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Aims and Scope

Health Sciences Quarterly (Health Sci. Q.) is an open-access journal that publishes original research papers, case reports, and reviews, clinical studies covering a wide range of subjects in life sciences and medicine as well as clinical and experimental investigations only in English.

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HSQ aims to supply scientists of health with resources in order to provide the scientific knowledge through the publication of peer-reviewed, high quality, scientific papers and other material on all topics related to Medicine, Pharmacy and pharmaceutical sciences, Dentistry, Nursing, Bioethics, History of medicine, Health economics, Pharmacoeconomics, Medical education, Public health, and Epidemiology.

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ORIGINAL ARTICLE

The comparison of the postoperative complications, mortality, and morbidity of the eversion technique and the classical technique in carotid endarterectomy

Alper Selim Kocaoğlu[1] **Cengiz Ovalı**[2]

[1] Department of Cardiovascular Surgery, Eskişehir City Hospital. Eskişehir / Türkiye
[2] Department of Cardiovascular Surgery, Faculty of Medicine, Eskisehir Osmangazi University. Eskişehir / Türkiye

Abstract

In the present study, the purpose was to compare the postoperative early and mid-term results of Eversion Carotid Endarterectomy (ECEA) and Classical Carotid Endarterectomy (CCEA) techniques used in the surgical treatment of carotid artery disease. A total of 269 patients who underwent carotid endarterectomy (105 ECEA and 164 CCEA) were included in the study. The 1st, 6th, and 12th-month follow-ups of 266 patients were performed because three patients died in the early postoperative period. All patients were started on acetylsalicylic acid, clopidogrel, and statin treatment in the postoperative period. When the postoperative results were evaluated, it was found that the cross-clamp and operation times of the surgeries performed with the ECEA technique were shorter than the CCEA at statistically significant levels (p=0.0002). Although there statistically significant differences were detected in terms of bleeding/drainage, need for reoperation because of bleeding, and restenosis, ECEA had more positive results than CCEA, and there were no statistically and proportionally significant differences between the two methods in terms of postoperative stroke and mortality. Considering the experience of the surgical team, the use of the ECEA technique has more positive results in terms of operation time and cross-clamp time compared to CCEA. We think that extending the follow-up periods of patients in the postoperative period and conducting multicenter studies with more patients would be more accurate in comparing these two methods.

Keywords: Carotid endarterectomy, eversion, stroke

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Corresponding Author:
Alper Selim Kocaoğlu
Email: dr.aselimkocaoglu@gmail.com

Introduction

Carotid artery stenosis because of atherosclerosis of the carotid arteries is the main cause of ischemic stroke, and carotid artery disease has high morbidity and mortality rates. Stroke is still the third most common cause of mortality in Western societies following heart diseases and cancer [1]. The most important cause of extracranial ischemic cerebrovascular event (CVE) is atherosclerosis which affects the carotid bifurcation [2]. Although the symptoms vary according to the affected area of the brain, symptoms such as weakness, paralysis, numbness, and tingling can be seen in the contralateral extremity. Aphasia can also be seen in cases if dominant hemisphere is affected. Depending on the occlusion of the carotid plate in the ipsilateral retinal artery, temporary or permanent, total or partial vision loss (Amarosis fugax) may also be seen [2]. It may progress asymptomatically when there is severe stenosis in the carotid arteries or symptoms as a result of embolism may also be seen in the ulcerated lesions without severe stenosis [3].

Combined with optimal medical management, surgical intervention in the form of Carotid Endarterectomy (CEA) plays important roles in preventing subsequent strokes in properly selected patients. In the 2021 Guideline of the Society of Vascular Surgery (SVS), CEA was found to be superior to Carotid Artery Stenting (CAS) in symptomatic carotid artery disease in 50% or more patients with low surgical risk, CEA is recommended compared to medical treatment in asymptomatic stenosis between 70-99% in low-risk surgical patients [4]. However, routine CEA is not recommended for asymptomatic patients [5]. Considering the additional characteristics of patients, asymptomatic patients with 60% or more stenosis should be evaluated for surgery.

There are Classical Carotid Endarterectomy (CCEA) (Figure 1) and Eversion Carotid Endarterectomy (ECEA) among the surgical techniques (Figure 2). In previous studies, no significant differences were reported in terms of factors such as stroke, death, local findings, restenosis rates, *etc.* between ECEA and CCEA, but differences were detected in conditions such as long plaque, tortuous Internal Carotid Artery (ICA), difficulty in access, and bleeding risk [6].

In the present study, among the patients operated on for carotid artery disease, the postoperative early and mid-term results of those who underwent ECEA and those who underwent CCEA were evaluated and compared in terms of infection, cerebrovascular event, permanent sequelae, death, bleeding, restenosis rates at one, six and twelve months, and preoperative risk factors.

