PFR rate = [postoperative mJOA - preoperative mJOA/Normal value (18) - preoperative mJOA] ×100.

The postoperative functional evaluation was conducted at 12-month intervals, to allow the optimum time for recovery after CSM therapy (12,13).

Surgery

Surgical decompression of the cervical spine was performed in all patients. The suitable approach, number of cervical levels to be treated,

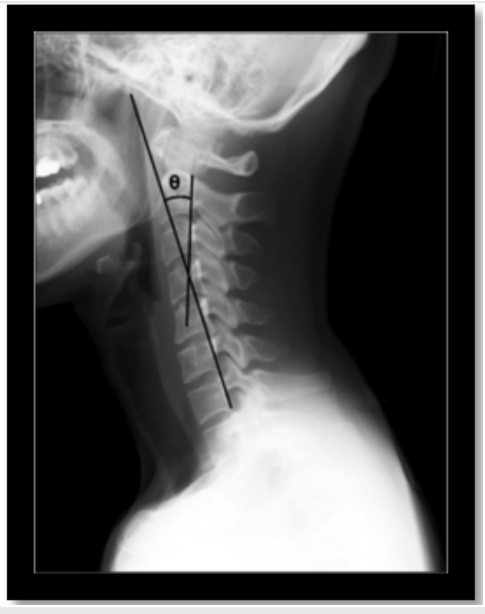

Figure 1. Diagram of Harrison's posterior tangent method

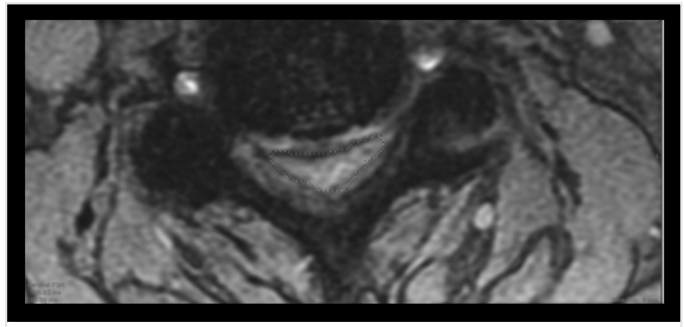

Figure 2. Axial section area measurement using 64-bit Sante DICOM Viewer Pro v. 11.7.3 software

and fixation option were decided according to the CSM treatment algorithms. Three approaches were applied, namely, anterior, posterior, or combined approaches.

The anterior approach included discectomy and/or corpectomy with fusion. In the anterior cervical approach, anterior discectomy is performed up to three levels to remove the disks or osteophytes pressing on the spinal cord to relieve compression on the spinal cord. Then, a graft for interbody fusion is placed in the disk space (2,14). This technique has become a preferred method since it limits the defect by removing less bony structures (14,15).

The posterior approach included laminectomy, fusion with laminectomy, and laminoplasty. To reduce post-laminectomy kyphosis, laminectomy alone is no longer performed in treating CSM. Fusion with laminectomy includes posterior decompression and stabilization, which prevents kyphosis and instability in the late postoperative period. In stabilization, fusion to the facet joint space should be planned with instrumentation. Laminoplasty is performed to prevent the development of postoperative kyphosis and to maintain neck movement.

Postoperative Course

The patients that postoperatively showed no recovery or improvement were reassessed to rule out the non-spondylotic causes of myelopathy (16). Straight and dynamic cervical radiographs, computed tomography (CT) images, and MRI with axial, coronal, and sagittal sequences were thus obtained.

Statistical Analysis

All variables with normal distributions were analyzed using descriptive statistics. The relationships among continuous variables were evaluated using Spearman's correlation and univariate linear regression analysis. The t-test was used when a variable was continuous, while the other was categorical. For categorical data, the chi-square test was used.

The Mann-Whitney U test was used to analyze the relationship between categorized variables and changes in postoperative score and recovery rate since these scores did not follow the Gaussian distribution. Values were reported as mean ± standard error of the mean.

A multiple linear regression model was calculated using forward stepwise regression. Univariate analysis was performed to identify statistically and clinically significant variables for evaluation in exploratory data analysis. SPSS version 21 (IBM Corp. Armonk, NY, USA) was used for statistical analysis, and $p<0.05$ was considered statistically significant.

For statistical comparisons, the patients were divided into two age groups (≥65 years and <65 years), and the preoperative clinical course was accepted as short if the duration of symptoms ≤12 months and long (chronic) if it >12 months (17). The study analyzed a relatively small sample size, and were data obtained from a single center. All cut-off values were obtained from larger data sets reported in the literature.

Results

The demographic, clinical, and radiological characteristics of the patients are summarized in Table 1. Seventy patients underwent an

Table 1. Patient demographics and clinical variables of the investigated patients

Demographics and clinical variables	Patients (%)
Preoperative clinical course (months)	16.4±12.9
Age (years)	55.4±10.7
<65	79 (80.6%)
≥65	19 (19.4%)
Sex	
Male	50 (51.0%)
Female	48 (49.0%)
Severity of CSM (mJOA scores)	
Mild (mJOA >15)	48% (47)
Moderate (mJOA 12-14)	39.8% (39)
Severe (mJOA <12)	12.2% (12)
Cross-sectional area of the spinal cord (mean ± SD)	0.76±0.022
<0.76 cm^2	49% (48)
≥0.76 cm^2	51% (50)
Anatomical level of stenosis	
C2-C3	5% (5)
C3-C4	32% (32)
C4-C5	66% (65)
C5-C6	87% (86)
C6-C7	53% (52)
Number of segments with spinal compression	
1	5% (5)
2	49% (48)
≥3	46% (45)
Myelopathic etiologies	
OPLL	31% (30)
Spondylosis	75% (73)
Calcified disk herniation	33% (33)
Hypertrophic ligamentum flavum	25% (25)
Subluxation	5% (5)
The number of myelopathy etiology number	
1	33% (33)
2	59% (57)
>3	8% (8)
Cervical alignment	
Lordosis	36% (35)
Neutral	51% (50)
Kyphosis	13% (13)
Dynamic pressure	
Present	62% (61)
Absent	38% (37)
Surgical approach	
Anterior	72% (70)
Posterior	21% (21)
Combined	7% (7)

mJOA: modified Japanese Orthopedic Association

anterior decompressive approach (discectomy, corpectomy, and fusion instrumentation), 21 underwent a posterior decompressive approach (laminectomy and fusion with posterior instrumentation), and 7 underwent a combined approach. In all cases, the spinal cord was confirmed to be sufficiently decompressed on CTs conducted in the early postoperative period and assessed by two experienced neuroradiologists. No patients were reoperated due to insufficient decompression.

Postoperative Complications

Cerebrospinal fluid (CSF) fistula was reported in 4 patients (3 posterior approach, 1 anterior approach), which was treated with primary suture fibrin sealants (17). No patient was reoperated for the CSF fistula. Unilateral C5 paralysis occurred in two patients. One patient underwent a posterior approach, and the paralysis manifested late, on the 15th postoperative day. The symptoms completely resolved with conservative treatment. The second patient underwent an anterior approach, and the paralysis was identified early. Unfortunately, the patient did not improve. Anterior displacement of the graft and plate-screw system was observed in the early control radiographs of three patients who underwent an anterior approach. Both cases were followed closely, and, eventually, fusion occurred without any malalignment. Salivary fistula related to esophageal perforation occurred in one patient. Oral feeding was stopped, and the symptoms resolved after 20 days.

Factors Affecting the Preoperative mJOA Score

The results of the univariate analysis of the relationship between the aforementioned demographic, clinical, and radiological characteristics of the patients and their preoperative mJOA scores are presented in Table 2.

Age: The preoperative mean mJOA score of patients >65 years old was 14.32±0.19, whereas those >65 years old was 12.68±0.50. The younger patient group showed better functional status, and the relationship between the preoperative mJOA score and age group was significant (p=0.001).

Symptom duration: The mean preoperative mJOA score of patients with a short preoperative clinical course (symptom duration <12 months) was 14.39±0.23, whereas that of patients with chronic symptoms (symptom duration >12 months) was 13.3±0.31. As the symptom duration increased, the mJOA score worsened (p=0.007).

Table 2. Factors affecting the preoperative modified Japanese Orthopedic Association score

	Mean preoperative mJOA score	95% CI	p	R^2
Age group			0,0011*	0,118
<65	14,32	13.9-14.7		
>65	12.68	11.6-13.7		
Sex			0.0242*	0.052
Male	14.44	14.0-14.88		
Female	13.58	12.98-14.18		
Duration of symptoms			0.007*	0.073
<12 months	14.39	13.93-14.84		
>12 months	13.33	12.70-13.97		
MRI signal properties			0.0261	0.005
Normal T1/normal T2	14.75	13.64-15.86		
Normal T1/hyperintense T2	13.78	10.89-15.91		
Hypointense T1/hyperintense T2	13.40	11.78-15.78		
Cross-sectional area of the spinal cord (cm^2)			0.117	0.025
<0.76 cm^2	13.75	13.14-14.36		
>0.76 cm^2	14.24	13.36-14.75		
Number of segments with spinal compression			0.007*	0.072
1	13.00	10.68-15.32		
2	14.81	14.43-15.20		
>3	13.24	11.19-15.29		
Cervical alignment			0.881	0.00
Lordosis	13.71			
Neutral	14.12			
Kyphosis	14.31			
Dynamic pressure			0.827	0.001
Present	13.97	13.51-14.42		
Absent	14.05	13.36-14.75		

mJOA: modified Japanese Orthopedic Association, CI: Confidence interval, MRI: Magnetic resonance imaging, PFR: Postoperative functional recovery

Sex: The average preoperative mJOA value for women in the study group was 14.4±0.22, whereas for men it was 13.6±0.3. Although no difference was found between the sexes in terms of symptom duration (p=0.567) and age grouping (p=0.504), a significant difference was found in preoperative mJOA scores (p=0.029). The preoperative functional neurological status of the male sex was significantly better.

MRI signal properties: The preoperative mJOA scores of patients with MRI signal changes were significantly lower than those with normal T1 and T2 signal intensity (p=0.026).

Several compression segments: The mJOA score was found to be significantly lower in the group with compression in 3 or more segments (p=0.007). No significant difference was found compared to 1 or 2 compression groups in terms of mJOA scores.

Other variables: Significant relationships of the cross-sectional surface measurements of the spinal cord (p=0.117), presence of dynamic pressure (p=0.827), and cervical sagittal alignment characteristics (p=0.881) with preoperative mJOA score were not observed.

Factors Affecting the Postoperative Functional Outcomes (PFR rates)

Preoperative functional status: A highly significant relationship was observed between the preoperative mJOA score groups and the degree of postoperative functional improvement (p=0.000, R^2=0.22). Patients with a higher mJOA (i.e., good preoperative functional status) had better surgical outcomes.

Age: No significant relationship was found between age and the PFR rate (p=0.153, R^2=0.021). The PFR rate was higher (69.3% vs. 59.9%) in the younger group (<65 years) than in the older group (≥65 years). However, the difference was not significant.

Sex: A significant difference was found between the sexes in terms of functional improvement. The postoperative recovery rate of the female sex was better (p=0.008 and R^2=0.07).

The duration of symptoms: Patients presenting with signs and symptoms for a shorter period (<12 months) had higher PFR values (p=0.007, R^2=0.074).

Dynamic compression: According to the classification system defined previously using cervical dynamic MRI, the PFR rates of the cases with one or more phase changes in the compression phase were significantly higher (p=0.001, R^2=0.115).

Other variables: No significant statistical relationship was found between the spinal cord cross-sectional area, MRI signal characteristics, the number of segments with compression, cervical alignment, or surgical approach with the degree of functional improvement. No significant correlation was found between cervical sagittal alignment and functional status before (p=0.881, R^2=0.00) or after surgery (p=0.185, R^2=0.021) (Table 3).

Multiple linear regression analysis was performed to predict the PFR rate according to the preoperative mJOA score and the presence of dynamic compression. A high preoperative mJOA score (>15), with the presence of dynamic compression, was identified as a significant predictor of the PFR rate. The two variables accounted for 28% of the variance in the PFR rate. Both variables can thus separately predict the PFR rate (p<0.05). The predictive values of a high mJOA score and the presence of dynamic compression were β=0.42 and β=0.32, respectively.

Factors Affecting the Change in mJOA Scores

Preoperative functional status: A significant statistical relationship was observed between the preoperative mJOA score and change in mJOA (ΔmJOA) score or PFR (p=0.000, R^2=0.217). The ΔmJOA is higher in patients with a lower preoperative mJOA score (Table 4).

Age: The ΔmJOA was higher in the older (≥65 years) group, and the difference between the age groups was statistically significant (p=0.042, R^2=0.042).

Several compression segments: The ΔmJOA in the group with three or more compression segments was significantly higher (p=0.000, R^2=0.078).

Dynamic compression: In the presence of dynamic compression, the difference in the mJOA score between the pre- and postoperative periods were significantly higher in the group with dynamic compression than in the group without (p=0.000, R^2=0.163).

The type of surgical approach: According to the type of surgical approach, the improvement in mJOA score was significantly higher in those who underwent a posterior or combined approach than in those who underwent an anterior approach alone (p=0.000, R^2=0.167).

Other variables: The effect of sex, symptom duration, MRI signal characteristics, spinal cord cross-sectional area, and cervical sagittal alignment on ΔmJOA could not be demonstrated (Table 4).

Multiple linear regression analysis was performed to predict postoperative ΔmJOA according to preoperative mJOA score and the presence of dynamic compression. A moderate preoperative mJOA score (12-14) and dynamic compression are significant predictors of postoperative ΔmJOA. The two variables together explain 28% of the ΔmJOA variance. Both variables can independently predict mJOA (p<0.05). A medium mJOA score (ß=0.37) and the presence of dynamic compression (ß=0.34) could predict ΔmJOA. No significant differences were found in the PFR rate and the complications among all approaches (p=0.196 and p=0.21, respectively).

Discussion

The prognosis of CSM is most significantly affected by age at diagnosis, symptom duration (preoperative clinical course), and the severity of myelopathy. Age was reported in most previously published studies as a prognostic factor for patients with CSM (18). Some authors have shown that the prognosis and surgical outcomes were better in younger patients (<60 years) (8,19-21). This may be related to the length of the preoperative clinical course. An international consensus study showed that age >65 years is an unfavorable prognostic factor for CSM (22). We found no significant relationship between age and postoperative functional outcomes (PFR rate). However, female sex was a good prognostic factor in our study.

Several previous studies have shown that patients with CSM who had a longer preoperative clinical course (i.e., longer symptom durations) have

Table 3. Factors affecting the postoperative functional outcomes (PFR rates)

	Mean PFR	95% CI	p	R^2
The preoperative mJOA score			0.001*	0.22
Mild (mJOA >15)	76.59	69.77-83.41		
Moderate (12> mJOA >14)	65.29	59.10-71.49		
Severe (mJOA <12)	38.74	19.19-58.28		
Age group			0.153	0.021
<65	69.27	63.67-74.87		
>65	59.93	46.95-72.91		
Sex			0.008*	0.070
Male	60.88	52.51-69.25		
Female	74.31	68.92-79.70		
Duration of symptoms			0.007*	0.074
<12 months	72.72	66.87-78.57		
>12 months	58.40	49.17-67.63		
MRI signal properties			0.120	0.025
Normal T1/normal T2	70.62	61.37-79.87		
Normal T1/hyperintense T2	67.55	61.45-73.65		
Hypointense T1/hyperintense T2	51.00	0.48-101.5		
Cross-sectional area of the spinal cord (cm^2)			0.711	0.001
<0.76 cm^2	69.42	61.57-77.26.		
>0.76 cm^2	65.58	58.74-72.42		
Number of segments with spinal compression			0.392	0.021
1	54.83	24.46-85.19		
2	68.95	63.19-77.50		
>3	65.79	57.84-73.74		
Cervical alignment			0.185	0.021
Lordosis	60.68	53.87-71.29		
Neutral	70.09	62.54-77.63		
Kyphosis	70.49	57.66-83.32		
Dynamic pressure			0.001*	0.115
Present	74.16	69.26-79.06		
Absent	54.61	46.18-66.65		
Surgical approach			0.196	0.021
Anterior	69.80	63.50-76.11		
Posterior	61.54	51.57-71.50		
Combined	61.78	38.21-85.35		

mJOA: modified Japanese Orthopedic Association, CI: Confidence interval, MRI: Magnetic resonance imaging, PFR: Postoperative functional recovery

a poorer prognosis (22-24), with that of Yamazaki et al. (25) and Chagas et al. (19) defining a long clinical course as longer than 1 and 2 years, respectively. Karpova et al. (8) suggest that the duration of symptoms was related to the preoperative functional status, but it did not affect the postoperative outcome. We found that a short preoperative period was an independent factor associated with good surgical outcomes and a higher PFR rate in our patients.

Some studies have reported that myelopathic findings have also been associated with changes in the cross-sectional area on axial and signal intensity on T1 and T2 sequences (8,26). Some authors suggest that, although the cross-sectional area of the spinal cord does not indicate CSM severity, it can determine the surgical prognosis (8-10). Fukishima et al. (27) reported a critical value of 0.45 cm^2 for the spinal cord cross-sectional area on the axial sequences and suggested that irreversible functional impairment would begin below this value. In this study, the number of cases with a critical value ≤0.45 cm^2 was quite low. Therefore, the 0.76 cm^2 value, which is the arithmetic mean of the whole group, was taken as the critical value of the cross-sectional area for statistical comparisons. The different values obtained may be related to the software used for area measurement.

Table 4. Factors affecting the change in modified Japanese Orthopedic Association score scores (ΔmJOA)

	ΔmJOA	95% CI	p	R^2
Preoperative mJOA score			0.001*	0.217
Mild (>15)	1.85	2.68-3.31		
Moderate (12-14)	3.00	1.47-4.36		
Severe (<12)	2.91	1.65-2.04		
Age group			0.042	0.042
<65	2.31	2.07-2.55		
>65	2.94	2.15-3.74		
Sex			0.327	0.01
Male	2.32	1.93-2.70		
Female	2.56	2.25-2.87		
Duration of symptoms			0.83	0.00
<12 months	2.42	2.12-2.71		
>12 months	2.47	2.01-2.92		
MRI signal properties			0.274	0.038
Normal T1/normal T2	2.25	1.87-2.62		
Normal T1/hyperintense T2	2.56	2.25-2.87		
Hypointense T1/hyperintense T2	1.60	(-0.06)-3.26		
Cross-sectional area of the spinal cord (cm^2)			0.115	0.016
<0.76 cm^2	2.60	2.21-2.99		
>0.76 cm^2	2.28	1.97-2.58		
Number of segments with spinal compression			0.006*	0.078
1	2.4	1.28-3.51		
2	2.10	1.81-2.39		
>3	2.80	2.38-3.21		
Cervical alignment			0.731	0.002
Lordosis	2.48	2.04-2.92		
Neutral	2.44	2.09-2.79		
Kyphosis	2.30	1.63-2.97		
Dynamic pressure			0.001*	0.163
Present	2.81	2.51-3.12		
Absent	1.8	1.46-2.15		
Surgical approach			0.001*	0.167
Anterior	2.12	1.88-3.26		
Posterior	3.28	2.60-3.96		
Combined	3.00	2.07-3.92		

mJOA: modified Japanese Orthopedic Association, CI: Confidence interval, MRI: Magnetic resonance imaging

The severity of symptoms in CSM is evaluated using disability indexes, mJOA score, and Nurick's score. Most articles suggest that poor baseline functional status scores are associated with a worse prognosis (18,22). In contrast, no index has been established to provide a reliable preoperative assessment of the functional status (18). The JOA score and its modifications are most frequently used to assess functional status during the presentation. Tetreault et al.'s (22) review found that an mJOA score ≥12 indicated a good prognosis. Su et al. (20) concluded that preoperative mJOA scores increased preoperative signal intensities on MRI, and age are independent factors that significantly affect the disease prognosis and surgical outcomes. In our study, we found a highly significant relationship between the preoperative mJOA score and PFR rate.

A few studies have investigated the relationship between cervical sagittal balance (C2-C7 SVA) and the severity of myelopathy. Although the cervical translational sequence is associated with the mJOA score, the cervical C2-C7 Cobb angle (lordosis/kyphosis) did not correlated with the mJOA score (28). Tang et al. (29) found that the surgical outcomes of patients who underwent posterior cervical fusion were correlated with C2-C7 SVA. However, the study only included postoperative patients and represents a mixed set of indications, including primary cervical

deformity. In our study, cervical sagittal posture measurements were made using the posterior tangent method (7). Our findings showed no significant correlation between cervical sagittal alignment and functional status either pre- or postoperatively.