Materials and Methods

The approval of Eskişehir Osmangazi University Faculty of Medicine Non-Interventional Clinical Research Ethics Committee was obtained for the study (E-25403353-050.99-146237). The files and hospital admission records of 403 CEA patients operated on for carotid artery disease in our hospital between January 2016 and December 2019 were reviewed retrospectively. It was found that 127 of the operations did not come to the clinic follow-ups in the postoperative period, 276 patients regularly came to the clinical follow-ups. Seven of the patients were excluded from the study because there would be differences in their medical treatments because of atrial fibrillation in the postoperative period, and a total of 269 patients were included in the study. All cases were done by the same surgical team. All patients were scheduled to have surgery after the examination and decision of the Neurology Stroke Clinic together with the results of Dupplex Ultrasonography (USG) and Computed Tomographic Angiography (CT Angiography). Sixteen of the patients had bilateral carotid artery stenosis and the side where the stenosis was more critical was operated on first. Among the patients who were included in the study, 105 (39%) had ECEA, and 164 (61%) patients underwent CCEA. The Cerebral Oximetry Device was used in all patients during the operations. A shunt was used in patients who had a decrease of more than 20% in cerebral oximetry after clamping the carotid artery or who had weak retrograde flow from the ICA.

In the Eversion CEE Method, the ICA was separated from the bifurcation area by cutting a full thickness, and the plaque was removed from the wall with the help of an elevator, the ICA was everted distally and the plaque was then removed. The inside of the ICA was washed, anastomosis was made with a continuous suture to the bifurcation area, the air was removed, and the surgery was completed in this way. In the Classical CEA Method, following a longitudinal incision from the Common Carotid Artery (CCA) to the ICA, the plate was removed with the help of an elevator and then the incision on the artery was closed. Since three patients died in the early postoperative period, they were not included in the data analysis. All the remaining patients were those who received a postoperative 24-hour intravenous (IV) Heparin infusion followed by twelve months of Acetylsalicylic Acid (ASA), Clopidogrel, and statin therapy. All patients who underwent Classical CEA were those who underwent primary closure. From patient files and clinical follow-ups, the demographic characteristics, preoperative and postoperative neurological status, amount of postoperative drainage, bleeding complications, reoperation requirements, sequelae and infection status, death status, and restenosis status were evaluated by looking at the Carotid Doppler USG and ICA/PSV ratios and were transferred to the data table. Carotid Doppler USG follow-ups and measurements were made by the same team with the Samsung Sonoace X7 ultrasound device. The patients were divided into two groups as those who underwent CCEA and ECEA during the analysis.

Statistical Analysis

The Statistical Package for Social Sciences (SPSS) software, version 21 was used for statistical analysis and a $p<0.05$ value was taken as statistical significance. Continuous variables such as age

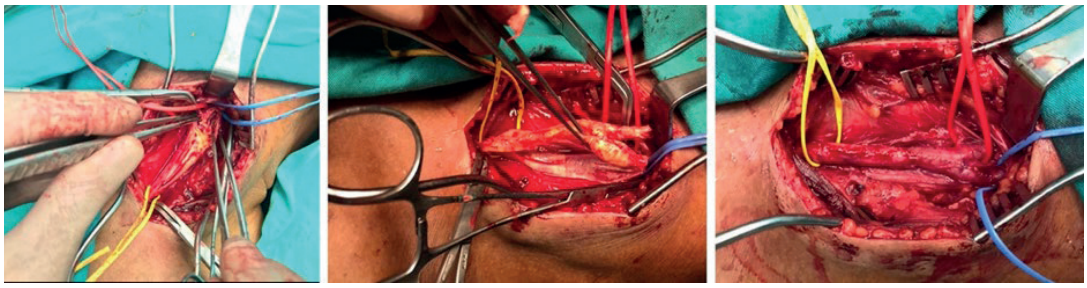

Figure 1. Classical carotid endarterectomy technique

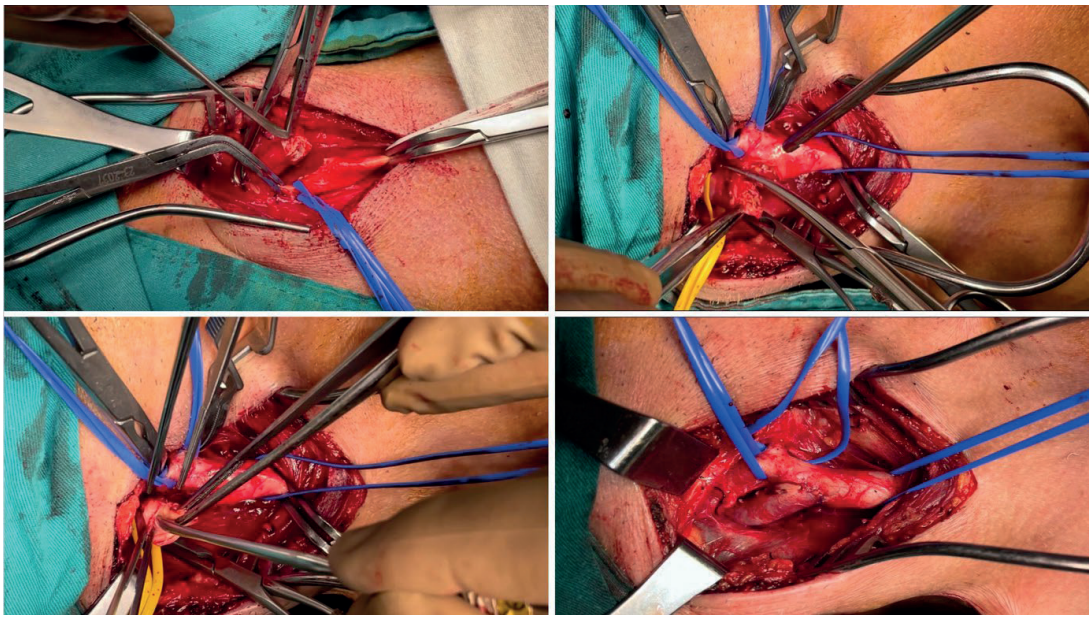

Figure 2. Eversion carotid endarterectomy technique

and the amount of postoperative drainage were evaluated in terms of the normal distribution with ICA, Peak Systolic Volume (PSV), and ICA/CCA PSV histogram, Q-Q graph, and *Shaphiro-Wilk* Test at postoperative first, sixth, and twelfth months. It was found that continuous variables did not have a normal distribution, and are given as median (minimum-maximum) values, and the Student's *t*-test was used to compare the continuous variables. The data of the categorized variables are given as frequency and percentage distribution. The *Fisher's* and/or *Pearson* Chi-Square Tests were used to compare the categorized variables.

Results

The median age of the study population, which consisted of a total of 269 patients, was found to be 69.3 years (41.8-89.6 years). A total of one hundred and ninety (70.6%) patients were male and 79 (29.4%) patients were female and 229 (85.1%) of them were symptomatic. Considering the degree of stenosis of all patients, it was determined that the majority of patients (n=110, 40.9%) had stenosis at a rate of 70-89%. The degree of carotid stenosis was between 50-69% in 11 (4.1%) patients, 90-99% in 97 (36.1%) patients, and near occlusion in 51 (19%) patients.

When all patients were evaluated, the eversion technique was applied to a total of 105 (39%) patients, and the primary closure technique was applied to 164 (61%) patients. Carotid artery diameter was greater than 6 mm in all patients who underwent the primary closure technique. Intravascular shunts were used for a total of 10 (3.7%) patients. Revisions were performed in 17 (6.2%) patients because of postoperative bleeding/hematoma and infection was detected in one (0.4%) patient. CVE developed in a total of 14 (5.2%) patients in the postoperative period and permanent sequelae developed in the same number of patients. Permanent sequelae were detected in the right hemiplegia in four patients (1.5%), monoparesis in the right upper extremity in four patients (1.5%), left hemiplegia in two patients (0.7%), monoplegia in the left upper extremity in two patients (0.7%), monoplegia in upper right extremity in one patient (0.4%), and hemiparesis in lower right extremity in one patient (%0.4).

The data used to compare the eversion technique with the classical technique as a surgical technique and the demographic characteristics of the patients are summarized in Table 1. No significant differences were detected between the groups in terms of side (p=0.575) and urgency (p=0.900). Also, shunt use (p=0.745) and symptomatic/asymptomatic patient distribution (p=0.829) did not differ at significant levels between the groups. No significant differences were detected in the rates of transient ischemic patients (p=0.983) or patients with permanent sequelae (p=0.586) in the preoperative period. Considering the duration of the surgery and the duration of the clamping of the carotid artery, ECEA had a statistically significantly shorter duration than the CCEA (p=0.0002). The use of shunt, which was determined by retrograde flow after carotid incision and/or more than 20% decrease in cerebral oximetry following the carotid clamping, was significantly higher in patients who were taken to emergency CEA when compared to those who were taken to elective surgery (11.4% vs 2.6%, p=0.029). Three patients (8.6%) who underwent emergency CEA had CVE in the postoperative period and eleven patients (4.7%) who underwent elective CEA had CVE in the postoperative period. Although the rate of incidence in patients who underwent emergency surgery in the development of postoperative CVE was approximately 2-fold higher, it was not found to be at a statistically significant level (p=0.404). When the mean amount of drainage between the eversion and the classical technique was examined, the amount of drainage was higher in the classical technique, but with no statistically significant differences (p=0.063). Although the rates of reoperation and postoperative hematoma because of bleeding in the early postoperative period were found to be higher in the classical endarterectomy group, the difference was not at a statistically significant level (p=0.088). Although CVE rates were higher in the classical endarterectomy group in the early postoperative period, it was not at a statistically significant level (p=0.576). The distribution of concomitant coronary artery disease in the groups was equal and coronary angiography was performed for 64 patients who did not have any history of intervention in the last one

year. No need for intervention was detected in 52 patients, coronary stenting was performed for seven patients, and coronary artery bypass surgery was performed simultaneously with CEA in five patients.

A total of 266 patients were followed up at the 1st, 6th, and 12th months because three of the patients included in the study died in the postoperative period. Therefore, the findings of the evaluations for the development of re-stenosis are given in Table 2.

In the first month follow-ups, 261 (98.1%) patients did not have recurrent carotid stenosis, but three (1.1%) patients had <49% and one patient (0.4%) had 50%, one patient 69%, and one patient 70%-98% stenosis. Although there was no recurrent carotid stenosis in 244 (91.7%) patients at 6-month follow-ups, stenosis was <49% in

Table 1. Comparison of the eversion and conventional carotid endarterectomy techniques and demographic characteristics of the study population.