Eck et al. (30) showed that accelerated degenerative changes and increased stress load may lead to adjacent segment disease after anterior cervical fusion surgery. As the degeneration progresses, the disk space becomes narrower, and hyperplasia begins in the facet and Luschka joints. The formation of osteophytes and further bone bridges occurs on the anterior and/or posterior edges of the vertebral body. The intervertebral disk activity decreases or even disappears. This situation is equivalent to "auto fusion." Due to this "auto fusion" at the CSM level, adjacent segments undergo accelerated degeneration and a compensatory increase in mobility, resulting in cervical segmental instability. CSM and subaxial cervical instability may be different stages of cervical degenerative disease, and subaxial cervical instability occurs after CSM (31). In our study, the compression on the spinal cord is mostly dynamic (62%); thus, we assumed that limited segmental movement persists, the duration of compression is not full-time, the CSM process is not long enough to result in auto fusion, and rigid formations that will limit segmental movement (bridge osteophytes, facets, and ligament hypertrophy) have not yet occurred. Consequently, the signs and symptoms of CSM may be reversible. Our findings indicate no correlation between the presence of dynamic compression and preoperative mJOA; however, the PRF rate was significantly higher in the group with dynamic compression.

Patients who have benefited in the early period after surgery or whose condition has at least been stabilized by surgery may undergo late-term regression of neurological functions. Slightly more than half of the patients who underwent anterior surgery and up to a third of the patients who underwent laminectomy in the late-term controls showed improvement according to their preoperative status. Reasons for delayed recovery or postoperative worsening include inadequate decompression of the spinal cord, progression of spondylosis in untreated areas, soft disk herniation, kyphotic deformity, and post-laminectomy membrane formation, misdiagnosis of the cause of myelopathy, and advanced age. Severe and long-term loss of neurological function were listed among irreversible pathologies that include high-level involvement and atrophy in the spinal cord (32). Hirabayashi and Satomi (32) studied 35 patients who had undergone laminoplasty for multiple-level spondylosis and found that 54% showed improved symptoms and preserved long-term canal width. In our study, fusion laminectomy was performed in patients who underwent a posterior approach. No differences were found in the PFR rate and the complications among all approaches in our patients.

Study Limitations

This study had some limitations. First, the sample size studied was relatively small (n=98), which included patients treated surgically at our hospital and met our study criteria. Thus, the patients evaluated are unrepresentative of the population of the Asian part of İstanbul. Furthermore, the nature of the study is retrospective, the follow-up period is relatively short, and the findings only represent the experience of a single center. Further randomized prospective studies involving larger samples from multiple centers that sufficiently represent a geographical area with a sufficiently long follow-up period must improve the generalizability of our findings.

Conclusion

Demographic, clinical, and radiological factors, such as sex, preoperative functional status, preoperative clinical course, and the number of dynamic compression phases can impact the surgical outcomes in CSM. Early diagnosis is extremely important in reducing persistent neurological deficits associated with CSM. Early surgical intervention often has good results. The data of this study should be used to discuss the possible consequences of surgery and properly manage patient expectations in CSM. These expectations need to be met, given the increasing importance of patient satisfaction in the performance-based health system.

Ethics Committee Approval: Our study was approved by the Clinical Research Ethics Committee of University of Health Sciences Turkey, Fatih Sultan Mehmet Training and Research Hospital under a decision number (approval number: 2020/3).

Informed Consent: Verbal and written consent were obtained from all patients who agreed to participate in this study.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Surgical and Medical Practices - H.D.; Concept - E.Ç.; Design - H.D.; Data Collection or Processing - E.Ç.; Analysis or Interpretation - H.D.; Literature Search - E.Ç.; Writing - E.Ç., H.D.

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Hand-sewn versus Stapled Anastomosis for Billroth II Gastrojejunostomy After Distal Gastrectomy: Comparison of Short-term Outcomes

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ABSTRACT

Introduction: Subtotal gastrectomy is usually performed in patients with distal gastric cancer. After distal gastrectomy, which reconstruction method can be used is still controversial. This study evaluated the effect of the stapler and hand-sewn techniques on postoperative results.

Methods: Patients who underwent distal gastrectomy in a single center were evaluated retrospectively in this study. Patients who underwent the Billroth II reconstruction method were analyzed. Hand-sewn and stapled techniques were compared in terms of operative and short-term postoperative outcomes.

Results: Two hundred fourteen patients were included. Most of the patients (66.8%) were male. The median age was 61 years. Billroth-II reconstruction with hand-sewn was performed in 161 (75%) patients, and the double stapler technique was performed in 53 (25%) patients. When the hand-sewn and stapled groups were compared, no difference was found in age, sex, or American Society of Anesthesiology scores. There was no difference in choosing antecolic or retrocolic as the surgical technique (p=0.19). A shorter length of hospital stay was detected in the stapled group (p=0.01). The overall complication rate was higher in the hand-sewn group (21.7% vs. 7.5%, p=0.02). Clavien-Dindo grade 3 and above complications were significantly higher in the hand-sewn group (13.7% vs. 3.8%, p=0.02).

Conclusion: Our study showed that the stapler anastomosis technique for Billroth II gastrojejunostomy after distal gastrectomy led to fewer overall complications and shortened hospital stays.

Keywords: Surgical staple, hand-sewn anastomosis, anastomosis technique, Billroth II, gastroenterostomy, gastric cancer

Introduction

Gastric cancer is the fifth most common cancer and the fourth most common cause of cancer-related deaths (1). Today, in most cases, surgical resection is still the only curative treatment option for gastric cancer. Subtotal or distal gastrectomy is frequently applied for patients with gastric cancer in the lower 2/3 of the stomach (2). After distal gastrectomy, Billroth I, Billroth II, and Roux-en-Y reconstruction methods can be used for gastrointestinal anastomosis (3). Postoperative conditions such as delayed gastric emptying, dumping syndrome, reduced food intake, and reflux esophagitis are defined as postgastrectomy syndromes, usually affecting patients' quality of life (4). These reconstruction procedures may cause postgastrectomy syndrome, and all these techniques are still contentious (3). When we think that we have chosen the most suitable reconstruction method for our patient, we must make a second decision: Should we do the anastomosis hand-sewn or stapled? The most appropriate approach for gastrojejunostomy anastomosis is still controversial (3,5,6).

This study evaluated the effect of the stapler and hand-sewn techniques on postoperative outcomes.

Methods

Patients who underwent subtotal gastrectomy for gastric cancer were retrospectively evaluated between January 2014 and January 2020 at Marmara University Hospital. Local approval was obtained from the Ethics Committee of Marmara University (approval number: 09.2021.1088, date: 08.10.2021).

The demographics, reconstruction procedures, surgical approaches, comorbid diseases, and postoperative complications were analyzed retrospectively. Patients who underwent elective surgery because of gastric cancer in whom radical gastrectomy without multiorgan

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resection were included in the study. Patients who underwent the Roux-en-Y reconstruction method, urgent surgery, multiorgan resection, and palliative surgery were excluded from the study. Two grams of intravenous cefazolin (ciprofloxacin for allergic patients) were administered for prophylaxis. For venous thromboembolism prophylaxis, low molecular weight heparin was given to all patients perioperatively. All patients underwent an open DSG. After resection, the reconstruction technique was performed differently due to surgeon preference. Postoperative complications were graded according to the Clavien-Dindo classification (7).

Surgical procedure

The primary surgeon of the operation decided whether the gastrojejunostomy anastomosis would be performed using the Billroth-II or Roux-en-Y reconstruction technique. Similarly, the primary surgeon determined whether antecolic/retrocolic and stapler/ hand-sewn anastomosis techniques could be applied to the anastomosis. A linear stapler was used for duodenal stump closure in all patients.

We applied a linear stapler (GIA 100 mm Stapler with DST Series, Medtronic, MN, USA) on the lesser curvature side for the transection line in the hand-sewn technique. The greater curvature side was cut by cautery, and hand-sewn anastomosis was performed between the jejunum and the cautery-cut side of the remnant stomach, as follows. The jejunum was brought into the stomach pouch about 12-15 cm from the ligament of Treitz. The antimesenteric aspect of the jejunum was measured, and an area of approximately 5 cm was determined. The first posterior suture line was placed behind this suture line but parallel to it. The jejunum was attached to the gastric pouch with 2-0 black silk seromuscular Lembert sutures placed approximately 5 mm apart. After cutting off the remaining silk tails, the first and last sutures were left long and held with a hemostat. An incision was made with electrocautery along the antimesenteric scratch line in the jejunum. The jejunal mucosa was open and checked for bleeding points. The incision in the jejunum was kept a few millimeters shorter than the diameter of the opening in the gastric pouch. Then, the inner layer of anastomosis was completed with 3-0 vicryl and posterior and anterior all-layer sutures. The anterior layer was completed with a row of interrupted 2-0 black silk seromuscular Lembert sutures. A crown stitch was inserted at the medial margin of the anastomosis (8,9).

A linear cutting stapler was placed on the proximal surgical margin and fired to complete the resection with the double stapler technique. After a complete transection of the stomach, stapled anastomosis was performed between the posterior side of the stomach and jejunum by using a linear stapler (GIA 60 mm Stapler with DST Series, Medtronic, MN, USA).

Statistical Analysis

We performed statistical analyses using the Statistical Package for Social Sciences for Windows Version 20 (SPSS Inc., Chicago, IL, USA). Two-tailed chi-square or Fisher's exact tests were used to compare categorical variables. Independent two-sample t-tests or Mann-Whitney U tests were used to compare ordinal data. After adjusting for potential confounders, regression analyses were used to evaluate the relationship between demographic characteristics and delayed gastric emptying. P values less than 0.05 were considered statistically significant.

The primary outcome of this study was to compare the short-term outcomes of two different anastomosis techniques in patients who underwent distal gastrectomy. Secondary outcomes are other potential risk factors for postoperative complications.

Results

Two hundred seventy-five patients were evaluated. Twenty-three patients who underwent Roux-en-Y reconstruction methods, 14 patients who underwent an urgent operation, and 11 patients who underwent multi-visceral resection were excluded. In addition, 13 patients were excluded from the assessment because of palliative resection. Two hundred fourteen patients were included in the study; 143 (66.8%) patients were male, and 71 (33.2%) patients were female. The median age was 61 years (32-87). The American Society of Anesthesiology (ASA) scores of the patients were mostly ASA I and ASA II (Table 1).

All patients underwent gastrojejunostomy anastomosis with Billroth-II reconstruction. Billroth-II reconstruction was performed by hand-

Table 1. Demographic and perioperative characteristics of patients

Parameters	**n=214 (%)**
Age (median-range)	61 (32-87)
Sex	
Female	71 (33.2)
Male	143 (66.8)
ASA scores	
I	68 (31.8)
II	97 (45.3)
III	43 (20.1)
IV	6 (2.3)
Comorbidity	
Diabetes mellitus	33 (15)
Hypertension	68 (32)
Coronary artery disease	33 (15)
Chronic obstructive pulmonary disease	18 (8)
Smoking (present)	133 (46)
Neoadjuvant therapy	11 (5.1)
Anastomosis technique	
Hand-sewn	161 (75.2)
Stapled	53 (24.8)
Clavien-Dindo classification	
No complication	229 (78.6)
Grade 1	21 (7.2)
Grade 2	6 (2)
Grade 3	20 (6.8)
Grade 4	0 (0)
Grade 5	8 (2.7)
Length of stay (median-range)	5 (2-63)

ASA: American Society of Anesthesiology

sewn in 161 (75%) patients. However, the double stapler technique was performed in 53 (25%) patients. Demographic and perioperative characteristics are shown in Table 1.

Patients were divided into hand-sewn and stapled technique groups. When the two groups were compared, no difference was found in age, sex, or ASA scores (Table 2).

When the complications were examined between hand-sewn vs. stapled groups, anastomotic leakage, stump leakage, bleeding, postoperative ileus, delayed gastric emptying, and other (pulmonary) complications occurred in hand-sewn groups 6, 8, 1, 7, 9, and 4 patients, respectively, and occurred in stapled group 0, 0, 1, 3, 0, and 0 patients, respectively. The total of these was evaluated as overall complications, and patients with and without complications were compared; there was no significant difference in sex, ASA score, hypertension, diabetes mellitus, or coronary artery disease. Overall complications were more common in older patients (65 vs. 61 years p=0.03) and patients with chronic obstructive pulmonary disease (COPD) (23% vs. 5% p=0.001).

The overall complication rate was higher in the hand-sewn group (21.7% vs. 7.5%, p=0.02). Clavien-Dindo grade 3 and above complications were significantly higher in the hand-sewn group (13.7% vs. 3.8%, p=0.02). There was no difference in choosing antecolic or retrocolic as the surgical technique (p=0.19). While reoperation was more common in the hand-sewn group (7.5%), mortality was observed in 4 (2.5%) patients in this group (Table 2).

The factors affecting the occurrence of total complications were examined. Age, presence of COPD, and hand-sewn anastomosis were evaluated as independent risk factors in the univariate analysis (p=0.03, p=0.001 and p=0.02 respectively). Multivariant analysis showed COPD and hand-sewn anastomosis as significant risk factors for overall complications (p=0.001, p=0.008, respectively) (Table 3).

Discussion

There are various anastomosis techniques defined for distal gastrectomy. These have been compared in the literature, but different results have been found regarding postoperative outcomes (10). Billroth II anastomosis is frequently performed because of its simplicity and low risk of anastomotic tension, but it can cause biliary reflux gastritis, esophagitis, or dumping syndrome (11). Mechanical staplers have been used for gastrointestinal surgery for almost 50 years and are now widely used during open or laparoscopic gastrectomy for gastric cancer. Many studies did not show a significant difference in the occurrence of suture failure between hand suturing and mechanical stapling (12-14).

Table 2. Comparison of hand-sewn and stapled groups

Parameters	Hand-sewn technique (n=161) (%)	Stapled technique, (n=53) (%)	p-value
Age (years, SD)	62 (12)	61 (11.4)	0.7
Sex			
Female	58 (36)	13 (25)	0.12
Male	103 (64)	40 (75)	
ASA scores			
I	53 (33)	15 (28)	0.7
II	70 (43)	27 (51)	
III	34 (21)	9 (17)	
IV	4 (3)	2 (4)	
Comorbidity			
Diabetes mellitus	26	7	0.6
Hypertension	52	16	0.71
Coronary artery disease	28	5	0.2
Chronic obstructive pulmonary disease	10	8	0.05
Antecolic	86 (55.5)	24 (45.3)	0.19
Retrocolic	69 (44.5)	29 (54.7)	
Duration of operation (minutes)	120	121	0.8
Overall complications			
Present	25 (21.7)	4 (7.5)	0.02
Clavien-Dindo classification			
Grade 3 and above	22 (13.7)	2 (3.8)	0.02
Reoperation	12 (7.5)	1 (1.9)	0.14
Length of hospital stay (days, mean)	6.6	5.0	0.01
Mortality	4 (2.5)	0	0.22

ASA: American Society of Anesthesiology, SD: Standard deviation

Table 3. Univariate and multivariate regression analyses for risk factors for overall complications

Variables	Univariate			Multivariate		
	HR	95% CI	p-value	HR	95% CI	p-value
Age	1.034	1.002-1.067	0.03	1.026	0.993-1.060	0.12
COPD	0.181	0.066-0.492	0.001	0.125	0.03-0.407	0.001
Anastomosis type	3.403	1.143-10.07	0.02	5.365	1.56-18.41	0.008
Sex	0.75	0.35-1.66	0.46			
ASA score	0.68	0.11-4.22	0.37			

ASA: American Society of Anesthesiology, COPD: Chronic Obstructive Pulmonary Disease, CI: Confidence interval, HR: Hazard ratio

Some studies suggest that the stapled anastomosis technique is shorter than hand-sewn anastomosis and affects surgical outcomes by shortening the operation time. Additionally, some studies do not show a time difference between the two techniques (6,15). In this study, we found that the hand-sewn or stapled technique did not affect the duration of surgery. We did not compare the two methods, particularly in terms of anastomosis time, but based on our experience, we can say that there is a minimal difference. We think that the duration of hand-sewn anastomosis depends on surgical experience; therefore, it did not make a difference in operation time in our study.

Postoperative anastomotic leakage is associated with increased morbidity and mortality. There are studies in the literature reporting different results in terms of anastomotic leakage compared with hand-sewn and stapled techniques (5,6,13,14). In our study, we found a more anastomotic and stump leakage in the hand-sewn group. Stapling anastomosis is thought to prevent anastomotic edema or stenosis and facilitate easier drainage of food contents (16). In line with this, we found a lower delayed gastric emptying rate in the stapled technique group. Although we could not find a difference when we examined the complication rates one by one, looking at the overall complications and classifying according to Clavien-Dindo, the hand-sewn group had significantly higher rates. Simultaneously, this high complication rate in the hand-sewn group did not affect reoperation or mortality rates.

Contrary to many studies, we found a shorter length of hospital stays in the stapled group (12,13,17). We think this is due to the prolonged length of hospital stay due to complications in the hand-sewn group.

Study Limitations

Our study had several limitations. It is a single-center and low-volume study. This study is a retrospective analysis, so selection bias cannot be eliminated. We analyzed the data for one surgical method, but different surgeons performed the surgeries. The power of statistical evaluation may have been influenced by the proportion of patients between the two groups with different numbers. The gastrojejunostomy time was not recorded for all patients. This study reported only short-term results; further analysis is needed to determine long-term outcomes.

Conclusion

There are various anastomosis techniques defined for distal gastrectomy. Our study showed that the stapler anastomosis technique for Billroth II gastrojejunostomy after distal gastrectomy led to fewer overall complications and shortened hospital stays. However, prospective randomized studies with many patients are needed to determine which complications are particularly affected by the anastomosis technique.

Ethics Committee Approval: Local approval was obtained from the Ethics Committee of Marmara University (approval number: 09.2021.1088, date: 08.10.2021).

Informed Consent: Retrospective study.

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Infantile Esotropia: Clinical Features and Results of Bilateral Medial Rectus Recession

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ABSTRACT

Introduction: To define the characteristics of infantile esotropia and evaluate the results of bilateral medial rectus recession in infantile esotropia.

Methods: A retrospective review was performed on medical charts of patients diagnosed with infantile esotropia. All patients underwent an ophthalmological examination to detect the conditions that accompany infantile esotropia. Patients with two years of age or older and without fixation preference or amblyopia underwent bilateral medial rectus recession.

Results: There were a total of 117 patients with infantile esotropia patients. Infantile esotropia was accompanied by inferior oblique hyperfunction, fixation preference, cross-fixation, pseudoabduction deficit, pattern deviations, nystagmus, dissociated vertical deviation, convergence insufficiency, and abnormal head position. Approximately forty percent of the patients compatible with visual acuity measurements had amblyopia. Bilateral medial rectus recession decreased the mean esotropia from 43.1±15.3 to 7.8±12.8 prism diopters (PD) in 65 patients. Postoperatively, 41 patients had an ocular alignment within 10 PD of orthotropia, 22 patients showed undercorrection and 2 overcorrection.

Conclusion: The characteristics of infantile esotropia in our study are substantially consistent with those of early reports, except for convergence insufficiency. This study also showed that bilateral medial rectus recession appears to have a high percentage of undercorrection in short-term postoperative follow-up in infantile esotropia.

Keywords: Esotropia, fixation, recession, rectus

Introduction

Infantile esotropia is a stable angle convergent eye deviation that has an onset within the first six months of life in neurologically normal children with a reported incidence of approximately 1% in the general population (1-3). Alternating esotropia, cross-fixation with pseudoabduction deficit, manifest-latent nystagmus, inferior oblique overaction (IOOA), dissociated vertical deviation (DVD), mild amblyopia, slight hypermetropia, and reduced binocular vision are often associated with infantile esotropia (3-6).

Although botulinum toxin injection into the medial recti muscles is an alternative therapy, muscle surgery is the mainstay of treatment in infantile esotropia. The aim of surgical treatment is to enhance the development of binocular vision by aligned visual axes. More discussions have centered on the best age for surgery in infantile esotropia for decades. Most investigators advocate that early surgical intervention is useful for obtaining good eye alignment and stereopsis; on the other hand, some point out the low surgical success rate and the scarcity of binocular function in patients with infantile esotropia patients who underwent early surgical correction (1,7-10). Although the most effective surgical procedure has not yet been univocally defined, several surgical options have been introduced for treatment, including unilateral medial rectus recession with lateral rectus resection, bilateral medial rectus recession, bilateral medial rectus recession with resection of one lateral rectus, and bilateral medial rectus recession combined with resections of both lateral recti (7,8,11,12).

The aim of this study aimed to describe the clinical features of patients with infantile esotropia and evaluate the results of bilateral medial rectus recession surgery for the correction of infantile esotropia.

Methods

This study retrospectively reviewed the medical charts of patients who were diagnosed with infantile esotropia during the period from 2011 to 2019. Preoperatively, written informed consent for patient information and images to be published had been obtained from the parents or

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legal guardians of the patients who underwent surgery. The study was ethically approved by the İnönü University Institutional Review Board (approval number: 2020/869) and conducted according to the principles of the Declaration of Helsinki.

All selected patients demonstrated the following characteristics: esodeviation onset before six months of age, esodeviation angle equal to or greater than 30 prism diopters (PD), hypermetropia less than 3D, absence of obvious neurological disorders, or any other ocular diseases. Patients with restrictive or paralytic strabismus, accommodative esotropia, a history of previous strabismus surgery, or uncomplete data were excluded from the study.

All patients underwent complete ophthalmological and orthoptic examinations. Spectacles were prescribed for refractive errors of +2.50 or more to eliminate the accommodative effects on esotropia following cycloplegic refraction measurements in all patients. Amblyopic patients were identified based on visual acuity measurements performed using the Snellen or Lea chart. Amblyopia was always managed with occlusion therapy. In patients with a fixation preference, the preferred eye had patching to obtain alternating fixation. Anterior segment and fundus examination were performed using a slit-lamp and indirect ophthalmoscope, respectively. Horizontal angle deviations were measured at near and distance by the prism cover test or, in too young, uncooperative patients by the Krimsky test after total correction of refractive errors, if necessary. IOOA was graded in all patients, using a scale from 0 to +4, where the +4 indicated the most serious form of inferior oblique hyperfunction. Lateral recti hypofunctions, nystagmus, pattern deviations (A or V variations), cross fixation, DVD, convergence insufficiency and abnormal head posture (AHP) were recorded when present.

Surgical Interventions

Considering the surgical timing, two main parameters were examined: age and the presence of alternating fixation. Surgical intervention was performed only in patients with 2 years of age or older and a freely alternating fixation. All patients underwent bilateral medial rectus recession under general anesthesia. For the medial rectus recession procedure, a limbal conjunctival incision was performed in the nasal quadrant of each eye to expose the nasal aspect of the sclera. The medial rectus muscle was isolated and secured, and then cut from the sclera after a careful dissection. The muscle was then sutured to the sclera with a 6-0 double-needle polyglactin suture with all recession measurements marked with a curved scleral ruler from the original insertion. The amount of recessions was based on the recommendations of a standard surgical dosing table developed by Santiago and Rosenbaum (13), and adjusted based on our clinical experience. The amount of medial rectus recession ranged between 4.5 and 6.5 mm. Patients with IOOA underwent concurrent inferior oblique weakening surgery; more clearly those with +1 or +2 IOOA had inferior oblique recession surgery, and those with +3 or +4 IOOA had myectomy surgery. Postoperative alignment was evaluated at 1 month, 3 months, 6 months, 12 months, and annually after that. A satisfactory outcome was defined as a distance ocular alignment within 10 PD of orthotropia with appropriate refractive correction at the postoperative sixth month. Reoperation was performed when esodeviation greater than 20 PD persisted at 6 months postoperatively despite optical correction.

Statistical Analysis

SPSS for Windows statistical software (ver. 22.0; IBM Corp., Armonk, NY, USA) was used for the analysis. The collected data were summarized using descriptive statistics. The results are expressed as mean ± standard deviation.

Results

Overall, 117 patients were included in the study, 59 (50.4%) males, 58 (49.6%) females. The mean age at the time of diagnosis was 23.0±23.4 months. The mean follow-up time was 34.6±28.7 months. The mean spherical equivalent at the initial visit was +2.15±1.68 D in the right eye and +2.22±1.68 D in the left eye. Thirty-two (27.3%) patients were compatible with the visual acuity measurements at the initial visit, 13 (40.6%) of these compliant patients had amblyopia. The average best spectacle-corrected visual acuity of the right and left eyes were 0.75±0.32 and 0.84±0.2 decimal, respectively. The most common conditions accompanying infantile esotropia patients are presented in Table 1. Convergence assessment could be performed in 39 patients, among them 5 (12.8%) demonstrated convergence insufficiency. Only one (0.8%) patient had an AHP. Spontaneous recovery was observed in one (0.8%) patient.

Bilateral medial rectus recession was performed in 65 (55.5%) patients. The mean age at the time of surgery, mean preoperative and postoperative esotropia, success rate, and mean postoperative follow-up time in the surgical group are presented in Table 2. Twenty-four (37%) patients had an undesirable result, 22 (33.9%) showed undercorrection and 2 (3.1%)

Table 1. The most common clinical features accompanying infantile esotropia patients in our study

Clinical feature	Frequency, n (%)
Alternating fixation	63 (53.8)
Inferior oblique hyperfunction	55 (47)
Cross-fixation	43 (36.7)
Pseudoabduction deficit	22 (18.8)
Pattern strabismus	
V-pattern	12 (10.2)
A-pattern	1 (0.8)
Nystagmus	12 (10.2)
Dissociated vertical deviation	5 (4.2)

Table 2. The mean age at the surgery, mean pre- and postoperative esotropia, success rate and mean postoperative follow-up in the surgical group

Mean age at the surgery	44.6±24.6 (m)
Mean preoperative ET	43.1±15.3 PD
Mean postoperative ET	7.8±12.8 PD
Success rate	63%
Mean postoperative follow-up	26.8±23.4 (m)

m: Months, ET: Esotropia, PD: Prism diopters

showed overcorrection. Of these patients with undercorrection, 8 (12.3%) underwent additional surgery for residual esotropia. In 39 (60.0%) patients with IOOA, the horizontal muscle surgery was performed along with the inferior oblique muscle weakening surgery.

The remaining 52 (44.5%) patients who did not undergo surgery, those with amblyopia and without alternating fixation received occlusion therapy, while those with alternating fixation less than 2 years old waited to reach the age of 2 to undergo surgery.

Discussion

This retrospective study consisted of a very close percentage of female and male gender with 49.6% female and 50.4% male. In a study by Magli et al. (3), the percentage of female and male gender in infantile esotropic patients were reported to be approximately 41% and 59%, respectively. In another study, 42.8% of infantile esotropic patients were female and 57.2% male (5). On the other hand, Shauly et al. (14) reported a close rate of female and male gender with 50.5% female and 49.5 male. Similarly, in a study by Kim and Choi (8), 51.2% of infantile esotropic patients were female and 48.8% male. It seems that the disease has no gender predilection.

In our study, only 32 (27.3%) patients could answer the visual acuity tests, and 40.6% of these cooperative patients were diagnosed with amblyopia. Magli et al. (5) reported amblyopia in 20.2% of infantile esotropic patients who underwent corrective surgery for esotropia before 4 years of age. Birch et al. (15) determined amblyopic patients by fixation preference testing and reported amblyopia in 57% of infantile esotropic patients. In another study by Shauly et al. (14), amblyopia was found in 48.5% of infantile esotropic patients. We believe that the differences in the rate of amblyopia are related to the age of patients in each study, as well as the differences in diagnosing amblyopia in each study.

In a study on the patients with infantile esotropia performed by Birch et al. (15), the mean spherical equivalents of the right and left eyes were reported to be +2.54±1.83 and +2.55±1.82 D, respectively. In another study by Lee et al. (16), the mean preoperative spherical equivalent of both eyes in infantile esotropia patients was found to be +1.61±1.47 D. Kim and Choi (8) reported a mean spherical equivalent of +1.76±1.65 D in patients underwent bilateral medial rectus recession and +0.91±3.29 D in patients underwent unilateral medial rectus recession with lateral rectus resection. In our study, the mean spherical equivalent at the first visit was +2.15±1.68 D for the right eye and +2.22±1.68 D for the left eye. Our findings on the refractive status of infantile esotropia were consistent with the previous reports (8,15,16).

Na et al. (17) observed alternating fixation in 33.9% of infantile esotropic patients at baseline examination. Magli et al. (5) found alternating fixation in 47.5% of infantile esotropia patients who underwent surgery before 4 years of age. In another study conducted by Singh et al. (18), 69.0% of patients with infantile esotropia demonstrated alternating fixation. We found alternating fixation in 53.8% of infantile esotropia patients, which falls into a priorly reported range of 33.9-69.0% (5,17,18).

Infantile esotropia patients with cross-fixation use the right eye to see the left side and the left eye to see the right side (19). We detected cross-fixation in 36.7% of infantile esotropic patients, which is between a previously reported range of 34.1-74.4% (3,5). On the other hand, 18.8% of our patients had lateral recti hypofunction, resulting in a significant pseudoabduction deficit. Our results regarding the rate of lateral recti hypofunction were inconsistent with previous reports, with one study reporting lateral recti hypofunction in 63.8% of infantile esotropia patients (3), while in another, 58.84 of infantile esotropia patients had lateral recti hypofunction (5).

The reported frequency of IOOA in patients with infantile esotropia ranged from 7.5% to 43.3% (8,16,18). We diagnosed IOOA in 47% of infantile esotropia patients. The rate of IOOA found in our study is similar to the formerly reported rates.

In A or V pattern variation associated with esotropia, the angle of horizontal deviation changes with the position of gaze in the vertical meridian (20). The reported incidence of pattern deviations (A or V) in patients with infantile esotropia was between 6.4% and 77.8% (3,5,21,22). We detected A or V pattern strabismus in 11.1% of infantile esotropic patients, which falls in the previously reported range.

In our sample, 10.2% of participants were diagnosed with nystagmus, which was reported to have a variable incidence ranging from 9.7% to 19.4% in previous studies on infantile esotropia (3,5,18).

DVD is a slow upward drifting of the non-fixing eye with unknown etiology (23). DVD is more commonly seen in infantile esotropia with a variable reported incidence ranging between 3.7% and 73.7% (3,5,8,14,16-18,22). In our study, 4.2% of cases demonstrated DVD.

One study reported AHP in 45.9% of infantile esotropia patients (3). In another study, AHP was reported in 35.8% of infantile esotropia patients (5). Elsewhere, no patient was found to have an AHP in infantile esotropia (22). In our sample, one paient developed an AHP.

The Congenital Esotropia Observational Study reported that early-onset esotropia resolved in 46 (27%) patients without surgery, in 42 (24.7%) patients spontaneously, and in 4 (2.3%) with spectacle wear (24). Shon and associates reported spontaneous resolution in 3 cases with a relatively small angle infantile esotropia (25). We observed the resolution of infantile esotropia in one (0.8%) patient without any treatment.

At the initial visit, we determined convergence insufficiency in 5 (12.8%) of 39 patients who were cooperated with orthoptic examination. Previous studies have reported no data on the frequency of convergence insufficiency in patients with infantile esotropia.

Bilateral medial rectus recession is widely used for the surgical treatment of infantile esotropia patients. This procedure is technically simple, not time-consuming, less traumatic, leaving the lateral rectus muscles untouched for cases requiring a second surgical intervention, but it carries a risk for the possibility of undercorrection in large-angle esotropia (8,21,26).

Singh et al. (18) performed bilateral medial rectus recession in 78 infantile esotropia patients and reported that this procedure is most effective in eliminating of infantile esotropia with a reoperation rate of 5.3%. In the study by Shauly et el. (14), bilateral medial rectus recession was used in the majority (83.4%) of patients with infantile esotropia

as an initial surgical procedure and 35 additional surgical procedures required for correcting of residual esotropia or consecutive exotropia in the postoperative period. In the study by Kim and Choi (8), 80 patients with infantile esotropia were selected for either bilateral medial rectus recession or unilateral medial rectus recession with lateral rectus resection, and bilateral medial rectus recession was demonstrated to have a higher final success rate and a lower reoperation rate than the unilateral approach. Lee et al. (16) performed bilateral medial rectus recession in 46 patients for correcting of infantile esotropia and reported surgical success in 31 (67.3%) patients (16).

In our study, patients with fixation preference at the initial examination had occlusion treatment before surgery, and surgery was postponed until they showed alternate fixation. Also, all amblyopic patients had patching therapy before surgery. The surgery was never performed in patients with amblyopia or younger than 2 years of age. In all cases, the amount of medial rectus recession was within the usual limits ranging from 4.5 to 6.5 mm.

We performed bilateral medial rectus recession in 65 patients and obtained a surgical success in 41 (63%) patients when a successful outcome is considered a distance ocular alignment within 10 PD of orthotropia at 6 months postoperatively. The mean preoperative deviation was 43.1±15.3 PD, while the mean postoperative deviation was 7.8±12.8 PD. Figure 1 shows pre- and postoperative images of a patient who underwent bilateral medial rectus recession due to infantile esotropia. In the postoperative period, 22 (33.9%) patients showed undercorrection and 2 (3.1%) showed overcorrection. In patients with undercorrection, the postoperative residual deviation was between 10 and 20 PD in 14 patients, and more than 20 PD in 8 patients. An additional corrective surgery was performed in the 8 (12.3%) patients who had a residual esotropia greater than 20 PD during the follow-up period after 6 months from the initial surgery. Both surgical success and reoperation rates in our study are comparable with those reported in previous studies that used bilateral medial rectus recession as an initial surgery for infantile esotropia (8,14,16,18).

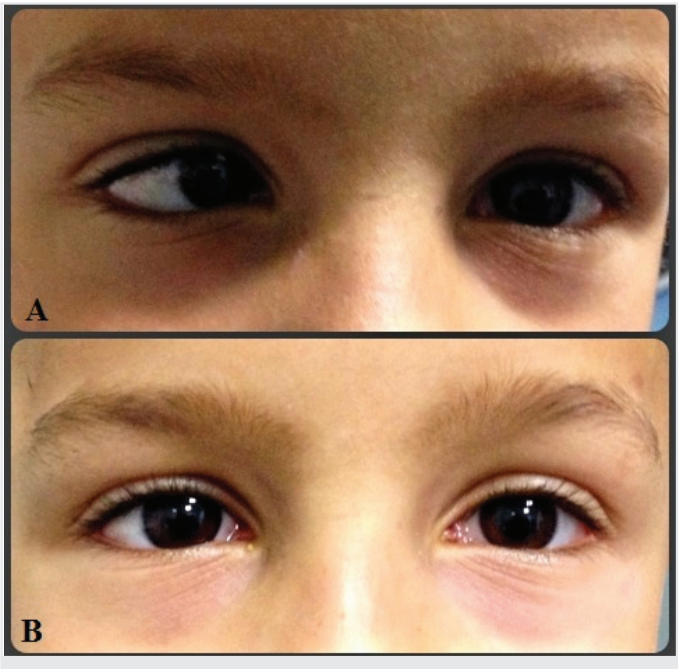

Figure 1. A patient with infantile esotropia, preoperative appearance (A), and postoperative appearance (B). Written informed consent for images to be published had been obtained from the parents

In the presence of an IOOA associated with infantile esotropia, we never postponed the inferior oblique weakening surgery, approaching the medial rectus muscles together with the inferior obliques. Figure 2 represents pre- and postoperative images of a patient who underwent inferior oblique weakening surgery with simultaneous medial rectus muscle recession.

Study Limitations

Our study has some limitations related to the retrospective design. First, the study has no data from the sensory state, which is aimed to be restored with surgery in patients with infantile esotropia. However, most of the younger patients in our sample appeared to have a lack of compliance for sensorial status testing. Moreover, undercorrection, a well -known complication of two-muscle surgery in large-angle infantile esotropia, occurred in 22 cases after the bilateral medial rectus recession procedure. If we had performed three-muscle surgey in patients with large-angle infantile esotropia, undercorrection may not be a serious problem in our study. Finally, the average postoperative follow-up time is short (26.8±23.4 months). It has been shown that consecutive exotropia tends to develop over a long period after infantile esotropia surgery. Thus, a longer postoperative follow-up is needed to assess the outcomes of infantile esotropia surgery, it is likely that longer follow-up periods would be associated with increasing rates of consecutive exotropia.

Conclusion

Most of the clinical features of patients with infantile esotropia in this study were comparable with the findings from previous reports, except for convergence insufficiency. Although, the surgical success and reoperation rates in this study were non-conflicting with those reported in early studies that used bilateral medial rectus recession surgery, the

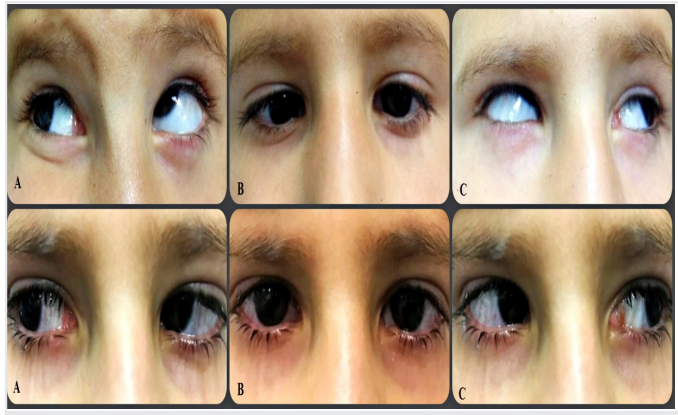

Figure 2. A patient with infantile esotropia and bilateral inferior oblique overaction, preoperative (above); overelevation of the left eye in adduction (A), esotropia in the primary position (B), overelevation of the right eye in adduction (C); postoperative (below); no elevation of the left eye in adduction (A), orthotropia in the primary position (B), no elevation of the right eye in adduction (C). Written informed consent for images to be published had been obtained from the parents

occurrence of high percentage undercorrection may indicate a need for three-muscle surgery in large-angle infantile esotropia. Studies with longer follow-up times were required to confirm our surgical results because the duration of follow-up is an important parameter for evaluating surgical success rates in all strabismus surgeries.

Ethics Committee Approval: The study was ethically approved by the İnönü University Institutional Review Board (approval number: 2020/869) and conducted according to the principles of the Declaration of Helsinki.

Informed Consent: Obtained.

Peer-review: Externally peer reviewed.

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Prevalence of Chronic Diseases Among Elementary School Students in Şanlıurfa, Turkey

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ABSTRACT

Introduction: Chronic diseases, one of the main reasons for morbidity and mortality in all ages, are becoming a significant health problem all over the world in recent times. The population of children with chronic diseases is increasing day by day. While chronic illnesses make life difficult for school-age children, they have a detrimental impact on academic progress. Therefore, studies on this topic are required to improve their quality of life and reduce chronic disease morbidity and mortality rates. This study determines the prevalence of chronic diseases and children's health conditions in elementary school students aged 5 to 12 years.

Methods: This research was designed as a descriptive and cross-sectional study. Between September 2018 and June 2019, 158,445 students in 45 elementary schools in central Şanlıurfa was screened for chronic diseases. The sample was composed of 125 students diagnosed with chronic disease by a doctor.

Results: The prevalence of chronic diseases was determined as 78.89 for every 100,000 students [95% confidence interval (CI), 66.1-94.0]. Asthma (29.6%), epilepsy (14.4%), and hypertension (10.4%) were found as the three most prevalent diseases, and for every 100,000 students, their prevalence was determined as 23.35 (95% CI: 17.0-32.2), 11.36 (95% CI: 7.0-18.3), and 8.2 (95% CI: 5.0-14.0), respectively.

Conclusion: To the best of our knowledge, this is the first study examining the prevalence of chronic diseases and health conditions in the elementary school population. According to the results, the prevalence of chronic diseases was found to be very high among elementary school students and students' health was not at the desired and expected level. Taking into account the results of this study, the employment of school nurses seems a necessity, especially in order to increase students' life quality and school success.

Keywords: Chronic diseases, prevalence, elementary school students, school, public health

Introduction

Today, chronic diseases are a significant health problem across the world, and the pediatric population with chronic diseases is increasing day by day (1-3). Between 10% and 15% of children under the age of 18 have a chronic condition globally. However, this ratio increases over time such that an increase occurred significantly over the past two decades (2,4-6). Similarly, among approximately 25 million children in Turkey, a significant portion of children suffer from chronic diseases (3).

Chronic diseases negatively influence children's health and their school and social life. The school life of children diagnosed with a chronic illness can be interrupted due to frequent hospitalizations, check-ups, treatment, and side effects of medications, resulting in problems in children's adaptation to school (1,5,7-10). Children who cannon attend school due to a chronic condition may lag their peers in the classroom and their academic achievement may decrease as their learning process is hindered.

According to The International Council of Nurses, supporting individuals with chronic diseases to better manage their health problems takes part in the roles of nurses for the control of chronic diseases. In this outlook, public health nurses providing professional health assistance can have responsibilities for children with chronic diseases. Considering that children spend 40% of their lives at school, school nurses, a branch of public health nursing, can take part and perform important activities and unique roles for children in coping with chronic diseases, meeting their complicated healthcare needs, facilitating their school adaptation, increasing school success, and preventing social withdrawal and introversion (7-9).

The American Nurses Association has stated that increasing studies show a positive relationship between school attendance and academic achievement in schools with school nurses (5-11). Hill and Hollis reported that elementary school students' learning time increased with the school nurse; otherwise, teachers spent an extra hour teaching (12). Even a study reported that for each US dollar invested in a school nursing

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program, society would gain benefits worth 2.20 US dollars (5). As a result, the employment of well-trained school health nurses in schools will contribute to the improvement of individual and community health (7-17).

Except for certain private and boarding schools, school nurses are not employed at schools in Turkey. In addition, Community Health Centers provide health services primarily individual follow-ups for children having chronic diseases and being accordingly in the need of follow-up (11,13,15). Therefore, current health services do not meet the need and are inadequate for the management of chronic diseases.

Objective

The population of children in Şanlurfa is higher than those in other cities in Turkey such that every year approximately sixty thousand children start attending elementary school each year (3). Children generally start elementary school at the age of 5. Primary education lasts 4 years. However, to our knowledge, the prevalence of children with chronic diseases among elementary school children aged 5-12 years has not been reported to date. Based on this, the objective of this study was to determine the prevalence of chronic diseases and health conditions of students (aged: 5-12) enrolled at elementary schools in central Şanlurfa. Thus, it was aimed to take a step forward in the management of chronic diseases.