	Surgical technique		
Variable	**Eversion (n= 105) n (%)**	**Classical (n= 164) n (%)**	***p* value**
Age, *year*	67.1 (42.3 – 86.2)	70.3 (49.1 – 89.6)	
Sex			
Female	32 (30.5)	47 (28.7)	
Male	73 (69.5)	117 (71.3)	
Side			
Right	45 (42.9)	76 (46.3)	0.575[a]
Left	60 (57.1)	88 (53.7)	
Urgency			
Urgent	14 (13.3)	21 (12.8)	0.900[a]
Elective	91 (86.7)	143 (87.2)	
Degree of stenosis			
%50 – 69	5 (4.8)	6 (3.7)	0.830[a]
%70 – 89	40 (38.1)	70 (42.7)	
%90 – 99	38 (36.2)	59 (36.6)	
Near occlusion	22 (21)	29 (17.7)	
Şhunt usage			
Yes	3 (2.9)	7 (4.3)	0.745[b]
No	102 (97.1)	157 (95.7)	
Clinical			
Symptomatic	90 (85.7)	139 (84.8)	0.829[a]
Asymptomatic	15 (14.3)	25 (15.2)	
Systemic diseases			
Hypertension	74 (70.5)	116 (70.7)	0.964[a]
Hyperlipidemia	46 (43.8)	55 (33.5)	0.090[a]
Diabetes mellitus	41 (39)	61 (37.2)	0.760[a]
Coronary artery disease	38 (36.2)	57 (34.8)	0.810[a]
Peripheral artery disease	12 (11.4)	15 (9.1)	0.543[a]
Chronic renal insufficiency	6 (5.7)	7 (4.3)	0.590[a]
Tobacco use	50 (47.6)	82 (50)	0.703[a]
Carotid cross clamp time, *min*	13.7 ± 4.5	21.5 ± 6.7	**0.002[c]**
Operation time, *min*	88 ± 22	107 ± 15	**0.002[c]**
Postoperative drainage, *ml*	13 (8 – 62)	29 (8 – 68)	0.063[c]
Reoperation for bleeding	5 (4.7)	12 (7.3)	0.088[a]
Postoperative hematoma	6 (5.7)	10 (6)	0.087[a]
Postoperative infection	1 (1)	0 (0)	0.391[b]
Postoperative cerebrovascular event	5 (4.8)	9 (5.5)	0.576[b]
Postoperative permanent sequel	5 (4.8)	9 (5.5)	0.794[a]
In-hospital mortality	1 (1)	2 (1.2)	1.0[b]

[a]Pearson chi square test, bFischer's exact test, cStudent's t test.

twelve (4.5%) patients, 50-69% in eight (3%) patients, and 70% - 98% in 2 (0.8%) patients. In the twelfth month follow-up, 237 (89.1%) patients did not have recurrent carotid stenosis, but twelve (4.5%) patients had <49%, eleven (4.1%) patients had 50-69%, and six (2.3%) patients had 70-98% stenosis. The results obtained when the rates of recurrent stenosis in the first, sixth, and twelfth-month follow-ups were compared according to the surgical techniques are given in Table 3. In this regard, when the distribution of recurrent stenosis degrees was examined in the postoperative first, sixth, and twelfth months, no statistically significant differences were detected between the two techniques in the postoperative first and sixth-month follow-ups. In the 12th month follow-up, although the rate of 50% or more restenosis was higher in the classical endarterectomy technique, no statistically significant differences were detected because of the surgical technique (p>0.05). None of the four patients who underwent surgical treatment with the Eversion CEA technique and had more than 50% restenosis required re-surgical intervention. In the 1-year follow-up of the patients, restenosis rates were found to be between 50-60%, and no symptoms were detected. As a result of the evaluations made by the neurology stroke clinic after symptom development, carotid artery stenting was used for three patients with 50% or more restenosis among those who were treated with the Classical CEA technique.

Discussion

Stroke is an important cause of mortality and morbidity worldwide and can be detected because of parenchymal hemorrhages or disruption of blood flow in the vessels going to the brain because of atherosclerosis and embolism. As a result of the disruption of the flow in the stenosis area because of the carotid artery stenosis, thrombus formation and deterioration of cerebral flow may cause neurological symptoms and ischemic strokes might occur when the pieces of plaque in the carotid artery go directly to the cerebral arteries. Although the risk of stroke is 1% in patients with 60% or less stenosis, this risk increases 3-5-fold in 80% or more stenosis [7,8].

In a study conducted by Cao et al., (1997) comparing 240 patients who underwent CCEA and 274 patients who underwent ECEA, the carotid clamp time was found to be 28.3 ± 10.1 minutes in the CCEA group and 25.5 ± 7.4 minutes in the ECEA group, and this difference was at a statistically significant level (p=0.0001)

Table 2. Distribution of the degree of stenosis in the 1st, 6th, and 12th month follow-up.

	Follow-up visits		
Degree of stenosis	**1st month**	**6th month**	**12th month**
No stenosis	261 (98.1)	244 (91.7)	237 (89.1)
<%49	3 (1.1)	12 (4.5)	12 (4.5)
%50 - 69	1 (0.4)	8 (3)	11 (4.1)
%70 - 98	1 (0.4)	2 (0.8)	6 (2.3)

Table 3. Comparison of the surgical techniques regarding restenosis in the 1st, 6th, and 12th month follow-up

Variables	Degree of stenosis	Eversion (n= 104)	Classical (n= 162)	*p* value
Postoperative 1th month	<%50	103 (99)	161 (99.4)	1.0[b]
	≥%50	1 (1)	1 (0.6)	
Postoperative 6th month	<%50	100 (96.2)	156 (96.3)	1.0[b]
	≥%50	4 (3.8)	6 (3.7)	
Postoperative 12th month	<%50	100 (96.2)	149 (92)	0.770[b]
	≥%50	4 (3.8)	13 (8)	

[b]Fischer's exact test.