Methods

Population and Sample

This research was designed as a descriptive and cross-sectional study. Şanlurfa city center consists of three districts, namely Eyyübiye, Haliliye, and Karaköprü. There are 61 elementary schools and 214,558 students in these three districts. To determine the number of students with chronic diseases in each school which has usually 2,000-3,000 students, 158,445 students aged 5-12 years in a total of 45 elementary schools in central Şanlıurfa were screened for chronic diseases between September 2018 and June 2019. The percentage of students reached is 73.8% of the total population. No students with chronic diseases were identified in 22 schools. The sample comprised 125 students diagnosed with a chronic disease by a doctor in 23 elementary schools. Before the study, verbal consent was obtained from children with chronic diseases and written consent from their families. At the preliminary stage of the study, ethical approval was obtained from the Clinical Studies Ethics Board of Harran University (appoval number: 02-01, date: 09.02.2017).

Data Collection Tools

Data were collected from both children and families via separate forms. The student form had three parts composed of a total of 27 questions. The first part was the Sociodemographic Information Form, which contained questions about students' age, sex, and socioeconomic status (13 questions). The second part was the Disease Process Evaluation Form, which included questions on the students' chronic disease, treatment, and course of treatment (10 questions). The third part covered questions on the evaluation of the school lives of the students (4 questions). Students filled out the children's form in the counselors room of the school by themselves. Only unclear points were clarified by the researcher. The average time to answer the questions was 15-20 min. Other data were collected using the family form, composed of questions on the medications and health reports of the students from their families through face-to-face interviews at schools or telephone calls.

Statistical Analysis

The analysis of the collected data, descriptive statistics (frequency, percentage, mean, standard deviation) were used with the SPSS (Statistical Package for the Social Sciences) 23.0 software. Prevalence rates of chronic diseases were calculated on the basis of 100,000 students.

Results

In this study, a total of 158,445 students in 45 elementary schools located in the center of Şanlurfa were screened for chronic diseases to determine the prevalence of children with chronic diseases among elementary school children aged 5-12 years and the number of students with chronic diseases was determined as 125 students diagnosed with a chronic disease by a doctor in 23 elementary schools. No students with chronic diseases were identified in 22 schools. Based on these data, the prevalence of chronic diseases was calculated as 78.89 per 100,000 [95% confidence interval (CI): 66.1-94.0].

According to Table 1, asthma was found to be the most prevalent chronic disease among the participants (n=37) with a ratio of 29.6%. Asthma was followed by epilepsy (n=18, 14.4%), hypertension (n=13, 10.4%), chronic renal failure (n=12, 9.6%), musculoskeletal diseases (n=10, 8%), and dermatological diseases and gastrointestinal diseases (n=9, 7.2%) (Table 1). Psychological diseases and endocrine diseases except diabetes are given in the section titled "other chronic diseases" (n=7, 6.4%) (Table 1). The prevalence of asthma was calculated as 23.35 per 100,000 children (95% CI 17.0-32.2), the prevalence of epilepsy was 11.36 per 100,000 (95% CI 7.0-18.3), and the prevalence of hypertension was 8.2 per 100,000 (95% CI: 5.0-14.0).

The mean age of the students with chronic diseases was 8.14±1.285 years and 60.8% of them were 5-8 years old. While 40% of the students with chronic diseases were diagnosed between the ages of 1-4, 32% of the students were diagnosed younger than one year. 68.9% of the students pointed out that they had no knowledge about their diseases. 48% of the students stated that they were regularly taking medication for their chronic diseases. In addition, 75% of these students implied that the dose of medication was adjusted by their mother during school hours. As shown in Table 1, 76.8% of the participants did not follow their diet as a part of their treatment. Moreover, 63.2% of the students claimed that they did not take the necessary precautions for the illness at school, such as diet, activity, medication, etc.

Of the children with chronic illness, 52.3% indicated that their academic achievement was average (medium, Table 1). 24% of the students stated that they did not attend school and 64.5% of them stated that their diseases caused them to be absent from school (Table 1).

Examining the demographic data of the participants revealed that 56.8% of them were male, 48.8% had four or more siblings, and 72.0%

were raised in nuclear homes. Furthermore, it was found that 46.4% of the student parents were consanguineous marriages. 19.2% of the participants had a family member with a chronic disease (n=24) such that 75% of the participants had a mother, father, or sibling with a chronic disease. Hypertension and asthma account for 29.2% of the stated chronic diseases.

Table 2 shows the types of chronic diseases based on the sociodemographic characteristics of the participants. As seen in Table 2, 88.9% of the participants with dermatological diseases were female, and the majority of those with asthma (67.6%) and epilepsy (77.8) were male. As a result, the type of chronic disease varies depending on gender as shown in Table 2.

Discussion

One of the significant global health problems is chronic diseases that have negative effects on aged 5-12 years children's health and social and school life. Therefore, the determination of prevalence ratios and children's health conditions is of paramount importance for the management of chronic diseases to improve children's quality of life and increase academic performance. In this context, the study, which is the first in this field to the best of our knowledge, examined the prevalence of chronic diseases and health conditions in the elementary school population.

According to the results, the prevalence of chronic diseases was found 78.89 in per 100,000 children among elementary school students. Moreover, more than half of the participants stated that school is an obstacle to controlling illness and that they can not attend school because of their diseases. Considering these results, this study revealed that school nurses should be employed in schools for the protection and improvement of students' health, early diagnosis, follow-up, and monitoring of chronic diseases in schools. Engelke et al. (10) reported that a school nursing program for chronic diseases in the school environment was effective in both improving children's health and increasing their school success as well.

Among chronic diseases, asthma was found as the most prevalent chronic illness among the participants (n=37) with a ratio of 29.6%, and after that epilepsy, hypertension, chronic renal failure, musculoskeletal diseases, dermatological and gastrointestinal diseases were determined as common chronic illnesses (Table 1). Similarly, Miller et al. (5) found asthma as the most prevalent chronic disease among 5,102 students aged between 8-18 years. According to one researcher in Şanlurfa, the prevalence of asthma and atopic diseases was significantly higher in children who have a family history of atopy, attend a central school, live in an apartment, have more rooms in their homes, and enjoy better economic conditions (18). Moreover, they reported that epilepsy, diabetes, food allergies, and hypertension follow asthma (5). According to the study by Yetiş (11), asthma was the second most common chronic disease among 234 primary school students in Turkey, while diabetes ranked first.

Male students showed a higher prevalence than female students (Table 1). As well as being male (19-23), exposure of male children to environmental factors more frequently, lack of knowledge of family members about chronic disease, use of coal as a means of heating in winter months, and smoking by family members can lead to asthma.

Most of the participants with asthma, epilepsy, and dermatological diseases were members of nuclear families (Table 2). Children with chronic diseases from extended families have significantly more behavioral disorders than those from nuclear families (13,21). Recently, turning extended families into nuclear ones can cause this result in our study.

According to the findings, epilepsy was the second most prevalent chronic disease (14.4%, Table 1) and male students had a higher prevalence (Table 2). In a recent study, the prevalence of epilepsy in children and adolescents was determined to be approximately 0.7% (24). In another study, the prevalence of epilepsy in children was calculated as 0.69% (5). In research conducted on children aged between 0 and 16 years in Turkey, the prevalence of epilepsy was found to be 0.8% (25). Since epilepsy seizures are more frequent in children aged below 15 years in developed countries (5,24,26), school nurses can play a role in designing healthcare services and follow-ups for school-age children with epilepsy and offer healthcare services for preventing their psychosocial problems and raising the quality of their lives.

Table 1. Disease-related characteristics of the participants

Variables	n	%
Chronic diseases		
Asthma	37	29.6
Epilepsy	18	14.4
Hypertension	13	10.4
Chronic renal failure	12	9.6
Musculoskeletal diseases	10	8.0
Dermatological diseases	9	7.2
Gastrointestinal diseases	9	7.2
Anemia	6	4.8
Diabetes	4	3.2
Other diseases	7	6.4
Age of diagnosis		
Younger than 1 year	40	32.0
1-4 years	50	40.0
After 4 years	35	28.0
Regular use of medications		
Yes	60	48.0
No	65	52.0
Following a specific diet		
Yes	29	23.2
No	96	76.8
School achievement level		
High	28	25.7
Medium	57	52.3
Low	24	22.0
Absenteeism at school		
Yes	27	24.8
No	82	75.2

Table 2. Types of chronic diseases based on the sociodemographic characteristics of the participants

	Types of chronic diseases																	
	Anemia		Hypertension		Dermatological diseases		Gastrointestinal diseases		Diabetes		Musculoskeletal diseases		Asthma		Epilepsy		Other	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Sex																		
Female	4	66.7	5	38.5	8	88.9	6	66.7	2	50.0	3	30.0	12	32.4	4	22.2	10	52.6
Male	2	33.3	8	61.5	1	11.1	3	33.3	2	50.0	7	70.0	25	67.6	14	77.8	9	47.4
Age																		
5-8 years	5	83.3	7	53.8	4	44.4	7	77.8	2	50.0	8	80.0	23	62.2	9	50.0	11	57.9
9-12 years	1	16.7	6	46.2	5	55.6	2	22.2	2	50.0	2	20.0	14	37.8	9	50.0	8	42.1
The number of siblings																		
0-3	3	50.0	5	38.5	3	33.3	5	55.6	1	25.0	6	60.0	20	54.1	10	55.6	10	52.6
4 or above	3	50.0	8	61.5	6	66.7	4	44.4	3	75.0	4	40.0	17	45.9	8	44.4	9	47.4
Family type																		
Nuclear	5	83.3	7	53.8	8	88.9	7	77.8	3	75.0	6	60.0	25	67.6	16	88.9	13	68.4
Extended	1	16.7	6	46.2	1	11.1	2	22.2	1	25.0	4	40.0	12	32.4	2	11.1	6	31.6
School achievement level																		
High	1	16.7	2	16.7	1	16.7	2	28.6	0	.0	0	.0	13	40.6	3	18.8	6	33.3
Medium	3	50.0	8	66.6	3	50.0	3	42.8	3	100.0	6	66.7	16	50.0	7	43.8	8	44.4
Low	2	33.3	2	16.7	2	33.3	2	28.6	0	.0	3	33.3	3	9.4	6	37.5	4	22.2
Absenteeism at school																		
Yes	3	50.0	2	16.7	1	16.7	2	71.4	0	.0	2	22.2	9	71.9	3	18.8	5	27.8
No	3	50.0	10	83.3	5	83.3	5	28.6	3	100.0	7	78.8	23	21.1	13	81.2	13	72.2

n: Number, %: Percent

In this study, hypertension was identified as the third most prevalent chronic disease among the participants (10.4 %, Table 1). A previous study demonstrated the prevalence of hypertension in children aged between 6-11 years as 0.04% (27). Today, the prevalence of hypertensive diseases in children and adolescents ranges between 3% and 5%. Also, half of the adults with hypertension has this disease in their childhood (27,28). It is noteworthy mentioning that blood pressure tests performed by school nurses can enable the diagnosis of hypertension, take urgent measures, and stop its progression at an early stage.

One of the important findings of this study is that 46.4% of the participants with chronic diseases were born because of consanguineous marriage since consanguineous marriage in Şanlurfa is quite common. Consanguineous marriages have a significant effect on the epidemiology of genetic diseases. Similarly, in a study conducted on 66 women whose parents were consanguineous, 13 women had chronic diseases (29).

Anemia and diabetes are among the chronic diseases that their prevalence constantly drops in children (30,31). Our study is compatible with the literature such that anemia and diabetes were at the bottom of prevalence rankings. However, recent studies showed that even though the prevalence of both anemia and diabetes (type 1) drops during childhood across the world, both diseases are still considered critical health issues in less developed and developing countries that have low levels of socio-economic welfare (29,30,31). Problems in school life such as inadequate health care, unhealthy nutrition, and restrictions arising from school rules may be a reason for this situation. School nurses can make great contributions to overcome such disadvantages. In the study by Ayaz (31) (2014), 92.7% of the teachers stated that nurses should be employed in schools and 91.9% stated that the employment of nurses in schools would contribute to the health of students (31).

Study Limitations

In this study, 16 of 61 primary schools were not screened because the school principals did not accept them. One of the limitations of this study is to go to a school once and not include children who have been diagnosed later. The fact that counselors do not know children with chronic diseases is another limitation. An appointment was made from the school outside class hours for all student interviews. Therefore, the data collection process lasted longer than expected time. The results of this study can only be generalized to children with similar characteristics.

Conclusion

In summary, the prevalence of chronic diseases in 158,445 elementary school students was found to be 78.89 per 100,000 students in the study. Asthma, epilepsy, and hypertension were found to be the three most prevalent diseases. Additionally, students' health was determined below the desired and expected levels. Taking into account the results of this study, the employment of school nurses seems a necessity, especially in order to increase students' quality of life and school success. The employment of well-trained school health nurses in schools will contribute to the improvement of individual and community health. However, future studies are needed to determine the effects of school

nursing programs on the management of chronic diseases including in Turkey.

Ethics Committee Approval: At the preliminary stage of the study, ethical approval was obtained from the Clinical Studies Ethics Board of Harran University (appoval number: 02-01, date: 09.02.2017).

Informed Consent: Before the study, verbal consent was obtained from children with chronic diseases and written consent from their families.

Peer-review: Externally peer reviewed.

Authorship Contributions

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

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Comparison of the Effects of Pharyngeal Packing and Gastric Aspiration with an Orogastric Tube on Postoperative Nausea, Vomiting and Sore Throat in Septorhinoplasty

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ABSTRACT

Introduction: We compared the effects of pharyngeal packing and gastric decompression with orogastric tube application on the incidence of nausea/vomiting, sore throat, and dysphagia. As a secondary objective, we assessed the effect of the selected method on the postoperative pain score and patient satisfaction.

Methods: In this randomized, prospective study were 60 patients aged 18-50 years who underwent elective septorhinoplasty. Nasopharyngeal packing was performed in group 1 and gastric decompression with an orogastric tube in group 2, and both procedures were terminated by the practitioner before extubation. Between-group demographic data, duration of operation/anesthesia, hemodynamic parameters, nausea, vomiting, additional antiemetic requirement, pain/dysphagia during swallowing, visual analogue scale (VAS), and patient satisfaction were measured at 24 h, and the group findings were compared.

Results: The demographic findings and durations of anesthesia/operation were not statistically different between the groups, and there was no difference in postoperative nausea and vomiting, VAS, and satisfaction scores. In contrast, sore throat was twice as common in the nasopharyngeal pack group but decreased over time.

Conclusion: The routine packing approach should be abandoned by anesthesiologists. Because pharyngeal packing is not a completely risk-free procedure, we do not recommend intraoperative packing during nasal surgery. If indicated for surgical reasons, however, protocols, checklists, and observation forms pre-prepared with the participation of the surgical and anesthesia teams should be used. All materials should be included in the surgical (scrub) count, and it should be ensured that all materials are removed before extubation with a matching count. Regardless of the method used, it should not be forgotten that the anesthesiologist is responsible for the examination of the oral cavity and throat via direct laryngoscopy and, if necessary, aspiration before extubation.

Keywords: Postoperative nausea and vomiting, sore throat, pharyngeal packing, aspiration with an orogastric tube

Introduction

Postoperative nausea and vomiting (PONV) is a significant complication that affects patient comfort, with an average rate of 30% in surgical patients and up to 80% in the high-risk groups (1). This condition can be extremely stressful and is directly associated with patient satisfaction. It may further lead to additional problems such as significantly longer post-anesthesia care unit stays, unexpected hospitalization of outpatients, impaired surgical success, and increased healthcare costs (1).

PONV is associated with the surgical method and risk factors such as gender, age, the method of anesthesia and smoking. During pharyngeal, orthognathic and nasal operations in particular, swallowing blood may lead to nausea and vomiting (2), and "pharyngeal packs" are used to reduce the amount of blood swallowed and to prevent the ingestion of foreign materials such as teeth, bone fragments and small items of surgical equipment (3,4). Pharyngeal packing has also been associated with complications such as ruptures of mucous membranes, hematoma, edema of the soft palate and uvula, and even the tongue, sore throat, and stomatitis. If not removed before extubation, serious complications such as airway obstruction and hypoxia may develop, which can lead to death (2,3,5,6). Another approach used in daily clinical practice is gastric decompression via an orogastric tube and aspiration of swallowed blood (7).

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The present study compares the effects of pharyngeal packing and gastric emptying with an orogastric tube on incidences of PONV, sore throat, and pain while swallowing (dysphagia) among patients undergoing septorhinoplasty. As a secondary objective, we assessed the effect of the selected method on postoperative pain visual analog scale (VAS) and patient satisfaction.

Methods

This randomized, prospective study of ASA I patients aged 18-50 years who were scheduled for elective septorhinoplasty in a university hospital's ear, nose and throat (ENT) clinic was launched after the granting of İstanbul Medipol University Ethics Committee approval (approval number: 611, date: 03.06.2021). Patients with chronic diseases other than ASA I (diabetes mellitus, heart failure, liver/kidney disease), individual or familial malignant hyperthermia, a history of muscular/neurological disease, dependence on opioids, alcohol or other drugs, menstruating and lactating women, patients with drug allergies, those using anticoagulants, non-smokers, those with a history of motion sickness in their daily life, and those with a history of nausea and vomiting in their medical history were excluded from the study. Informed consent was obtained from the patients.

The patients were scheduled as the first case in the morning (following 6-8 hours of fasting) and were randomly divided into two groups using the sealed envelope method before being taken to the operating room. In group 1 patients, a pharyngeal pack moistened with isotonic solution was placed after intubation and removed by the same physician before extubation. In group 2, an orogastric tube was inserted for drainage, as visualized by laryngoscopy after intubation. After the operation, a final aspiration was made, the orogastric tube was removed, and the patient was extubated. The same experienced anesthesiology and ENT teams participated in the operations of all patients. After being taken to the operating room, the patients' electrocardiographic, peripheral SpO_2, and non-invasive blood pressure was monitored. Vascular access was established and premedication with 0.05 $mg.kg^{-1}$ intravenous midazolam were administered. The induction of anesthesia was achieved with 2 $mg.kg^{-1}$ IV propofol, 1 $mcg.kg^{-1}$ IV fentanyl, and 0.6 $mg.kg^{-1}$ IV rocuroniums. Anesthesia was maintained with 1-2% sevoflurane and 50 mcg/h remifentanil in a 50% oxygen-air mixture. All patients underwent orotracheal intubation, and the mechanical ventilator was set to a tidal volume of 6-7 $mL.kg^{-1}$, and a PEEP of 2-3 cmH_2O in volume-control mode at an end tidal pCO_2 of 30-35 mmHg. When the heart rate or mean blood pressure increased by 20% from the pre-operative values, 25 mcg bolus fentanyl was administered.

In group 1, after intubation, a throat pack consisting of four gauze pads soaked in 0.9% isotonic solution, standardized, and attached with a wide cotton tie in a knotless roll was placed under direct vision by an experienced anesthesiologist, avoiding oropharyngeal trauma. In group 2, an orogastric probe was inserted under direct laryngoscopy by an anesthesiologist to prevent oropharyngeal trauma after intubation, and drainage was performed. The probe was gently aspirated one last time before extubation and then removed.

All patients were administered 1 g IV paracetamol and 0.5 $mg.kg^{-1}$ IV aldolan 30 min at the end of the surgical procedure for postoperative analgesia. To prevent concurrent nausea and vomiting, 4 mg IV ondansetron was administered. After the operation, a nasal silicone splint was placed in all patients by the ENT specialist. Spontaneous ventilation was performed, and 2-4 mg/kg bridion was used for decurarization. Once spontaneous ventilation was sufficient, the patient was extubated and taken to the recovery room (PACU). Perioperative pre-induction (T1) and post-extubation 10-minute (T2) hemodynamic measurements (MAP, HR) were made, and the demographic information and durations of anesthesia/operation of the patients were recorded. Kortilla's scale was used to determine postoperative PONV (8), which assesses PONV as follows:

No PONV: The absence of any emetic episode or nausea.

Mild PONV: Mild nausea or one emetic episode, or short-lasting (~10 min) nausea of any severity triggered by exogenous stimulus (e.g. drinking, eating or postoperative movement) followed by diminished nausea and the patient's feeling well throughout the entire observation period with no antiemetic drug requirement,

Moderate PONV: One or two emetic episodes or moderate or severe nausea without the exogenous stimulus or a single requirement for antiemetic therapy.

Severe PONV: More than two emetic or moderate to severe nauseous episodes requiring at least one antiemetic administration.

In the event of moderate or severe PONV, 4 mg ondansetron IV was administered for treatment. Pain was assessed using the VAS. Hemodynamic parameters, nausea, vomiting, additional antiemetic requirement, pain while swallowing/dysphagia, and VAS were examined in the postoperative post-anesthesia follow-up unit at postoperative 0 h (T2), 6 h (T3) and 24 h (T4). At 24 h, patient satisfaction was assessed using a four-option rating scale (1: Not at all satisfied, 2: Moderately dissatisfied, 3: Satisfied, 4: Completely satisfied).