[9]. Similar to the results of other studies in the literature, when Schneider et al. (2015) compared the operation times, the mean operation time was found to be 121 ± 50 minutes in the CCEA group and 115 ± 57 minutes in the ECEA group, and the difference was at a statistically significant level (p<0.001) [10]. In the present study, similar to the results of the studies in the literature, the mean operation time in patients who underwent CCEA was found to be 107 ± 15 minutes, and the mean operation time in patients who underwent ECEA was 88 ± 22 minutes (p=0.0002). Similarly, the mean cross-clamp time in the patients who underwent ECEA was 13.7 ± 4.5 minutes (p=0.0002) and the mean cross-clamp time was 21.5 ± 6.7 minutes in the patients who underwent CCEA. The results were found to be statistically significant showing that the ECEA operation has a shorter cross-clamp and operation time.

One of the most important parameters in the follow-up after CEA is the development of restenosis in the surgical treatment of carotid artery diseases. The development of restenosis may occur because of the surgical method as well as additional risk factors that accelerate atherosclerosis such as diabetes mellitus (DM), hypertension (HT), hyperlipidemia, and smoking. The most commonly used examination in follow-up is Carotid Doppler USG because it is fast and cost-effective. In the meta-analysis conducted by Paraskevas et al. (2018), when ECEA and CCEA were compared in terms of restenosis rates, ECEA was found to be superior to CCEA in terms of stenosis of 50% or more (2.5% - 5.2%, p=0.00036), however, no statistically significant differences were detected between ECEA and CCEA in using a patch [11]. A total of 678 CCEA and 675 ECEA patients were included in the EVEREST Study, which is the most comprehensive of the randomized studies to compare CCEA and ECEA in carotid artery diseases and conducted in a multicenter. When the restenosis rates were evaluated in the 33-week mean follow-up results of this study, it was found that this rate was 2.8% in the ECEA group, 7.9% in the primary CCEA group, and 1.5% in the CCEA group with a patch [12,13]. Cao et al. (2002) conducted a study in which five studies were included and 2465 CEA patients were examined, stenoses above 50% were considered as restenosis. When the rates of restenosis were examined, restenosis was detected in 32 (2.5%) of the 1290 patients in the ECEA group and 66 (5.2%) of the 1267 patients in the CCEA group, this difference was found to be at a statistically significant level (p=0.0007) [14]. In the present study, Doppler USG follow-up was performed on the patients at the 1st, 6th, and 12th months in the postoperative period, and a stenosis of 50% or more was accepted as restenosis. According to the 1-year follow-up results, no statistically significant differences were detected between CCEA and ECEA in terms of restenosis rates (p=0.770), but it was found that there was 2-fold more restenosis in the CCEA group when compared to ECEA. We think that this difference occurred because patients who underwent ECEA were more suitable for the anatomical position after anastomosis, and that a statistically significant difference might occur between the two methods in terms of restenosis by increasing the number of patients and the follow-up times.

The most important consequences of carotid artery disease are stroke and death. When these two techniques were evaluated in this respect, in a single-center randomized controlled study conducted by Dakour-Aridi et al., no statistically significant differences were detected between the two techniques in terms of in-hospital and first 30-day stroke and mortality rates and 1-year stroke/mortality rates [15]. However, in the meta-analysis conducted by Paraskevas et al., it was reported that there were significant decreases in 30-day death, stroke, and mortality/stroke cases in favor of ECEA. In the Cochrane Library Review, which investigated the effectiveness of ECEA and CCEA techniques used in carotid artery stenosis, prospective randomized studies were evaluated and 2590 operations in 5 studies were included. No statistically significant differences were reported in stroke rates between the two methods [12,13]. Also, in the study conducted by Djedovic et al., both methods were compared and no statistically significant differences were reported between the two methods in terms of stroke and mortality [16]. In the present study, when the stroke rates of the patients were evaluated, stroke was detected in five patients

(4.8%) in the ECEA group and 9 patients (5.5%) in the CCEA group, and this difference was not at a statistically significant level (p>0.005). Similarly, no statistically significant differences were detected between ECEA and CCEA in terms of mortality rates (1-1.2%, respectively; p=1).

If the experience of the surgical team is adequate, we think that the eversion technique is more effective in terms of perioperative and postoperative stroke/death rates, as seen in the results of the present study, since this technique reduces the postoperative restenosis and the need for re-intervention, does not cause negativities such as aneurysm and infection because of patch use, provides a shorter operation and cross-clamping time, and is a more suitable method for natural anatomy. We also think that patients should be followed up for a longer period and future studies should be conducted with the participation of more patients.

Conclusion

In conclusion, the experience of the surgical team in choosing the method is very effective on the perioperative and postoperative morbidity and mortality rates. ECEA technique has shorter cross-clamp and operation time than CCEA technique. This means that less anesthetic effect and more brain perfusion in ECEA technique compared to CCEA.The treatment of carotid artery disease requires a multidisciplinary study in which neurology, anesthesia, and cardiovascular surgery work in agreement and support each other.