Statistical Analysis

The statistical analysis of the study findings was carried out using IBM SPSS Statistics (Version 23.0. Armonk, NY: IBM Corp.) based on descriptive statistical methods (mean, standard deviation, median, frequency, ratio, minimum, maximum and Q_1-Q_3 quartiles). Kolmogorov-Smirnov, Shapiro-Wilk, and Skewness-Kurtosis tests and graphical assessments were used to test the normality of the distribution of quantitative data. An Independent samples t-test was used to compare the normally distributed quantitative data of two groups, while a Mann-Whitney U test was used to compare the non-normally distributed data of two groups. A Repeated Measures test (Analysis of Variance in repeated measurements) was used to evaluate the follow-up of normally distributed variables. A Friedman test was preferred for the follow-up evaluation of the variables without a normal distribution, and a Bonferroni Dunn test was used for the evaluation of pairwise comparisons. Qualitative variables were compared using Pearson's chi-square test, Fisher's exact test, and Fisher-Freeman-Halton exact test. The level of significance was considered $p<0.05$.

Results

The study was conducted between 01.07.2021 and 30.11.2021, and involved a total of 60 cases, of which 90.0% (n=54) were female and 10.0% (n=6) were male. The patients were aged 18-47 years, with a mean age of 27.35±6.96 years; the mean body mass index of the cases was 22.82±3.09 kg/m^2 (17.6-31.3 kg/m^2); the duration of anesthesia was in the range of 115-260 min, with a mean of 165.33±35.77 min; and the mean operation duration was 150.43±37.30 min (103-249 min.). The mean age, gender distribution, height, weight, and BMI measurements, and the durations of anesthesia and operation did not differ statistically between the two groups (p>0.05). All these data are summarized in Table 1.

The mean values were not within the pathological limits in any of the patients' hemodynamic measurements (MAP, HR) at the (T1, T2, T3, T4) time points. Between- and intragroup comparisons revealed no statistically significant difference between GI and GII (p>0.05). The data are presented in Table 2.

There was no statistically significant difference in the incidence rates of nausea and vomiting at postoperative 0 6, and 24 h between the GI and GII groups (p>0.05). In both groups, the rate of PONV underwent a statistically significant decrease over time (Graphic 1). There was also no difference in antiemetics use between the groups. In GI, the use of antiemetics increased after 6 h compared to 0 h, but had decreased significantly by 24 h compared to 6 h. In GII, in turn, the use of antiemetics did not significantly differ between the hours. Sore throat complaints were statistically and significantly more common in GI in GII. In GI, there was no difference between hours 0 and 6, while pain decreased significantly at 24 h. In GII, in turn, no difference was found between measurement times (Graphic 2). There was also no significant difference in dysphagia between and within the groups. All the data on complications are presented in Table 3.

Table 1. Evaluation of descriptive characteristics by groups

		Total (n=60)	Group 1 (n=30)	Group 2, (n=30)	Test value
Age (years)	Median (min.-max.)	17-47 (26)	17-47 (25.5)	20-45 (27)	t: -0.571
	Mean ± SD	27.35±6.96	26.83±7.80	27.87±6.11	**[a]p: 0.570**
Gender; n (%)	Female	54 (90.0)	27 (90.0)	27 (90.0)	-
	Male	6 (10.0)	3 (10.0)	3 (10.0)	
Height (cm)	Median (min.-max.)	147-192 (165)	147-180 (164.5)	155-192 (165)	t: -1.038
	Mean ± SD	165.55±7.59	164.53±6.98	166.57±8.16	**[a]p: 0.304**
Weight (kg)	Median (min.-max.)	42-86 (62.5)	42-85 (62.5)	45-86 (61.5)	t: 0.236
	Mean ± SD	62.43±9.77	62.73±10.08	62.13±9.61	**[a]p: 0.814**
BMI (kg/m^2)	Median (min.-max.)	17.6-31.3 (22.8)	17.9-31.3 (22.8)	17.6-29.3 (22.7)	t: 0.849
	Mean ± SD	22.82±3.09	23.16±3.30	22.48±2.88	**[a]p: 0.399**
The duration of anesthesia (min)	Median (min.-max.)	115-260 (155)	115-260 (159)	125-255 (155)	t: -0.043
	Mean ± SD	165.33±35.77	165.13±36.99	165.53±35.14	**[a]p: 0.966**
The duration of operation (min)	Median (min.-max.)	103-249 (140)	103-249 (145)	105-235 (138.5)	t: -0.062
	Mean ± SD	150.43±37.30	150.13±37.48	150.73±37.76	**[a]p: 0.951**

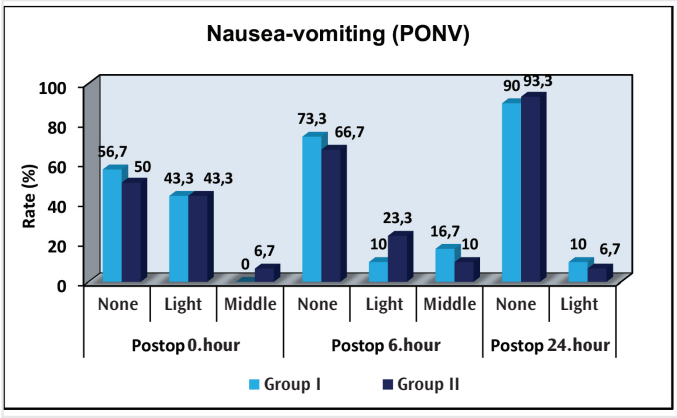
[a]Independent Samples t-test, min.-max.: Minimum-maximum, SD: Standard deviation, BMI: Body mass index

Table 2. Evaluation of mean hemodynamic measurements at follow-up by groups

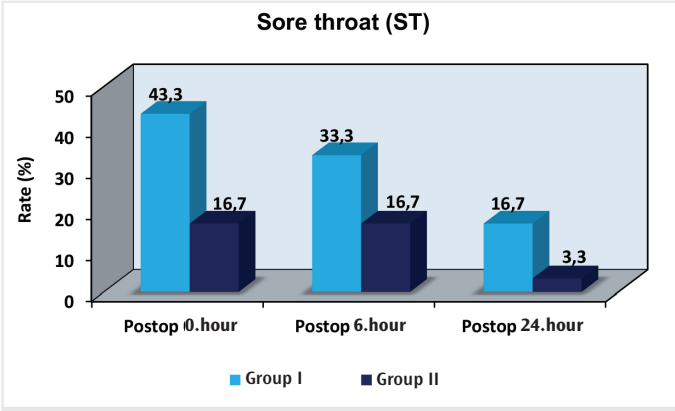
Mean ± SD		Group 1, (n=30)	Group 2, (n=30)	Test value: t	[a]p
		Mean ± SD			
MAP	Pre-operative	85.09±8.86	84.45±8.54	0.284	**0.778**
	Postoperative hour 0	83.38±7.65	84.20±7.78	**0.410**	**0.683**
	Postoperative hour 6	84.59±7.95	85.80±5.06	**0.704**	**0.484**
	Postoperative hour 24	84.43±6.76	86.63±7.30	**1.210**	**0.231**
	Test value: F	0.025	0.461		
	[b]p	**0.875**	**0.712**		
HR	Pre-operative	85.60±9.38	83.17±7.77	1.094	**0.278**
	Postoperative hour 0	83.53±8.44	84.3±10.21	-0.316	**0.753**
	Postoperative hour 6	85.13±7.91	85.53±5.12	-0.233	**0.817**
	Postoperative hour 24	84.67±7.29	85.83±5.85	-0.684	**0.497**
	Test value: F	0.289	0.706		
	[b]p	**0.833**	**0.557**		

[a]Independent Samples t-test, [b]Repeated Measures test, SD: Standard deviation

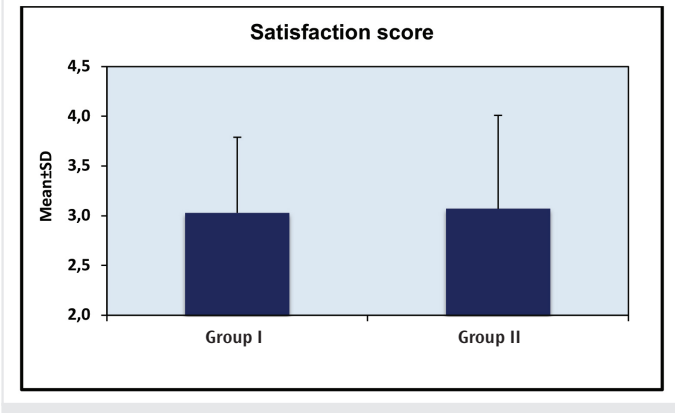
In the evaluation of VAS, neither group exceeded the limit considered as the mean significant pain (VAS ≥4) at any measurement time because of the routine clinical analgesic protocol. There was no difference in VAS between GI and GII, while within-group comparisons made in both groups revealed higher VAS values at 6 h than at 0 h, and at 24 h than at 0 h, and a significant decrease at 24 h when compared to 6 h. Furthermore, no difference was noted in the patient satisfaction scores of the groups (Graphic 3). The data on VAS and satisfaction are summarized in Table 4.



Graphic 1. Distribution of nausea-vomiting incidence rates at follow-up



Graphic 2. Distribution of sore throat incidence rates at follow-up



Graphic 3. Distribution of patient satisfaction scores at follow-up
SD: Standard deviation

Discussion

PONV is considered to be one of the most distressing factors among patients undergoing surgery under general anesthesia. Besides the adverse psychological adverse, PONV can also cause airway obstruction, aspiration pneumonia, subcutaneous emphysema, bleeding from surgical incisions, opening and healing delays, increased intracranial pressure, dehydration, electrolyte imbalance, and malnutrition. Prolonged hospital stays and increased costs may be experienced due to insufficient oral intake, and patients thus have negative impression about anesthesia and surgery (7).

Nasal and orthognathic surgery is growing in popularity worldwide for the correction of various growth disorders and congenital anomalies of the nasal, oral, and maxillofacial regions. Operations in these regions with high vascularization may cause severe bleeding, increasing the incidence of PONV due to blood swallowing in some patients (2,9,10). Therefore, the use of pharyngeal packs, which act as a physical barrier preventing the passage of blood, is standard practice in some countries (11). The study by Knepil and Blackburn (12) found a prevalence of use in the United Kingdom of 39%, while 52% were intermittent users and only 9% were never users. Although the available evidence is insufficient to justify the use of pharyngeal packs, many surgeons and anesthesiologists continue to use such packs during oral, nasal, and maxillofacial surgical procedures because of past experience, and have recommended different materials and packing types (2,4,11).

Although there has been no study to date reporting the rate of use of nasopharyngeal packing in our country, it is routinely used in many clinics in daily practice (11-13). Temel et al. (14), in their 2019 study, stated that pharyngeal packing reduced the increase in gastric volume associated with perioperative blood swallowing in elective nasal surgeries and that the method could be considered useful and safe for the reduction of the risk of perioperative pulmonary aspiration in such surgeries. However, there are opposing views stating that pharyngeal packing has no effect on PONV, contrary to the intended effect, and that there is potential for damage to the pharyngeal mucosa and postoperative sore throat, and even life-threatening complications (2,3,5,6,15-18). The study by Basha et al. (15) of 100 patients showed that pharyngeal packing had no effect on the incidence of PONV but increased the incidence of sore throat significantly, while opting not to carry out pharyngeal packing did not increase postoperative aspiration or vomiting. Many other studies, such as those by Korkut et al. (10), Meco et al. (13), Razavi et al. (17), Piltcher et al. (18) and Green et al. (19), have reached similar findings at different times. Piltcher et al. (18) reported no difference in the incidence of PONV between their pharyngeal packing group and their control group, in which no additional precautions were taken. Contrary to classical empirical thinking, this study argues that blood swallowing during surgery may not be a determinant of PONV. Furthermore, there have also been studies reporting that the removal of blood from the stomach using different methods, such as perioperative orogastric aspiration, also has no effect on PONV (20-22). It is also quite likely that besides

Table 3. Evaluation of postoperative complications by groups

Postoperative complications			Group 1, (n=30)	Group 2, (n=30)	Test value; χ^2	p
			n (%)	n (%)		
Nausea-vomiting (PONV)	Postoperative hour 0	No	17 (56.7)	15 (50.0)	1.776	[c]**0.586**
		Mild	13 (43.3)	13 (43.3)		
		Moderate	0 (0)	2 (6.7)		
	Postoperative hour 6	No	22 (73.3)	20 (66.7)	2.139	[c]**0.410**
		Mild	3 (10.0)	7 (23.3)		
		Moderate	5 (16.7)	3 (10)		
	Postop.hour24	No	27 (90.0)	28 (93.3)	0.218	[d]**1.000**
		Mild	3 (10.0)	2 (6.7)		
	Test value; χ^2		8.098	14.233		
	[f]p		**0.017**	**0.001****		
Intragroup pairs, [g]p	Postoperative hours 0-6		0.478	0.478		
	Postoperative hours 0-24		0.045*	0.020*		
	Postoperative hours 6-24		0.197	0.061		
Antiemetic use (AE)	Postoperative hour 0		0 (0)	2 (6.7)	2.069	[d]**0.492**
	Postoperative hour 6		5 (16.7)	3 (10.0)	0.577	[d]**0.706**
	Postoperative hour 24		0 (0)	0 (0)	-	-
	Test value; χ^2		10.000	2.800		
	[f]p		**0.007****	**0.247**		
Intragroup pairs, [g]p	Postoperative hours 0-6		0.019*	1.000		
	Postoperative hours 0-24		1.000	0.820		
	Postoperative hours 6-24		0.019*	0.301		
Sore throat (ST)	Postoperative hour 0		13 (43.3)	5 (16.7)	5.079	[e]**0.024**
	Postoperative hour 6		10 (33.3)	5 (16.7)	2.222	[e]**0.136**
	Postoperative hour 24		5 (16.7)	1 (3.3)	2.963	[d]**0.195**
	Test value; χ^2		12.250	5.333		
	[f]p		**0.002****	**0.069**		
Intragroup pairs, [g]p	Postoperative hours 0-6		0.582	1.000		
	Postoperative hours 0-24		0.002**	0.137		
	Postoperative hours 6-24		0.091	0.137		
Dysphagia (DSFG)	Postoperative hour 0		2 (6.7)	3 (10.0)	0.218	[d]**0.640**
	Postoperative hour 6		2 (6.7)	1 (3.3)	0.351	[d]**0.554**
	Postoperative hour 24		0 (0)	1 (3.3)	1.017	[d]**1.000**
	Test value; χ^2		2.667	4.000		
	[f]p		**0.264**	**0.135**		
Intragroup pairs, [g]p	Postoperative hours 0-6		1.000	0.250		
	Postoperative hours 0-24		0.472	0.250		
	Postoperative hours 6-24		0.472	1.000		

[c]Fisher Freeman Halton Exact test, [d]Fisher's exact test, [e]Pearson's chi-square test, [f]Friedman test, [g]Bonferroni-Dunn test, *p<0.05, **p<0.01, PONV: Postoperative nausea and vomiting

the above factors, modern surgical/anesthetic techniques and drugs has reduced the amount of bleeding compared to 20 years ago (5).

Study Limitations

Our study, like all those that came before it, could not demonstrate the superiority of pharyngeal packing over orogastric suctioning in the prevention of PONV and in the use of antiemetics. In the present study, limitations such as "comparison of different types of surgical application data, differences in operative times, the lack of information on the type of postoperative dressing, and differences in the packing localization/type" expressed by authors such as Appadurai and Tomkinson (23) against those who support the opposing view on nasopharyngeal packing were minimized through the choice of a single type of surgery - "septorhinoplasty", and using the same anesthesiology and surgical

Table 4. Evaluation of VAS and satisfaction measures by groups

				Group 1 (n=30)	Group 2 (n=30)	Test value;	
VAS	Postoperative hour 0	Median (Q^1-Q^3)		2 (0-2.25)	1 (0.75-3)	Z: -0.152	
		Mean ± SD		1.53±1.20	1.63±1.35	[h]**p: 0.879**	
	Postoperative hour 6	Median (Q^1-Q^3)		3 (2-6)	2 (2-6)	Z: -0.486	
		Mean ± SD		3.73±1.74	3.53±2.15	[h]**p: 0.627**	
	Postoperative hour 24	Median (Q_1-Q_3)		2 (2-2.25)	2 (2-2)	Z: -1.143	
		Mean ± SD		2.27±0.74	2.13±0.90	[h]**p: 0.253**	
			Total, (n=60)	**Group 1, (n=30)**	**Group 2, (n=30)**	**Test value: Z**	**[h]p**
			n (%)	**n (%)**	**n (%)**		
Satisfaction score		Median (Q_1-Q_3)	3 (3-4)	3 (3-4)	3 (3-4)	-0.480	**0.631**
		Mean ± SD	3.05±0.85	3.03±0.76	3.07±0.94		
		Score 1	4 (6.7)	1 (3.3)	3 (10.0)		
		Score 2	8 (13.3)	5 (16.7)	3 (10.0)		
		Score 3	29 (48.3)	16 (53.3)	13 (43.3)		
		Score 4	19 (31.7)	8 (26.7)	11 (36.7)		

[h]Mann-Whitney U test, [f]Friedman test, [g]Bonferroni-Dunn test, *p<0.05, **p<0.01. VAS: Visual analogue scale

teams. The generally accepted risk factors for the development of PONV in adults include a history of motion sickness or PONV, smoking status, use of inhalation anesthetics and/or nitrous oxide, intraoperative or postoperative opioid use, female gender, age, prolonged surgery, and certain types of surgical procedures (10,20). Our study established no difference in these risk factors between the groups. Furthermore, unlike researchers such as Korkut et al. (10), it was our aim to test what occurs under real conditions in the clinic through the use of the routine antiemetic/analgesic protocol in these operations. Although the PONV rate in both groups in the present study was consistent with the classical data, the absence of a control group in which no additional precautions were taken, the failure to determine the type/amount of gastric fluid aspirated by orogastric tube, and the numerical quantity of the groups can be considered limitations of our study. In our opinion, the higher incidence of PONV in ENT surgeries can be attributed to the "naso-emetic" reflex. The sensory nerves of the nose come from the ophthalmic and maxillary branches of the trigeminal nerve, and for various reasons, reflex stimuli during surgeries of the head, neck, and nose lead to vomiting because of stimulation of the vagal nucleus in the brainstem. The high incidence of PONV after nasal surgery may be a reflection of the trigeminal-vagal "naso-emetic" reflex. It is still unclear whether the vestibular input contributes directly to PONV in this reflex or whether the anesthetics used increase the sensitivity of the vestibular organ (10,11). In brief, in light of these facts, we believe PONV to be multifactorial, as previously underlined by many researchers, and cannot be prevented by nasopharyngeal packing or gastric decompression (1,18,21).

Another common complication after operations under general anesthesia is sore throat, with patients experiencing a sore throat at a rate of 10% during ventilation with a face mask, 5.8-34% with a laryngeal mask, 14.4-50% after intubation, and 61% with pharyngeal packing (24,25). The study by Elyassi et al. (25) reported that there was no significant difference in sore throat between those given conscious sedation and general anesthesia among elective rhinoplasty patients, and named the dry oxygen used during the operation and the mandatory intermittent oropharyngeal suction as the reason. Basha et al. (15) and Marais (26), on the other hand, reported that the use of pharyngeal packing caused sore throat twice as frequently, causing moderate pain that decreases over time and that can be partially controlled with analgesics. The findings of this study are consistent with those reported in the above studies. The rates of sore throat were 43.3% vs. 16.7% at postoperative 0 h in groups 1 and 2, respectively, and decreased to 33.3% and 16.7% at 6 h, and to 16.7% and 3.3% at 24 h, respectively. That said, other studies have reported different results to ours related to the prevalence of sore throat. According to Green et al. (19), patients who do not undergo pharyngeal packing experience more pain at 24 h following surgery than those with throat packing. Researchers such as Meco et al. (13) and Piltcher et al. (18), on the other hand, identified no difference in sore throat between their two groups. Following a different approach, Elhakim et al. (27) argued that sore throat could be reduced by ¼ through impregnation of the pharyngeal packing with tenoxicam rather than saline. Similarly, Vural et al. (2) recommended the use of pharyngeal packs impregnated with chlorhexidine gluconate 0.2% and benzydamine hydrochloride 0.15% for the same purpose, claiming that this method improves patient comfort and reduces sore throat.

It is known that pharyngeal packing can lead to localized trauma and inflammation of the mucosa (11), which in our opinion is the primary cause of increased postoperative sore throat. Again, the same process may lead to other major complications, such as pharyngeal plexus injury and swelling of the tongue, while local trauma may cause PONV by stimulating the vagal nucleus in the brain. In addition, an increased analgesic requirement contributes to PONV if opioids are preferred. It has been found that edemas and their potential outcome, pain - start to decrease 2 h after the operation (11). In our study, sore throat also decreased in both groups over time. Although most studies have tried to define, the common limitation of both the present study and earlier studies is that a standard scale has not been developed for the measurement of sore throat (11), which severely limits the comparison of data reported in different studies, making its reliability questionable.