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Conflict of interest

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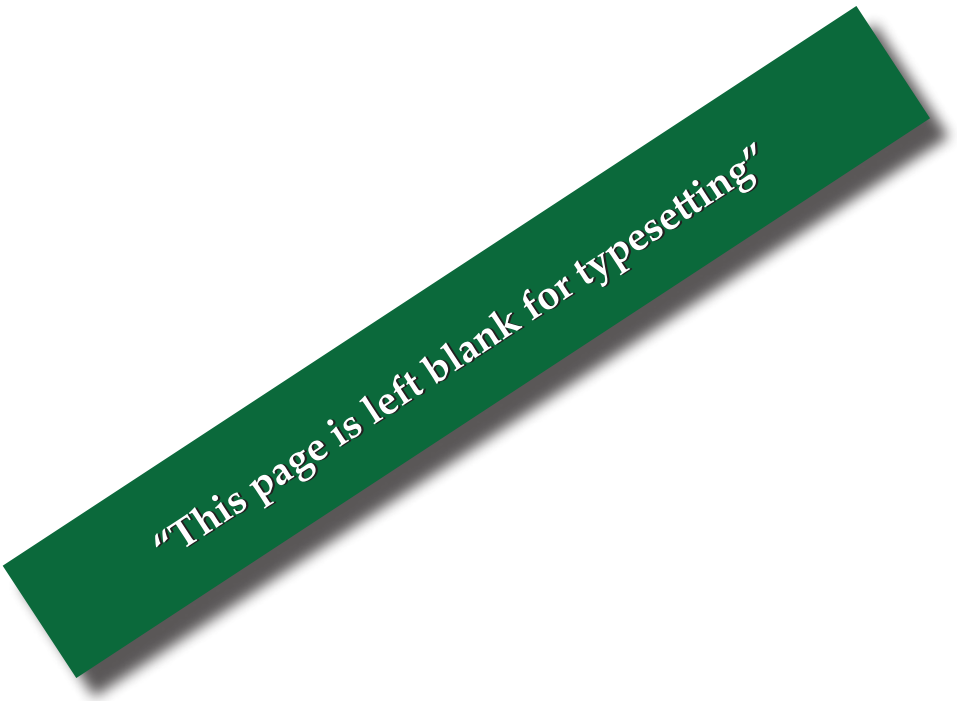
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ORIGINAL ARTICLE

Use of external fixator combined with titanium elastic nails in the treatment of tibia shaft fractures in children

İsmail Güzel[1] **İbrahim Ulusoy**[2]

[1] Department of Orthopedics and Traumatology, Faculty of Medicine, Turgut Özal University. Malatya / Türkiye
[2] Department of Orthopedics and Traumatology, Selahhadin Eyyubi State Hospital. Diyarbakır / Türkiye

Abstract

Tibia shaft fractures are common in all age groups. For these fractures; Conservative and surgical treatment methods are available. In surgical treatment, numerous surgical methods such as plate screw fixation, external fixator, and titanium elastic nail and K-wire fixation have been defined. The aim of the present study was to present the results of patients for whom external fixator combined with titanium elastic nails or titanium elastic nails alone were applied due to tibia shaft fractures. The study included 40 patients treated for tibia shaft fracture in our clinic between January 2016 and January 2019. Combined external fixator (EF) fixation was applied to patients who were found to be instable after Titanium elastic nail (TEN) application during the surgery. In clinical evaluation, Flynn classification, time to fracture union, fluoroscopy count, reoperation and time to full weight bearing were used. The results of patients for whom EF combined with TEN were applied were compared with the patients who had only TEN. Thirty patients were treated using TEN and 10 patients using EF combined with TEN. After 12 months of follow-ups, fracture union was achieved in all patients. There were 5% sagittal and 2.5% coronal plane angulation. Patients developed angular deformity of an average of 2.43 ± 1.9 degrees in the coronal plane and 2.65 ± 1.9 degrees in sagittal plane. Lower percentages of angular and rotational deformity were observed compared to the literature. Despite the disadvantages of using a greater number of fluoroscopy and longer operation periods in patients who underwent TEN+EF, these patients were mobilized earlier. It was concluded that combined EF application is a more feasible method in patients with pediatric tibia shaft fracture for whom stable fixation cannot be achieved with TEN.

Keywords: Tibia fracture, child, external fixator, elastic nail

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Corresponding Author:
İbrahim Ulusoy
Email: dr.ibrahimulusoy@gmail.com

Introduction

Tibia shaft fractures are common in all age groups [1,2]. They account for almost 15% of fractures in children [3]. For these fractures, plaster splints are preferred in children after closed reduction, and most patients can be successfully treated without the need for surgery. Unfortunately, in some patients, sliding or fracture non-union could be observed after splints and surgery is preferred in these patients. Surgical methods are also preferred in cases of instable fractures, open fractures, multiple trauma patients, in patients with compartment syndrome or neurovascular damage, surrounding soft tissue damage, firearm injury and in open fractures [4,5].

In surgical treatment, numerous surgical methods such as plate screw fixation, external fixator (EF), intramedullary nail, titanium elastic nail (TEN) and K-wire fixation have been defined. These treatments have advantages and disadvantages compared to each other. Especially in pediatric patients, open or major surgeries have been replaced by closed or minor surgeries due to the complications such as infection, growth problems and refracture [4,5].

TEN is one of the most popular methods today due to its advantages such as closed fixation, minimal infection rate, minimal soft tissue damage and early mobilization [6,7]. Despite these advantages, the technique is also known to have less stability in some types of fractures such as segmentary fracture, multiple or defective fracture [8].

External fixator applications are used for all fracture areas of all ages in combination with applications for open fractures, extensive tissue damage, intra-joint fractures, instable fractures and limited stabilizing applications [9]. There are numerous publications in the literature on pediatric patients who underwent TEN or EF for the treatment of tibia shaft fractures. However, there are only a limited number of publications related to patients with complex fractures treated with combined TEN and EF applications. Therefore, new studies are needed to find the right indication.

The aim of the present study was to present the results of the patients who were treated with TEN or TEN + EF methods for tibia shaft fractures.

Material and Methods

The study received ethical committee approval from Malatya Turgut Özal University Clinical Research Ethics Committee (approval no: 2021/19). Our study was retrospectively planned. The study included 40 patients treated with TEN or TEN + EF for tibia shaft fractures in our clinic between January 2016 and January 2019.

The inclusion criteria for this study were:

- 0-18 years of age
- Tibia shaft fractures
- Minimum follow-up period of 12 months

Exclusion criteria were:

- Adult patients
- Pathological fractures
- Patients with metabolic bone disease
- Patients with less than 12 months of follow-up period
- Cases with systemic diseases such as diabetes, hypertension.

Surgical Method

Patients were operated in supine position under general anesthesia. Two mini-incisions, one medial and the other lateral, were made at 2 cm distal of tibia epiphysis and TEN entry points were determined. First through lateral and then medial, a 2-4 mm TEN was sent towards the distal through the help of the guide accompanied by fluoroscopy, and the fracture line was passed.

In multiple fracture or segmentary fracture cases or in cases where effective stabilization could not be achieved with two TENs, two 3-mm pins were placed through tibia medial to the distal of fracture line, and two 3-mm pins were placed to the proximal of fracture line with the help of a drill. The axial external fixator device was placed on top of these four pins, and was fixed through achieving effective reduction and stabilization as accompanied with fluoroscopy. After the operation, both groups of patients were

immobilized with long leg splint for two weeks.

Post-Operation Evaluation

The patients were asked to move ankle and knee joints two days after the operation and to perform joint-range of motion exercises on the 15th post-operative day. Partial load mobilization was recommended when signs of fracture union were observed in X-rays taken for control purposes (six weeks on average). In the last follow-up examination, treatment results were classified as excellent, satisfactory and poor according to the TEN result scoring system developed by Flynn et al. [10].

IBM SPSS 19 software (IBM SPSS Statistics 19, SPSS Inc., an IBM Co., Somers, NY) was used in statistical analyses. Clinical data were expressed in number, percentage, or mean ± SD. The two-way Chi-square ($\chi 2$) test was used to evaluate the relationship between two categorical variables. Student's *t* test was used for continuous variables. $p \leq 0.05$ was considered statistically significant.

Results

The results of 40 patients were included in the study. Thirty patients were treated using TEN and 10 patients using EF combined with TEN. Demographic data of the patients included in the study are given in Table 1.

Data are given as mean ± standard deviation / Median / Minimum-Maximum or frequency, percentage *p:* Independent samples *t* test or Chi-square test were used.

After 12 months of follow-ups, 87.5% of patients had excellent and 12.5% had satisfactory outcomes. The mean duration of surgery and fluoroscopy counts was higher in patients treated using EF combined with TEN. However, time to full weight bearing was shorter in these patients. There was 5% sagittal and 2.5% coronal plane angulation. Patients developed angular deformity of an average of 2.43 ± 1.9 degrees in the coronal plane and 2.65 ± 1.9 degrees in sagittal plane. Two patients treated with TEN alone and one patient treated with TEN + EF combination developed superficial infections that were healed with a one-week oral antibiotic therapy.

Data are shown as mean ± standard deviation / Median / Minimum-Maximum or frequency, percentage *p:* Independent samples *t* test or Chi-square test were used. *p:* Between-subject comparison.

Discussion

Many methods have been used for the treatment of tibia shaft fractures in children. These fractures are first treated with closed reduction and casting fixation. When the successful fracture union is not achieved, surgical methods are used. TEN is one of the most popular surgical methods today. In the present study, we achieved successful outcomes with TEN methods in patients with tibia shaft fractures. Since we could not obtain stable fixation with TEN applications alone in 25% of the patients, we combined TEN with axial fixator to achieve 100% fracture union without experiencing any major complications.

Table 1. General characteristics of study groups.

	TOTAL	TEN	TEN+EF
n	40	30	10
GENDER (Male/Female)	22/18	15/15	7/3
SIDE (Right/Left)	19/21	14/16	5/5
AGE	11±2.6	10.5±2.5	12.4±2.5
Fracture type Short oblique Long oblique Transverse Spiral	6, 15% 15, 37.5% 14, 35% 5, 12.5%	5, 16.7% 11, 36.7% 10, 33.3% 4, 13.3%	1, 10% 4, 40% 4, 40% 1, 10%

Although some studies argued otherwise, TEN is still one of the best methods for pediatric tibia shaft fractures [7,11]. TEN which is applied as intramedullary provides a strong grip on the bone due to its Divergent C configuration [12]. Thus, contact is formed at six points on tibia medulla. Through allowing controlled movement in the fracture area, this method provides fracture union with the formation of external callus. It results in a more flexible fixation compared to plate-screw application. Therefore, there are risks of angulation, rotation, shortening and fracture malunion formation. O'Brien et al., [13] reported angulations more than 5° in 12.5% of the patients. Similarly, Sankar et al., [7] reported angulation in 25.2% of the patients (6.3% of the patients had 5-10% angulation in sagittal plane, and 18.9% of the patients had 5-10% angulation in coronal plane). In the present study, 5 and 2.5% angulations were observed in sagittal and coronal plans, respectively, which were considerably lower than those reported in other studies. During the surgery, we tested the reduction stability in all patients after TEN applications with rotational movements made in coronal and sagittal planes. We applied axial external fixators to patients who had poor stability. That's why the patients in our study had almost no rotation, shortening or fracture malunion. The angulation rates were very low in both sagittal and coronal planes. Therefore, we believe that supportive fixation methods can reduce such alignment problems by applying stability tests in these patients.