Conclusion

Contrary to the findings of researchers such as Erkalp et al. (6) (Aphthous stomatitis), Meco et al. (13), Smarius et al. (28), Seraj et al. (29) (airway soiling) and Fine et al. (30) (voice hoarseness), we did not observe any serious complications with nasopharyngeal packing, except for PONV and sore throat in the early or late postoperative period. We also did not encounter any life-threatening dramatic events such as pack migration or forgotten packs. In previous studies of this issue, the most common reasons for forgotten packs are forgetting the nasopharyngeal pack placement, inadvertent statements of removal by the surgeon, change of anesthesiologist during a long operation, inexperienced anesthesiologist in head/neck surgery, removal of fewer packs than placed, and earlier awakening of the patient from anesthesia than planned (12). We believe that we have not experienced such complications due to the experience of our ENT/anesthesiology teams and the availability of routine control/follow-up charts in our clinic, in line with the recommendations of Knepil and Blackburn (12). We should also state that the relatively low number of patients is also a limiting factor in our encountering of very rare complications.

The secondary aim of our study was to assess how the choice of method affected the postoperative pain score (VAS) and patient satisfaction. No VAS score of ≥4, which can be defined as pain, was reported by any of our patients, and there was no difference in the level of satisfaction of the two patient groups. We believe our routine analgesic and antiemetic protocol to be sufficient for the control of both PONV and pain, contributing to this finding. Furthermore, septorhinoplasty, which was the surgical approach selected for the study, is not a very painful surgical procedure, and we believe that the patients undergoing surgery at their own request and not out of necessity contributed to these findings.

In conclusion, routine packing practice should be abandoned by anesthesiologists. Given that pharyngeal packing itself is not a completely risk-free procedure, we do not recommend intraoperative packing during nasal surgery. If anesthesiologists are to routinely continue pharyngeal packing in operations in this region, they should do knowing that there is no objective evidence to support the practice. That said, nasopharyngeal packing as a surgical requirement may be needed for some orthognathic operations. For its limited use in such cases, each clinic should develop written protocols, checklists, and observation forms relating which operations require which principles are to be followed, with the participation of the surgical and anesthesia teams considering their surgical needs. If its use is decided, all materials should be included in the surgical (scrub) count, and it should be ensured that all materials are removed before extubation with a matching count. Anesthesia should be at a depth that will allow all these examinations and interventions to be completed, even if the operation is completed (30). Regardless of the method used, it should not be forgotten that the anesthesiologist is responsible for the examination of the oral cavity and throat with direct laryngoscopy and, if necessary, aspiration before extubation.

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Ethics Committee Approval: This randomized, prospective study of ASA I patients aged 18-50 years who were scheduled for elective septorhinoplasty in a university hospital's ENT clinic was launched after the granting of İstanbul Medipol University Ethics Committee approval (approval number: 611, date: 03.06.2021).

Informed Consent: Informed consent was obtained from the patients.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions: Surgical and Medical Practices - Y.G.G., H.C.C.; Concept - Y.G.G., A.H., H.C.C., A.Ş.K.; Design - Y.G.G., A.H., H.C.C., A.Ş.K.; Data Collection or Processing - Y.G.G., A.H., H.C.C., A.Ş.K.; Analysis or Interpretation - Y.G.G., A.H., H.C.C., A.Ş.K.; Literature Search - Y.G.G., A.H., H.C.C., A.Ş.K., E.U.; Writing - Y.G.G., A.H., H.C.C., A.Ş.K.

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Evaluation of Thromboembolism Risk in Patients with Cancer; Single Center Real-life Data

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ABSTRACT

Introduction: Venous thromboembolism (VTE) is an important cause of mortality and morbidity in cancer patients. Both cancer itself and its treatment have been reported to result in an increased risk of VTE. Several scoring systems have been developed to predict cancer-associated VTE risk. The aim of this study was to prospectively test the validity of the Khorana thrombosis score in predicting the risk of VTE development in cancer outpatients at a single centre.

Methods: One hundred and fifty-two consecutive patients diagnosed with cancer and scheduled to receive outpatient chemotherapy at University of Health Sciences Turkey, İstanbul Training and Research Hospital between August 2012 and August 2013 were included in the study. Khorana risk scores were calculated for each patient at study entry. Patients were then followed up for at least 24 months after diagnosis or until VTE developed.

Results: Thrombosis was detected in 13 of the 152 patients following cancer diagnosis. The median time from diagnosis to thrombosis was 4 months (1-48 months). Thrombosis was of venous and arterial origin in 7 and 6 patients, respectively. The Khorana score failed to differentiate high-risk patients. Scores in patients with and without venous thrombosis were not statistically different (p=0.38).

Conclusion: It is important to identify cancer patients at high risk for VTE to decrease the thrombosis-associated dismal outcome. However, in an outpatient setting, the Khorana score failed to differentiate the target population. This could be partly explained by the heterogeneity and the relatively small number of patients included.

Keywords: Cancer, risk scores, venous thromboembolism

Introduction

Cancer continues to be an important health problem with increasing frequency throughout the world. It is a common cause of death in Turkey comparable to that in developed countries. Both cancer itself and its treatment (i.e., chemotherapy, radiotherapy, surgical interventions, etc.) have been associated with venous thromboembolism (VTE). Several parameters including the primary site and histological features of the tumour, treatment modalities, and metastatic state were indicated to correlate with increased risk of VTE (1,2).

Development of a clinically significant thrombotic event per se and/or complications of the anticoagulant therapy, in particular, bleeding, may interfere with and impede the management of cancer. VTE not only impairs the quality of life of the patient by adversely affecting the general condition but also increases medical expenses (3). Additionally, mortality rates of cancer patients complicated with VTE have been reported to be more than twice those of uncomplicated patients, independent of the stage of the disease (4,5). Thus, VTE is a significant contributor to cancer patients' death and morbidity. To estimate the cancer patients' vulnerability to VTE and differentiate high-risk individuals that would gain advantage from primary thromboprophylaxis, a few scoring methods have been devised.

Primary VTE prophylaxis may decrease fatal vascular complications of deep venous thrombosis (DVT) or pulmonary embolism (PE) and decrease the risk of mortality and morbidity in cancer patients (6). Thus, it would ameliorate the quality of life of the patients and decrease the medical costs. It is therefore of utmost importance to identify patients who would benefit from anticoagulation. In the cancer outpatient setting, symptomatic VTE risk has been estimated to range from 5% to 7%. This rate is similar to the high-risk patients without cancer and have benefited from thromboprophylaxis (7).

Khorana et al. (8) developed a scoring system in their prospective observational cohort study in 2008, which was based on the laboratory

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as well as clinical characteristics of cancer patients at diagnosis and predicted the cancer-associated VTE risk. Primary thromboprophylaxis has been recommended for high-risk patients.

The current study aimed to prospectively assess the reliability of the Khorana thrombosis score in determining the possibility of VTE development in a population of cancer patients in an outpatient setting at a single center where there are no institutional directives for thromboprohylaxis.

Methods

The Study Group

One hundred and fifty-two patients who had been consecutively diagnosed with cancer between August 2012 and August 2013 at University of Health Sciences Turkey, İstanbul Training and Research Hospital were prospectively included in the study. Patients aged 18 or more with a histopathologically verified cancer diagnosis who were scheduled for an outpatient chemotherapy program could enter the study if they provided written informed consent and did not meet any of the following exclusion criteria:

- The history of prior cytotoxic, biological or immunological cancer therapy

- The history of prior radiotherapy

- The diagnosis of acute leukaemia, myelodysplastic syndrome, local non-melanoma skin cancer

- Pregnancy or lactation

- The history of bone marrow transplantation

- The presence of active chronic infection

- The history of previous VTE

- Bedridden or poorly mobilized patients

- The history of recent or current use of anticoagulants or antiaggregants

In Turkey, awareness of cancer-associated thromboembolic events among physicians is scarce and in house directives regulating the prophylactic usage of anticoagulant medications in those with cancer do not exist in most hospitals, including the hospital in which this study was conducted. Consequently, physicians neglect or avoid using anticoagulant therapy, especially if the patient is thrombocytopenic. Thus, this study was designed as a prospective observational study on thromboembolic events in a setting where routine anticoagulant prophylaxis was not practiced on a regular basis.

Method

Each patient's Khorana risk score was calculated at study entrance (8). Following diagnosis, patients were monitored for at least 24 months or until VTE manifested itself. At each visit during chemotherapy and every 3 months after that, patients were surveyed and examined for the presence of VTE (DVT, PE, abdominal venous thrombosis, etc). Confirmatory coagulation and imaging tests were performed in cases of clinical suspicion.

Statistical Analysis

The statistical evaluation was done using SPSS version 15.0. Results were given as mean ± standard deviation in the presence of a normal distribution. Nonparametric parameters were reported as medians. To compare the two groups, chi-square and Mann-Whitney U tests were utilized. $P<0.05$ was accepted to be statistically significant.

Results

Patient characteristics are listed in Table 1. Breast cancer was the most frequent type of cancer in the study group (42.9%), followed by colon cancer (23.8%) and lung cancer (11.4%). A complete list of malignancies diagnosed in the recruited patients is given in Table 2. Of the 152 patients in total, 98 (64.5%) and 54 (35.5%) had Eastern Cooperative Oncology Group (ECOG) performance scores of 0/1 and 2/3, respectively. Khorana risk scores were found 0 in 52 patients (34.2%), 1-2 in 84 patients (55.2%), and 3-4 in 16 patients (10.5%) (Figure 1). Following the cancer

Table 1. Patient Characteristics

The number of patients (n)	**152**
Age [year, mean (range)]	57 (23-84)
Gender (n, M/F)	53/99
Stage (n, early /metastatic)	87/65
ECOG [median (range)]	1 (0-3)
Radiotherapy (n, %)	63 (1.4)
Hormonal therapy (n, %)	30 (19.7)
Surgery (n, %)	112 (73.7)
The complete clinical response (n, %)	94 (61.8)
Relapsed cases (n, %)	15 (9.9)
Patients with catheter (n, %)	34 (22.4)
Patients with thromboembolic events (n, %)	13 (8.6)
Thrombosis (n, venous/arterial)	7/6
Time from diagnosis to thrombosis [months, median (range)]	4 (1-48)
Thrombosis score [median, (range)]	1 (0-4)
Coexisting disease (n, +/-)	61/91
Haemoglobin* (g/dL)	12.17±1.50
White blood cell count* (/mm^3, mean ± SD)	8160.92±2739.06
Platelet count* (/mm^3, mean ± SD)	355368.4±162309.6
LDH* (U/L, mean ± SD)	127.66±42.50
HDL* (mg/dL, mean ± SD)	50.93±14.38
Total cholesterol* (mg/dL, mean ± SD)	207.49±46.39
Triglyceride* (mg/dL, mean ± SD)	143.0±65.70
CRP* (mg/dL, mean ± SD)	1.87±3.33
D-dimer*(mg/dL, mean ± SD)	2.03±2.88
BMI* (mean ± SD)	27.47±5.10
Progression-free survival (months, mean ± SD)	18.87±15.94
Overall survival (months, mean ± SD)	20.58±17.89
The status at the last follow-up [n, dead/alive/unknown (%)]	18/112/22 (11.8%/73.7%/14.5%)

*At the time of diagnosis, M/F: Male/Female, ECOG: Eastern Cooperative Oncology Group performance score, SD: Standard deviation, BMI: Body mass index, LDH: Lactate dehydrogenase, HDL: High-density lipoprotein, CRP: C-reactive protein

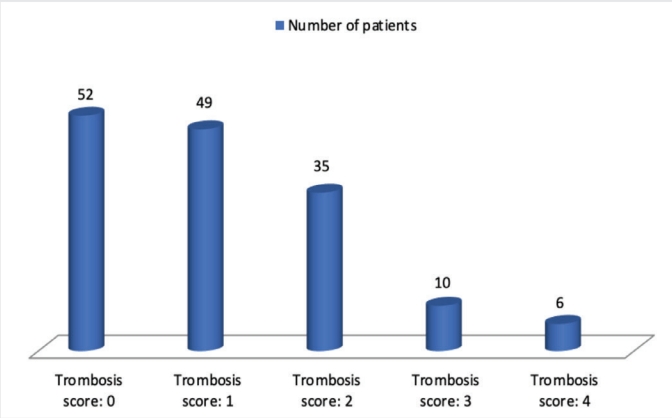

Figure 1. Distribution of Khorana scores

Table 2. Sites of tumour origin

Origin of the tumour	The number of patients, (n, %)	
Bladder	2	(1.3)
Breast	56	(36.8)
Colon	36	(23.7)
Gall bladder - intrahepatic bile ducts	2	(1.3)
Kidney	1	(0.7)
Larynx	1	(0.7)
Lung	16	(10.5)
Lymphoma	3	(2.0)
Multiple myeloma	1	(0.7)
Oesophagus	1	(0.7)
Ovary	8	(5.3)
Pancreas	2	(1.3)
Prostate	3	(2.0)
Rectum	4	(2.6)
Stomach	13	(8.6)
Testis	1	(0.7)
Thyroid	1	(0.7)
Uterus	1	(0.7)

diagnosis, clinically significant thrombosis was observed in 13 of 152 individuals. Median time from diagnosis to thrombosis was 4 months (1-48 months). Thrombotic attacks were of arterial and venous origin in 6 and 7 patients, respectively. Patients with and without VTE did not have substantially different median Khorana scores (p=0.38). In cases with VTE, Khorana scores were 1 in 46% and 2 in 23% of the patients. Among the group without VTE, the percentage of patients with 0, 1 and 2 Khorana scores was found to be 91%. Venous thrombosis was detected in one of the 52 patients with score 0, in 3 of the 49 patients with score 1, in 2 of the 35 patients with score 2, in none of the 10 patients with score 3, and in only 1 out of 6 patients with score 4.

Patients with arterial thrombosis consisted of 5 females and 1 male patient, with a median age of 65. The median thrombosis score was 1.5 (1-3). Platelet counts, Khorana, and ECOG performance scores at diagnosis were found to be statistically significant between patients with and without arterial thrombosis (p values: 0.047, 0.044, and <0.001, respectively). There was a higher possibility of arterial thrombosis with advanced age, male gender, and a history of surgical intervention (p values: <0.001, 0.02, and 0.005, respectively).

Patients with venous thrombosis consisted of 5 females and 2 males with a median age of 55 years and a median thrombosis score of 2 (1-3). Khorana thrombosis scores did not differ in patients with and without venous thrombosis (p=0.38). However, overall and progression-free survival durations were significantly lower in patients with venous thrombosis (p values: 0.021 and 0.022, respectively). Neither age, gender, BMI, presence of metastatic disease, nor the thrombotic risk score predicted venous thrombosis (p>0.05).

Surgical intervention within 4 weeks before diagnosis was found to have a significant impact on thrombosis development (p=0.02). Neither radiotherapy nor the type of chemotherapy was linked to increased risk of thrombosis (p=0.16 and 0.26, respectively). However, we observed a marked association between the presence of active and/or recurrent disease, ECOG performance score, and thrombosis occurrence. The use of a central venous catheter and/or concomitant comorbidities was not linked to the occurrence of VTE (p>0.05). Likewise, no significant difference could be identified in haemoglobin, leukocyte, platelet, low-density lipoprotein, high-density lipoprotein, total cholesterol, triglyceride, D-dimer, and C-reactive protein (CRP) levels at the time of diagnosis between patients with and without venous thrombosis. However, D-dimer and CRP levels were noticeably higher in patients with thrombosis when arterial and venous thromboses were taken together (p values: 0.047 and 0.03, respectively).

Discussion

Both morbidity and death in cancer patients are significantly influenced by VTE. The management of thrombosis may lead to delays for treating cancer and may result in life threatening complications such as bleeding. This, in turn, not only impairs the general condition of the patient but also increases the medical costs (5). Additionally, mortality rates have been found to be twice as high in patients complicated with VTE than in those without venous thrombosis (9). Prophylactic treatment with anticoagulants would decrease the rates of mortality and morbidity and improve survival of patients with cancer (10). Most of the previous studies dealing with thromboprophylaxis mainly included patients with metastatic breast and lung cancer and those with central venous catheterization (11-15).

Vascular complications with high rates of mortality such as DVT and PE can be avoided with primary VTE prophylaxis, which usually results in decreased rates of mortality and morbidity in high-risk individuals such as those who have cancer (6). Thus, by giving primary anticoagulant prophylaxis, one can ameliorate cancer treatment, improve the quality of life, and decrease medical costs. It is important to define a high-risk population to prevent the negative outcome of VTE. In cancer outpatients, symptomatic VTE is reported to be between 5% to 7%, which is similar to the rate of patients without cancer that have been shown to have benefited from thromboprophylaxis (e.g., hospitalized patients

receiving medical therapy) (7). In our study, venous thrombosis occurred at a rate of 4-6% and 8.5% of patients had both arterial and venous thrombosis.

Khorana et al. (8) developed a scoring tool to predict VTE risk for pofents with cancer by us clinical and laboratory data of prospectively followed 2071 outpatients with cancer. They recommended thromboprophylaxis for cancer patients with a high risk for developing VTE. In our study, we used Khorana risk scoring to assess the possibility for developing VTE in 152 outpatients with cancer when it was initially diagnosed. The patients were followed for an average of 17 months. Thrombotic attacks of arterial (6 cases) and venous (7 cases) origin were observed in 13 patients during follow-up. The site of cancer has been linked to VTE occurrence in previous studies. Cancers originating from the brain, pancreas, stomach, kidney, over, and lungs and hematological malignancies, especially lymphomas, have been reported as the leading causes of VTE (2,16). In a case control study, VTE was observed at the highest rate in patients with hematological malignancies, followed by the lungs and gastrointestinal system (1). In our study, the most frequent sites of involvement was the gastrointestinal system, lungs and blood. The highest risk of VTE development is in the first few months after the diagnosis (1). Between the cancer diagnosis and the thrombotic episode in our cohort, there was a 4-month median interval.

In large cohort studies, the stage of cancer is an important risk factor underlying VTE (9). However, other studies including outpatients with ovary cancer could not demonstrate any significant relationship between stage and VTE occurrence (17). Similarly, in our study, we could not reveal any correlation between stage and the risk of thrombosis. This can be explained by the relatively good performance status of our cohort with a median ECOG score of 1.

Performance status is a surrogate marker for immobility, another well-defined risk factor for VTE (10). In a prospective study, which consisted of lung cancer patients receiving chemotherapy, the VTE rate was found to be 31% in patients having poor performance status and 15% in the group having good status (18). Although there was no statistically significant difference, another investigation on outpatients with cancer discovered that the incidence of VTE was higher in patients with relatively poor performance status. Over 90% of the patients who were included in the analysis had extremely good performance status, which helped to explain this (2). Poor performance status is accepted to be associated with recurrent VTE occurrence in cancer patients (19). A statistically significant correlation between high ECOG performance scores and the potential for thrombosis was identified in our research. Subgroup analysis revealed that high ECOG scores predicted a significant risk of arterial thrombosis ($p \leq 0.001$) at our hands but not for venous thrombosis ($p=0.06$).

Recent findings indicate that VTE risk persists at high rates for a long time postoperatively (20). Khorana et al. (8), however, could not identify surgical intervention as a risk factor in their cohort, which was then explained by the fact that almost all patients were on postoperative thromboprophylaxis. In contrast, individuals with a history of surgical procedure had a higher prevalence of arterial but not venous thrombosis, according to our cohort analysis.

VTE is a major issue for hospitalized and old cancer patients (>65 years old) (21). However, age per se has been shown not to be a significant risk factor for VTE development in cancer outpatients if the performance status is good (2). In our cohort, age and gender were not related to thrombosis. However, when only the group of patients with arterial thrombosis was evaluated, male gender and age were noted as risk variables.

In a prospective observational trial on those who are undergoing chemotherapy for cancer, high platelet counts before treatment were found to be connected to an increase in VTE occurrence (2). Another retrospective trial, which included hospitalized cancer patients, found platelet counts over 350000/mm^3 to be predictive for VTE development (22). Recent studies have shown an association between white blood cell (WBC) counts and vascular events (23). In patients with myeloproliferative diseases, WBC counts were clearly shown to be a risk factor for venous thrombotic events (24). In our cohort, we could not identify any significant relationship between VTE occurrence and WBC and platelet counts at diagnosis. On the other hand, it was discovered that a significant predictor of arterial thrombosis was high platelet counts. However, this finding should be cautiously approached as the number of patients with arterial thrombosis is small and confounding factors such as comorbidities might have interfered with the outcome.

D-dimer levels are typically observed to be higher in cancer patients (20), which has been demonstrated to be a substantial predictor for recurrent VTE (19). Ay et al. (25) pointed out that adding plasma levels of D-dimer and soluble P-selectine to the scoring may improve the potential of the Khorana risk scoring system in predicting the risk of VTE. Our results also indicate a statistically significant association between D-dimer concentrations at the time of diagnosis and the risk of thrombosis. Similar to D-dimer, elevated CRP concentrations (>400 mg/dL), a predictor of inflammation, were observed to be associated with VTE in cancer patients (3). Our cohort study also found that high CRP levels were significantly related to thrombosis.

We observed clinically significant VTE events in our study without performing a routine screening for thrombosis. Although there is a non-negligible probability of recurrent thrombosis when VTE is unintentionally found, a recently published meta-analysis of cancer-related thrombosis demonstrated a low recurrence rate with incidental VTE (26). However, evidence is still conflicting and inadequate to suggest routine radiological and laboratory screening for thrombosis in cancer patients.

Khorana risk score is one of the recommended tools in the guidelines for preventing VTE in cancer patients who are outpatients (27,28). For real-life data emerge, risk scores should be applicable in general medical practice. However, a recent study showed that no high-risk cancer outpatient received thromboprophylaxis (29). On the other hand, the method of assessing the risk of bleeding in patients with an elevated likelihood of thrombosis, the duration of prophylactic anticoagulation, and the types as well as the doses of prophylactic anticoagulants remain unclear. Because thrombocytopenic patients and individuals having creatinine clearance below 30 mL/min were removed from the studies, the use of these thrombosis assessment tools in hematology practice

seems limited. More prospective, randomized studies are needed on these issues.

Study Limitations

The main limitations of this study are the heterogeneity of the cancer types and the relatively small number of patients included.

Conclusion

Thrombosis is an important issue contributing to the dismal outcome of cancer. Therefore, patients who are at a high risk of developing thrombosis should be identified. The available data point to the usage of thromboprophylactic medications for cancer patients who have a higher risk of thrombosis. The risk of VTE in cancer patients has been predicted using various risk assessment systems. We used Khorana risk scoring to assess its predictive potential and tested other risk factors that could indicate increased risk for arterial as well as venous thrombosis in a prospective real-life setting in patients with cancer who were not on thromboprophylaxis. Our results, in general, are in line with the current literature. Khorana scores, however, could not fully identify patients at risk in our cohort. Although statistically not significant, thrombosis frequency was higher in patients with higher scores (Khorana 3 and 4). This may be described by the tiny sample of patients in the cohort.

Ethics Committee Approval: The study was reviewed and approved by the University of Health Sciences Turkey, İstanbul Training and Research Hospital Local Ethics Committee (approval number: 173, date: 07.09.2012).

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

Peer-review: Externally peer-reviewed.

Authorship Contributions: Surgical and Medical Practices - S.E., R.U.G., M.H.E., M.C.A.; Concept - S.E., M.H.E., M.C.A.; Design - S.E., M.H.E.; Data Collection or Processing - S.E., R.U.G.; Analysis or Interpretation - S.E., M.H.E.; Literature Search - S.E., M.H.E.; Writing - S.E., M.H.E.

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Partial Atrophy of The Pancreas in Endoscopic Ultrasonography may be a Sign of Pancreatic Cancer

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ABSTRACT

Introduction: Solid and/or cystic lesions of the pancreas can range from benign to malignant, and the differential diagnosis of pancreatic carcinoma (PC) is of uttermost importance. Endoscopic ultrasonography (EUS) is frequently used and is helpful in detecting small (<2 cm) lesions and provides information about the extralesional pancreas. EUS also facilitates tissue diagnosis and allows the cyst fluid examination. Our aim was to evaluate the role of EUS findings and cyst characteristics of pancreatic lesions in predicting PC.

Methods: Records of patients with pancreatic lesions were retrospectively assessed. EUS findings, serum C19-9 levels, CEA levels, and cyst biochemistry of the patients were noted. The relationship between PC, mucinous pathologies, EUS findings, cyst characteristics, and serum biochemistry was evaluated.

Results: Two-hundred-four patients had EUS-guided biopsy for a pancreatic lesion (48% solid). Eighty-nine patients had PC. The serum CA19-9 cut-off value for PC was 37 U/mL (AUC: 0.81). In multivariate analysis, solid lesions, age, CA19-9>37 U/mL, and partial atrophy in the pancreas were independently associated with PC. For solid lesions, age and size >24 mm; and for cystic lesions, male gender and mucinous pathology were independently associated with PC. Thirty-six of the cystic lesions had mucinous pathology. Cyst and serum CEA, string sign, wesung connection, and tail location was associated with mucinous pathology. Cyst CEA cut-off for mucinous pathology was 80 ng/mL (AUC: 0.89). CEA >80 ng/mL was found to be associated with mucinous pathology in multivariate analysis.

Conclusion: High CA19-9, solid lesion, and lesion-related partial atrophy of the pancreas are associated with PC, and these should be alarming for clinicians in practice. The mucinous character, which is a significant risk of PC for cystic lesions, can be optimally defined with the CEA cut-off value of 80 ng/mL.

Keywords: Endoscopic ultrasonography, fine needle aspiration biopsy, pancreatic carcinoma, mucinous pathology, CEA

Introduction

Solid and/or cystic lesions can be detected in the pancreas, either symptomatic or incidentally and are generally more common with advancing age. These include benign inflammatory/post-inflammatory lesions, benign neoplastic lesions, and pre- or low/high-grade malignant lesions (1). Although the probability of solid lesions being neoplastic is higher than cystic ones, there is a premalign-malignant neoplastic potential also for cystic lesions, especially for those with mucinosis features (2). Among these lesions of the pancreas, the most feared in the differential diagnosis is pancreatic adenocarcinoma (PC), which is mostly diagnosed at an advanced stage when surgical treatment is no longer an option. Advanced PC is associated with very low survival rates and is still an important cause of cancer-related deaths worldwide (3). Recognizing PC and distinguishing them from other pathologies should be the aim of evaluation due to the potential aggressive clinical course.

Endoscopic ultrasonography (EUS) is frequently used in the examination of pancreatic lesions because it is superior to cross-sectional imaging methods in detecting small (<2 cm) and solid lesions of the pancreas (4). EUS also provides information about extralesional pancreas and adjacent tissues. Another advantage is that EUS facilitates tissue diagnosis by allowing fine-needle aspiration (FNA) biopsy in solid lesions during the examination and may also help the classification of cystic lesions by providing an opportunity for cyst fluid aspiration and biochemical examination.

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Sampling the cyst content allows biochemical analyses such as amylase, CEA, and glucose levels in the cyst fluid, as well as advanced genetic and molecular examination (5).

The aim of our study was to evaluate the role of EUS findings and cyst fluid characteristics in predicting PC and/or mucinous pathologies in solid and cystic lesions of the pancreas.

Methods

The records of patients who underwent EUS examination of the pancreas between January 2017 and 2022 were retrospectively assessed. The location, size, and characteristics (cystic or solid) of the lesions were evaluated and FNA and/or biopsy if performed was noted. Other parameters accompanying the lesion detected in EUS and evaluated were as follows: ductal dilatation (common bile duct and/or Wirsung), lymphadenopathy, presence of ascites, solid lesion in the liver suggesting metastasis, appearance compatible with vascular invasion (portal vein, splenic vein, splenic artery, superior mesenteric vein, artery, hepatic artery and celiac trunk), presence of chronic pancreatitis, and partial/local pancreatic atrophy that does not meet the criteria for chronic pancreatitis. Chronic pancreatitis was defined as having 5 or more of the 9 EUS criteria put forward by the International Working Group (6).

In cystic lesions, the presence of septation or mural nodule (solid component), the relationship of the cyst with Wirsung, the presence of a string sign if aspiration was performed, and the cyst CEA levels were also examined. If available, serum CA19-9 and CEA levels of the patients, which were measured within 2 weeks before the EUS procedure, were also included in the analysis.

All EUS examinations were performed by the same physician, and lesion biopsies were performed using a 22 G needle. Among the reported FNA biopsy results, categories 5 and 6 defined by the Pancreatic Cytopathology Study group were considered malignant (7,8). Lesions that were category 4b and showed mucinous components cytologically or lesions that underwent pancreatic resection and whose surgical pathology was reported as mucinous were considered as mucinous pathology. Clinical, radiological, and treatment (oncological) data of the patients were obtained from electronic medical records. Patients with malignant FNA results and/or patients who received oncological treatment for PC and/or patients with radiological evidence of metastatic disease with a primary origin of the pancreas (taking into account radiological work-up, FDG - positron emission tomography) were regarded as having PC. The relationship between PC, mucinous pathologies, and EUS findings, cyst characteristics, and serum biochemistry was evaluated.

This study was approved by the local ethics committee. The procedures used in this study comply with the principles of the Declaration of Helsinki.

Statistical Analysis

Mean and standard deviation were used for normally distributed data, median and IQR for non-normal distribution, and frequency for categorical data. Cut-off values and sensitivity specificity for CEA and CA19-9 were calculated using ROC analysis. Significant parameters related to pancreatic carcinoma (PC) and/or mucinous pathology were evaluated further by logistic regression analysis. IBM-SPSS v.29 Was used for statistical calculations.

Results

A total of 319 EUS procedures for the pancreas was evaluated. Of these, 204 (64%) patients had EUS-guided biopsy for a pancreatic lesion, and 78 of those who underwent biopsy also had cystic fluid aspiration available for biochemical analysis. Fifty-five percent (n=113) of the patients who underwent the procedure were women. The mean age was 58 years (±13.7). Forty-eight percent (n=98) of the cases were solid and the rest were cystic lesions. While 81% of cystic lesions were pure cystic, the rest had a solid component/mural nodule accompanying the cystic lesion (n=20). The lesion and demographic characteristics of the study group is summarized at Table 1.

The size of solid and cystic lesions was similar, and the median size for both was 30 mm (solid: minimum-maximum: 5-120; IQR: 19; cystic: 8-115; 21; p=0.85). Among cystic ones, lesions including the solid component were larger in size numerically than isolated cystic lesions [34 mm (8-115;19) vs 30 mm (19-80;23), respectively] but the difference between them was not significant (p=0.119).

The distribution of the lesions in the pancreas was evaluated; the most common site for the lesions was the head of the pancreas, while the least common site was the uncinate. Table 2 summarizes the distribution and solid-cystic features of the lesions. Cystic lesions were significantly more common in the tail than in other parts of the pancreas (p=0.007). There

Table 1. Lesion and demographic characteristics of the study group

Patient demographics	
Sex (F)	55% (113)
Age	58±13.7
Lesion characteristics	
Solid	48% (98)
Cystic	52% (106)
Pure cystic	81% (86)
Cystic with solid component	19% (20)
Cases with biopsy	100% (204)
Cases with aspiration	38% (78)

Table 2. Distribution of lesions by anatomical parts of the pancreas, and cystic-solid features

	Anatomic parts of the pancreas				
	Uncinate	**Head**	**Neck**	**Body**	**Tail**
Total, % (n)	9.3% (19)	39.7% (81)	15.2% (31)	23.5% (48)	12% (25)
Solid, % (n)	52% (10)	53% (43)	51% (16)	50% (24)	24% (6)
Cystic, % (n)	48% (9)	47% (38)	49% (15)	50% (24)	76% (19)

was no relationship between the localization of cystic lesions in the pancreas and the presence of solid component/mural nodules (p=0.702). No correlation was found between the location and size of cystic or solid lesions and between location and patient age (p=0.803 and p=0.744 for cystic lesions and p=0.554 for solid lesions, respectively).

In patients undergoing biopsy and/or aspiration, findings reported in EUS that may be related to the lesion and cyst features are summarized in Table 3.

Thirty-six of the cystic lesions had mucinous pathology. When the lesion characteristics were evaluated, in terms of predicting mucinous pathology, aspiration CEA value (p<0.001), string sign positivity (p=0.009), cyst connected to wesung (p=0.033), cyst located at body or tail of pancreas (<0.028), and serum levels of CEA >3.1 (p=0.020) were found to be associated with mucinous pathology. The cut-off value for cyst CEA level in predicting mucinous pathology by ROC analysis was calculated as 80 ng/mL (AUC: 0.89; Figure 1). For this value, the sensitivity was 82% and the specificity was 90%. When the cut-off value for CEA was taken as 192 ng/mL, which is reported in the literature, the sensitivity decreased to 76%, while the specificity increased to 97%. In the multivariate regression analysis of mucinous pathology-related factors, aspiration CEA >80 ng/mL was found to be associated with mucinous pathology [p=0.002; 81 (5.1-1290)].

In 133 patients, the final diagnosis was clinically and/or histopathologically confirmed, and 89 of these patients were followed up and/or treated with a diagnosis of PC. While the final diagnosis was benign in 31 patients, neuro-endocrine tumor was detected in 13 patients. In the ROC analysis, the cut-off value for serum CA19-9 in distinguishing PC was 37 U/mL, and the AUC value was calculated as 0.81 (Figure 1). For this value, the sensitivity of CA19-9 in terms of PC was 79% and the specificity was 78%. Also, ROC analysis was performed (AUC: 0.76; Figure 1) for serum CEA, and pointed a cut-off level of 3.1 ng/mL could predict PK with 70% sensitivity and 65% specificity. Univariate and multivariate analysis associated with PC are summarized in Table 4. In multivariate analyzes, the solid character of the lesion, increasing age, a CA19-9 value >37 U/mL, and presence of local atrophy in pancreas (without chronic pancreatitis) were found to be independently associated with PC.

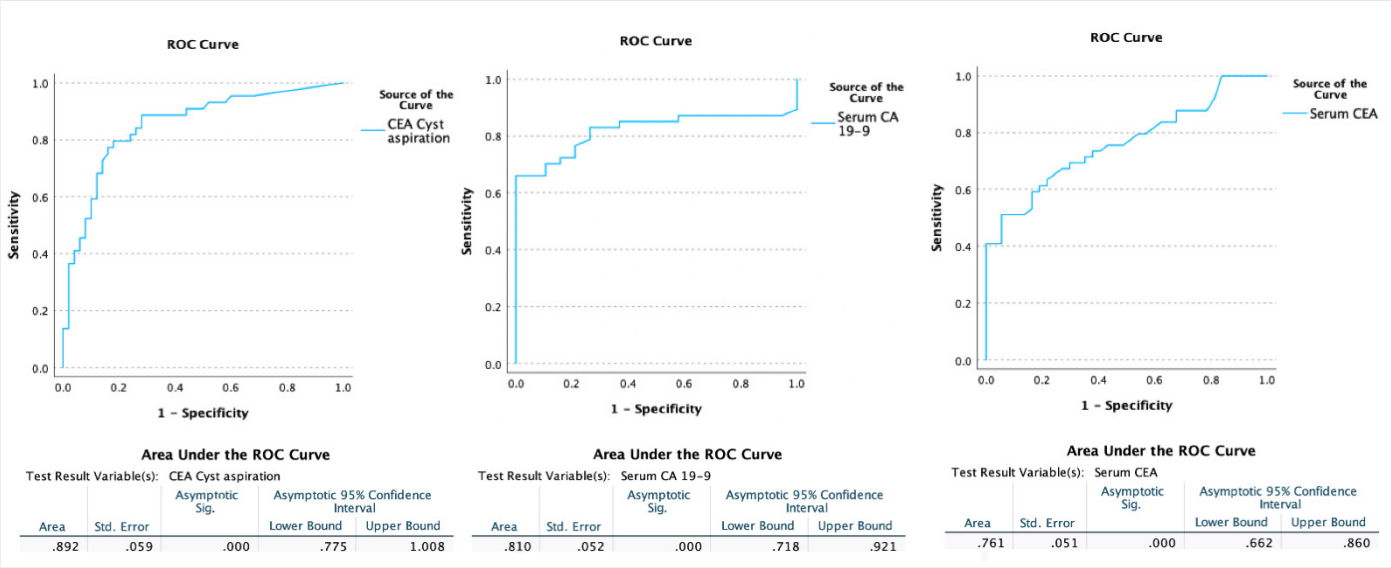
Table 3. Some findings reported in EUS related to the lesion, and cyst features

Vascular invasion	**13.2% (n=27)**	**Common bile duct and/or Wirsung dilatation**	**35% (n=71)**
Ascites	6% (n=12)	Double duct sign	10.8% (n=22)
Lymphadenopathy	15.1% (n=31)	Chronic pancreatitis	7.8% (n=16)
Suspected Liver Metastasis	2.8% (n=6)	Partial atrophy (no chronic pancreatitis)	18.4% (n=38)
Septation (cystic lesions)	58% (n=62)	String sign positivity	15% (n=14/92)
Cyst-Wirsung connection	45% (n=48)		

Table 4. Univariate and multivariate analyzes associated with PC

	Univariate analyses	**Multivariate analyses**	
	p	**p**	**OR**
Male sex	0.142	-	
Age	<0.001	0.012	1.08 (1.02-1.16)
Solid lesion	<0.001	0.025	6.6 (1.2-34.5)
Size	0.110	-	
Non-tail localization of lesion	<0.001	0.948	
Vascular invasion	<0.001	0.324	
Suspected liver metastasis	0.153	-	
Ascites	0.030	0.991	
Lymphadenopathy	<0.001	0.384	
Double duct sign	0.008	0.931	
Chronic pancreatitis	0.361	-	
Partial atrophy (without chronic pancreatitis)	0.005	0.041	3 (1.1-61)
Serum Ca19.9 >37	<0.001	0.017	13.3 (1.6-111)
Serum CEA >3.1	0.005	0.833	
Solid component/mural nodule$^{\varphi}$	0.243	NA	
Septation$^{\varphi}$	0.730	NA	
String sign$^{\varphi}$	0.212	NA	
Connection to Wirsung$^{\varphi}$	0.281	NA	

$^{\varphi}$Calculated for cystic lesions, OR: Odds ratio, PC: Pancreatic carcinoma



Area Under the ROC Curve

Test Result Variable(s): CEA Cyst aspiration

Area	Std. Error	Asymptotic Sig.	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
.892	.059	.000	.775	1.008

Area Under the ROC Curve

Test Result Variable(s): Serum CA 19–9

Area	Std. Error	Asymptotic Sig.	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
.810	.052	.000	.718	.921

Area Under the ROC Curve

Test Result Variable(s): Serum CEA

Area	Std. Error	Asymptotic Sig.	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
.761	.051	.000	.662	.860

Figure 1. ROC analysis of cyst CEA value for mucinous pathology, serum CA19-9 and CEA for pancreatic carcinoma

Investigations performed in the whole group regarding PC were also repeated for the cystic or solid lesion subgroups. In multivariate analysis, for solid lesions, age [p=0.036; 1.1 (1.01-1.2)] and size more than 24 mm [p=0.014; 15.5 (1.7-137)]; and for cystic lesions, male gender [p=0.022, 8 (1.6-88)] and mucinous pathology [p=0.041, 6 (1.1-64)] were found to be associated with PC. The size cut-off value for solid lesions was calculated by ROC analysis (AUC 0.68).

Discussion

Our study revealed PC-related factors of EUS-FNA findings. While the solid nature of the lesion and serum CA19-9 increase were found to be associated with PC, the relationship between the presence of local/partial atrophy in EUS and PC should be emphasized. In cystic lesions, the mucinous character was associated with malignancy, and another important finding of our study is that the cut-off level we found for the cyst CEA value was 80 ng/mL, lower than the previously proposed value (9).

Pancreatic cancer (PC) is a malignancy in which early diagnosis is crucial due to its poor prognosis (10). Although surgery is the only curative treatment method, 5-year survival is better in patients with small tumors without lymph node involvement (11). However, in 80% of the patients, surgery is not possible due to locally advanced or metastatic disease (12). Recent studies on the pathophysiology of PC suggest that the precancerous stage can be quite long (13,14). Although there is no general recommendation for population-based PC screening, this long interval period provides the chance for early diagnosis when the disease is still surgically curable, especially for people suitable for screening with a defined genetic mutation or a familial PC history (15). EUS has its place in such PC screening because of its many advantages. EUS's success in revealing small pancreatic lesions and its contribution to early diagnosis is quite high (16). In addition, it can provide many accompanying findings related to the nature of the lesion. In addition, it can contribute to the pathological diagnosis in an accurate and safe way because it offers the possibility of FNA (17). In the differential diagnosis of malignant solid and cystic lesions of the pancreas; for solid lesions, lymphoma, metastasis, neuroendocrine tumor, chronic pancreatitis, autoimmune pancreatitis, solid pseudo papillary tumor; for cystic lesions, pseudocyst, serous cyst adenoma, and mucinous cystic neoplasia are pathologies that should be considered (1). While the role of surgery for treating most of these pathologies is quite limited, the recognition of early-stage PC is crucial for surgical curability (10).

EUS examination provides information about the location and size of the pancreatic lesion, its cystic or solid nature, its relation to the surrounding structures or pancreatic canal, and the characteristics of the extra-lesional pancreatic tissue, and may reveal extra-pancreatic findings such as accompanying lymphadenopathy, liver metastasis, or ascites in some patients (18). In our study, nearly half of the cases had solid lesions, and nearly half of them were located in the pancreatic head. Although no evaluation was made in the study design regarding the EUS indications of the patients, the accumulation of solid lesions in this region may be related to the higher potential of a lesion in the pancreatic head to be symptomatic due to its close relationship to the ampulla Vater and biliary system. On the other hand, no correlation was shown between the size and location of the lesion. The distribution of cystic lesions was found in favor of the pancreatic tail, which may be related to the more frequent localization of some cystic pathologies such as serous cyst adenoma and mucinous cystic neoplasia to this region (1).

Other rare findings that can be revealed by EUS examination may guide the clinician. Among these findings, vascular invasion (13%), suspicion of liver metastasis (approximately 3%), and accompanying lymphadenopathy (15%), which we found in our study, can be listed. Since histological sampling for lymphadenopathy was not performed and there were no liver lesion biopsies, it is not possible to comment on the contribution of these findings to histological diagnosis in our study, but the clinical guidance of these findings is clear.

In our study, the presence of partial atrophy in the pancreas related to the lesion was also associated with PC in regression analysis. The impact

of this finding, independent of the other two related factors age and the solid characteristic of the lesion is, to our knowledge, new to the literature and should be alarming for the clinician performing EUS in terms of PC. On the other hand, the double duct sign that is reported to be associated with PC in the literature could not be shown to be independently related to PC in our study.

Another parameter that we found to be related to PC is the high serum CA19-9 level (19). The cut-off value of CA19-9 that we found in distinguishing PC in our patient group was 37 U/mL, in line with the literature, and the sensitivity and specificity for this value were parallel to those reported in similar studies (79-81%, 82-90%, respectively) (20).

When solid and cystic lesions were evaluated separately, we showed that size was associated with the risk of PC for solid lesions, and a lesion larger than 2.4 cm was associated with PC regardless of other accompanying findings. In a study examining the diagnostic accuracy of EUS FNA, increased size was associated with higher diagnostic accuracy (21). In lesions smaller than 2.4 cm, the diagnostic contribution of EUS-FNA may be lower, which may have caused us to overestimate the cut-off value of size for predicting PC. On the other hand, in the same study, parallel to our findings, while the highest rates of PC were found for lesions more than 20 mm (20-30 mm 81.6%; 30-40 mm 86.4%; >40 mm, 80.8%), PC was reported as 13.9% in lesions <10 mm, and 64% in lesions of 10-20 mm.

Regarding cystic lesions, male gender and mucinous pathology were determined as independent risk factors related to PC. This effect of gender can be explained by the fact that some benign/relatively benign cystic neoplasms are more common in women (22). The cut-off value we found for the cyst fluid CEA level was lower than the value of 192 ng/mL emphasized in the literature, and for our cut-off value of 80 ng/mL, the sensitivity was 82% and the specificity was 90% (9). Increasing the cut-off value increased the specificity in exchange for a decrease in the sensitivity. In this study, we showed the relationship of mucinous pathology with PC in cystic lesions; we believe that the high sensitivity is more important for the recognition of mucinous lesions, and therefore, we think the cut-off value we calculated will have a place in clinical use. If a higher value is to be considered, other parameters such as string sign positivity and cyst-Wirsung connection may also be guiding. The serum CEA cut-off value (3.1 ng/mL) we found for predicting mucinous pathologies had low sensitivity and specificity in terms of predicting PC, so may be of value in predicting prognosis and in follow-up of patients, rather than as a diagnostic tool (23).

Study Limitations

The most important limiting factor of our study was its retrospective design. Therefore, parameters such as glucose level of cyst fluid, which may guide the diagnosis of mucinous pathology, or genetic and molecular profile of tissue acquired by FNA to support the diagnosis of PC could not be evaluated (24,25).

Conclusion

In conclusion, age, high CA19-9 values, and solid nature of the lesion as well as lesion-related partial atrophy of the pancreas are associated with PC, and these should be alarming for clinicians in practice. The mucinous character, which is a significant risk of PC for cystic lesions, can be optimally defined when the CEA cut-off value of 80 is used if cyst fluid analyses are available.

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Ethics Committee Approval: This study was approved by the İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine Local Ethics Committee (approval number: 83045809/604.01/02-279716).

Informed Consent: The study and according to local ethic committee guidelines, the study exempted from written informed consent.

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The Experience of Ibrutinib in Chronic Graft-Versus-Host Disease in Patients Undergoing Allogeneic Hematopoietic Stem Cell Transplantation: Single Center Experience

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ABSTRACT

Introduction: Chronic graft-versus host disease (GVHD) is a serious complication that develops in 35-50% of patients in the late period after allogeneic hematopoetic stem cell transplantation. About half of the patients are resistant to corticosteroids, which is the first-line treatment of chronic GVHD, and therefore new treatment options that can be effective in chronic GVHD are needed. In the present study, we aimed to share our experience with the use of ibrutinib therapy in patients with steroid-resistant chronic GVHD who have previously received multiple lines of systemic therapy.

Methods: The characteristics and clinical outcomes of steroid-resistant chronic patients with GVHD receiving ibrutinib were retrospectively reviewed.

Results: A total of 10 steroid resi-stant chronic patients with GVHD who received ibrutinib was included. While 50% of the patients had more than one organ involvement, 50% had a single organ involvement. The most commonly affected organs were the skin and liver. The patients received a median of three lines of systemic therapy before ibrutinib. After a median of 210 days of ibrutinib usage, the complete response rate of patients was 40% and the partial response rate was 40%. Corticosteroids were completely discontinued in 30% of patients after ibrutinib were initiated. Before ibrutinib, patients were given a median of 0.3 mg/kg methylprednisolone. The median methylprednisolone dose after ibrutinib was 0.03 mg/kg.

Conclusion: Ibrutinib therapy causes a quite high overall response in steroid resistant chronic patients with GVHD and appears to be a good option in these patients.

Keywords: Steroid-resistant graft-versus host disease, ibrutinib, corticosteroids, allo-HSCT, chronic GVHD

Introduction

Allogeneic hematopoetic stem cell transplantation (allo-HSCT) is a curative treatment option for many hematological diseases such as acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), myelodysplastic syndrome, aplastic anemia and paroxysmal nocturnal hemoglobinuria. However, early (<3 months) and late (>3 months) complications that cause transplant-related morbidity and mortality are observed in many patients after allo-HSCT.

Early complications of allo-HSCT include graft-versus host disease (GVHD), bacterial, viral and fungal infections, engraftment syndrome, hemorrhagic cystitis, capillary leak syndrome, graft failure, hepatic sinusoidal obstruction syndrome, pulmonary complications and transplant-related thrombotic microangiopathy (1,2). The mortality rate due to early complications varies between 5% and 40%, depending on factors such as transplantation from donor, pre-transplant regimen, age, and comorbidities of the patient (3).

Late complications following allo-HSCT include chronic GVHD, idiopathic pneumonia, bronchiolitis obliterans, pulmonary and nonpulmonary infections, hypogonadism, osteopenia, hypertension, hypothyroidism, dyslipidemia, diabetes mellitus, chronic kidney disease, cardiomyopathy,

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heart failure, and secondary malignancies (4). Although allo-HSCT is a curative option for treating many hematological diseases, life expectancy after allo-HSCT is still lower (5,6). The most common causes of mortality in the late period following allo-HSCT are recurrence of primary malignancy, chronic GVHD, infections, secondary malignancies, pulmonary complications, and cardiac toxicity, respectively (6).

Chronic GVHD is a severe difficulty that improves in 35-50% of patients in the late period after allo-HSCT and is the second most common cause of mortality in patients with allo-HSCT (6,7). In patients with chronic GVHD, the most commonly involved organ is the skin, but other organs such as the mouth, eyes, liver, gastrointestinal system, lungs, joints, fascia, genital organs, and hematopoietic system can also be involved (8,9). In recent years, with the increasing number of patients with allo-HSCT, the number of patients with chronic GVHD has also increased. Approximately half of the patients are resistant to corticosteroids, which are the first choice for treating chronic GVHD; thus, new treatment options that can be effective in chronic GVHD are needed.

The guidelines recommend that patients should participate in well-designed clinical trials because there is no standard second-line treatment for chronic GVHD (10,11). In the absence of a clinical trial option, guidelines recommend the administration of one of the following agents: ibrutinib, ruxolitinib, abatacept, imatinib, calcineurin inhibitors, alemtuzumab, extracorporeal photopheresis, hydroxychloroquine, low-dose methotrexate, mTOR inhibitors, bortezomib, mycophenolate mofetil, pentostatin, rituximab. Ibrutinib has been approved by the US Food and Drug Administration for the treatment of chronic GVHD patients who are resistant to one or more lines of systemic therapy.

Due to the uncertainty of optimal therapy in corticosteroids resistant chronic GVHD patients, we aimed to present our experience in chronic GVHD patients who have previously received multiple lines of systemic therapy

Methods

Patients who developed chronic GVHD between February 2011-2021 and who were started on ibrutinib after at least two lines of treatment were included in the study. After the study was approved by the İnönü University Ethics Committee (decision no: 2022/2946), demographic, clinical, and laboratory data of the patients were retrospectively analyzed using the hospital electronic information system. Written informed consent was obtained from the patients included in the study.

Within the framework of the criteria recommended by the National Institutes of Health (NIH), chronic GVHD was defined as a complication occurring at any time after allo-HSCT and differentiated from acute GVHD with its clinical features (12). Chronic GVHD severity was defined as mild, moderate, and severe within the framework of the criteria recommended by the NIH (13). While systemic treatment was initiated with corticosteroids in patients with moderate to severe chronic GVHD, it was not preferred in patients with mild chronic GVHD.

Ibrutinib was initiated at a dose of 420 mg per day and continued at this dose until grade 3 or 4 toxicity occurred. We reduced the ibrutinib dose to 140 mg in patients who were given posaconazole as antifungal prophylaxis.

Ibrutinib-related adverse events were classified according to the Common Toxicity Criteria for Adverse Events version 5.0 (12).

As recommended by the NIH, patients with a resolution of all symptoms in all involved organs were considered to have a complete response to treatment. Patients with improvement in at least one involved organ without progression in other organs were considered to have a partial response to treatment. The overall response rate was considered as the sum of the complete response rate and the partial response rate (12).

Statistical Analysis

IBM SPSS 25.0 was used as the statistics program. Normality analysis of the data was performed using the Shapiro-Wilk test, and the data were given as median, range, and percentage.

Results

A total of 10 patients with steroid-resistant chronic GVHD who received ibrutinib were included in this study. Steroid resistant chronic GVHD

Table 1. Characteristic features of ibrutinib treated chronic GHVD patients

Patient no.	Age	Gender	Disease	Donor	Involved organ(s)	Severity
1	38	Male	AML	MRD	The skin, eye, mouth	Moderate
2	22	Male	AML	MRD	Liver	Moderate
3	22	Male	AML	UMD	Liver	Moderate
4	29	Female	AML	MRD	The liver, skin	Moderate
5	19	Male	AML	MRD	The liver, skin	Moderate
6	21	Male	BTM	MRD	Intestine	Severe
7	60	Male	AML	MRD	Skin	Severe
8	41	Male	AML	MRD	The skin, intestinal, liver	Moderate
9	19	Male	ALL	MRD	Skin, intestine	Moderate
10	19	Male	ALL	MRD	Liver	Moderate

GVHD: Graft-versus-host disease, AML: Acute Myeloid Leukemia, BTM: Beta thalassemia major, MRD: Matched-related donor, UMD: Unrelated-matched donor

developed in seven patients with AML, two with ALL, and one with beta thalassemia major. While 50% of the patients had more than one organ involvement, 50% had a single organ involvement. The most frequently involved ones are skin (60%) and liver (60%) (Table 1). All patients with skin involvement (n=6) had non-sclerotic features. There were no patients with sclerotic involvement.

All patients included in the study received myeloablative regimen before allo-HSCT. In our patients, chronic GVHD was diagnosed a median of 165 (50-500) days after allo-HSCT. Ibrutinib was initiated in a median of 150 (102-660) days after the diagnosis of chronic GVHD. Before ibrutinib, patients had received a median of 3 (2-4) lines of systemic therapy, including corticosteroids, cyclosporine, mycophenolate mofetil, and extracorporeal photopheresis.

Although the median follow-up time for 10 patients was 394 (100-750) days, it was 210 (30- days) under receiving ibrutinib. After a median of 210 days of treatment with ibrutinib, the complete response rate of patients was 40% and the partial response rate was 40% (Table 2).

Median time to onset of a response to ibrutinib in 8 patients was 52 (25-125), and median response duration of patients to ibrutinib was 143 (70-415) days. Organ involvement features of patients are given in Table 3.

After a median follow-up of 394 days, median failure-free survival could not be achieved in both the entire population and those who responded to ibrutinib (Figure 1, 2). No association was found between the severity of GVHD and the ibrutinib response (p=0.378). When those who received ≤3 lines of treatment before ibrutinib and those who did not receive more than 3 lines of treatment were compared, no difference was found between the GVHD response and OS of the two groups (p=1 and p=0.537, respectively).

We observed ibrutinib-related adverse events in two (20%) of 10 patients. In one patient (patient 2) with liver GVHD, ibrutinib was discontinued because of elevated liver enzymes (grade 3 alanine aminotransferase elevation) 30 days after initiation. This adverse event resolved 20 days after ibrutinib was discontinued. In another patient (patient 3), we observed grade 4 thrombocytopenia 50 days after initiation. Ibrutinib was discontinued for 27 days, the adverse event disappeared, and we continued ibrutinib at the same dose.

Corticosteroids were completely discontinued in 30% of patients after ibrutinib were initiated. Before ibrutinib treatment, patients were given a median of 0.3 mg/kg methylprednisolone. The median methylprednisolone dose after ibrutinib was 0.03 mg/kg. The median

Table 2. Clinical outcomes of ibrutinib trea-treatednic patients with GVHD

Patient no.	7-day survival	28-day survival	90-day survival	180-day survival	The partial response (%)	The complete response (%)	No response (%)	GVHD mortality	Non-GVHD mortality
1	+	+	+	+	Yes			No	No
2	+	+	+	+			Yes	No	Yes (relapse)
3	+	+	+	+	Yes			No	No
4	+	+	+	+		Yes		No	No
5	+	+	+	+	Yes			No	No
6	+	+	+	-			Yes	Yes	No
7	+	+	+	+		Yes		No	No
8	+	+	+	+		Yes		No	No
9	+	+	+	+		Yes		No	No
10	+	+	+	+	Yes			No	No
Overall response	100%	100%	100%	90%	40%	40%	20%	10%	10%

Table 3. Organ response of ibrutinib-treated chronic GHVD patients

Patient no.	Involved organ(s)	Response by organ(s)
1	The skin, eye, mouth	Skin
2	Liver	No response
3	Liver	Liver
4	The liver, skin	The liver, skin
5	The liver, skin	Liver
6	Intestine	No response
7	Skin	Skin
8	The skin, intestinal, liver	The skin, intestinal, liver
9	Skin, intestine	Skin, intestine
10	Liver	Liver

GVHD: Graft-versus-host disease

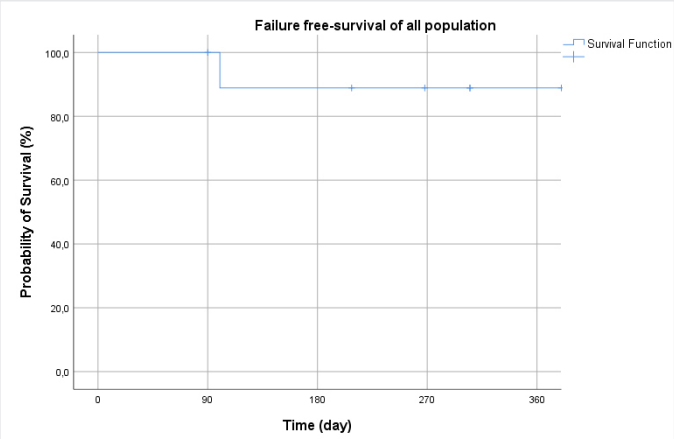

Figure 1. Failure free-survival of all population

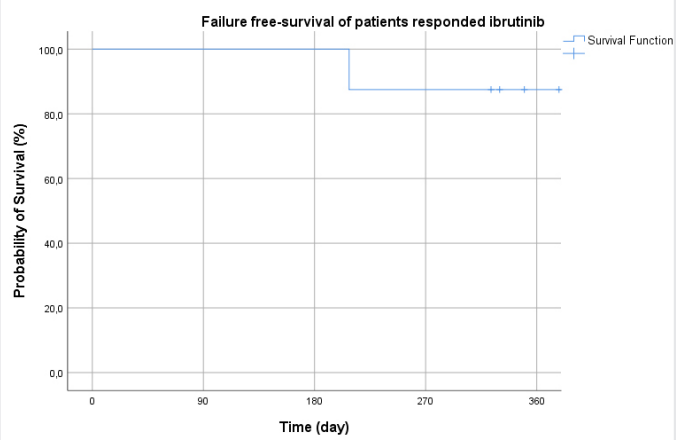

Figure 2. Failure free-survival of patients responded ibrutinib

time to reduce the steroid dose was 43 (15-295) days. In 3 patients, steroid was completely discontinued after a median of 96 (50-115) days.

Discussion

Chronic GVHD is the most important cause of non-relapse mortality and affects quality of life in the late period following allo-HSCT (6,14). The treatment approach is not standard in steroid resistant chronic patients with GVHD because well-designed comparative studies of in these patients are lacking.

In retrospective studies that evaluated the efficacy of mycophenolate mofetil, sirolimus, rituximab, pentostatin, and ruxolitinib in steroid resistant chronic GVHD patients, overall response rates ranged from 55-81% (15-19). In phase 2 studies evaluating the efficacy of imatinib, sirolimus (in combination with tacrolimus), rituximab, and pentostatin in steroid resistant chronic GVHD patients, overall response rates ranged from 27-63% (20-22). Because of the uncertainty of the optimal agent to be chosen in second-line therapy, treatment should be determined according to affected organs (eg. sirolimus for joint, ruxolitinib for skin), patient renal and liver functions, side effects of the agents, patient preferences and clinician's experience (7).

Ibrutinib has been shown to inhibit Bruton's tyrosine kinase and interleukin-2-inducible T-cell kinase, which play an important role in the pathogenesis of chronic GVHD, thereby reducing the activation of T- and B-cells in the murine chronic GVHD model (23). Based on this data, researchers designed a phase 1b/2 study to determine the safety and efficacy of ibrutinib in chronic GVHD patients who received at least 1 line of systemic corticosteroids therapy. Eighty-six percent of patients had mouth, 81% had skin, 36% had gastrointestinal system, 7% had liver, and 5% had a lung involvement. In this study, after the initiation of ibrutinib, a complete response was obtained in 21.4% (9/42) of patients and a partial response was obtained in 45.2% (19/42) of them in addition, 47.6% of patients (20/42) had a sustained response to ibrutinib for 20 weeks or longer (24). In the present study, two-thirds of the patients responded to ibrutinib, whereas the response rate was found to be slightly higher (%80) in our study evaluating fewer chronic GVHD patients.

In a retrospective single-center study in a total of 22 pediatric patients with chronic GVHD, a partial response was achieved in 54.5% of patients with ibrutinib at a dose of 250 mg/m^2. Ibrutinib was reduced by 50% in 16 patients who received voriconazole or posaconazole concomitantly. Of the 12 patients who responded to ibrutinib, the corticosteroids dose was reduced in 9 of them, and corticosteroids were discontinued in 2 of them (25). In our study, corticosteroids were completely discontinued in 3 of 8 patients who responded to ibrutinib, and the corticosteroids were reduced in 3 of them.

In a retrospective study of adult GVHD patients, a total of 17 patients with pulmonary chronic GVHD who received an average of 4 lines of treatment before ibrutinib and had an average of 5 organ involvement were included. Of the 14 patients who continued ibrutinib for 180 days, 2 (14.3%) had a partial response, 9 (64.3%) had a stable disease, and 3 (21.4%) had a disease progression (26). In this study, response rates to ibrutinib may have been found to be low because of the evaluation of the responses of patients with severe pulmonary chronic GVHD with multiple organ involvements and resistant to four lines of therapy. Patients in our study had less organ involvement and none the patients had the pulmonary involvement. Therefore, the response rate to ibrutinib in our study was found to be much higher than that in this study.

Study Limitations

The main limitations of the study are its retrospective design and the small number of patients.

Conclusion

Ibrutinib causes a quite high overall response in steroid resi-resistantnic patients with GVHD and appears to be a good option in these patients. However, prospective trials comparing the effectiveness of ibrutinib with other drugs used in chronic GVHD are needed, especially in lung involvement and/or multiorgan involvement.

Ethics Committee Approval: İnönü University Scientific Research and Publication Ethics Committee (date: 11.01.2022/decision no: 2022/2946).

Informed Consent: Written informed consent was obtained from the patients included in the study.

Peer-review: Externally peer reviewed.

Authorship Contributions

Concept: A.S., İ.K., E.K., A.K., L.H.T.; Design: A.S., M.A.E., E.K., E.H., A.K., Ö.F.B., S.G.Ö.; Data Collection or Processing: A.S., M.A.E., İ.K., E.K., İ.B., E.H., A.K., Ö.F.B., L.H.T.; Analysis or Interpretation: A.S., M.A.E., İ.B., S.B., E.H., A.K.; Literature Search: A.S., İ.K., İ.B., S.B., E.H., A.K.; Writing: A.S., S.B., L.H.T.

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