Li et al., [14] compared TEN combined with EF treatment and intramedullary nail treatment in 23-55-year-old patients with tibia shaft fractures. They found no difference in ankle functional scores and fracture union rates. They observed that blood loss and knee pain were less in patients treated with TEN combined with EF. In the present study, we treated 25% of the child patients using EF as a combination for the treatment because intraoperative stability was low with TEN only application. The patients for whom we practiced this approach were the children between the age of 10 and 16, who were taller and who had more developed bone structure than their peers. In these patients, we increased stability with less tissue damage and

Table 2. General characteristics of the study groups.

Variables	Total	TEN	TEN+EF	*p*
Flynn classification score	Excellent: n: 35, 87.5% Satisfactory: n: 6, 12.5% Poor: n: 0.0%	Excellent: n: 27, 87.5% Satisfactory: n: 3, 12.5% Poor: n: 0.0%	Excellent: n: 8, 87.5 % Satisfactory: n: 2, 12.5% Poor: n: 0.0%	<0.001
Time to fracture union (weeks)	16.6±2	15.9±1.8	18.5±1.6	<0.001
Fluoroscopy counts	9.7±2.6	8.7±2.1	12.9±1.1	<0.001
Reoperation	None	None	None	
Time to full weight bearing (weeks)	7.9±1.6	8.4±1.3	6.4±1.6	<0.001
Duration of the operation (min.)	30.7±7.6	27.4±8	40.2±7.1	<0.001
Coronal angular deformity (°)	2.43±1.9	2.07±1.8	3.5±1.6	0.016
Sagittal angular deformity (°)	2.65±1.9	2.23±1.9	3.9±1.1	0.006

in a shorter time using an additional surgical procedure without any incision. Our clinical outcomes were similar to those reported by Li et al [14]. As a result, we think that combined EF application could provide effective stability in a shorter time with less tissue damage and complications in children who are taller, who have better developed bone structures and who have less intraoperative stability than their peers. Sankar et al., reported the need to repeat the reduction under anesthesia in two patients treated with TEN due to loss of postoperative reduction [7]. A secondary anesthesia was needed in these patients because these patients weighed 39 and 55 kg and had more developed body structure compared to other patients. In the present study, the patients for whom an effective intraoperative stability could not be achieved were the ones who were well-built or overweight such as those in the study of Sankar et al. Thanks to the combined EF method we performed in these patients, a second surgical or anesthesia procedure was not required.

Pennock et al., compared the results of patients treated with TEN or plate-screw fixation method for pediatric tibia shaft fractures [15]. There was difference between the groups for fracture union rates. The plate-screw group had less casting time (an average of seven weeks), better anatomical reduction and lower second surgical requirement rate. In the TEN group, on the other hand, shorter surgical time and lower scarring problems were observed. In our study, we used shorter casting periods in patients treated with TEN+EF (two weeks) compared to the period used for plate-screw group by Pennock et al. Considering all patients in the study (EF+TEN and TEN groups), no patients required a second surgical procedure. Very few patients (n: 3, 7.5%) had wound problems. The results of our study showed that the need for major surgeries such as plate-screw fixation could be eliminated with the use of TEN method in patients with pediatric tibia shaft fractures and use of combined EF method in patients for whom stable fixation cannot be achieved.

Retrospective design of the study, limited number of patients and short follow-up periods were among the limitations of the study. More efficient studies with larger patient populations are needed.

Conclusion

In conclusion, TEN is a successful method in pediatric patients with tibia fractures. However, we believe that in patients for whom stable fixation be cannot achieved by applying TEN alone, combined EF application is a more viable method in pediatric patients with tibia shaft fracture.

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Conflict of interest

There are no conflicts of interest to declare.

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ORIGINAL ARTICLE

Violence against women during the pandemic from the viewpoint of a tertiary forensic medicine clinic

Mahmut Şerif Yıldırım[1] **Sude Sezen**[2] **Sevcan Aksakallı**[2]
Cemal Emre Savaş[2] **Mustafa Cengiz**[2] **Betül Pekşen Koç**[1]
Uğur Kayhan[1]

[1] Department of Forensic Medicine, Faculty of Medicine, Afyonkarahisar Health Sciences University. Afyonkarahisar / Türkiye
[2] Undergraduate student, Faculty of Medicine, Afyonkarahisar Health Sciences University. Afyonkarahisar / Türkiye

Abstract

COVID-19 pandemic and measures to combat the pandemic caused an increase in the risk of violence against women. In this study, it was aimed to examine the change in violence crimes against women evaluated in a tertiary forensic medicine clinic over a two-year period by focusing on periods of lockdown and domestic violence. Victims of violence against women who admitted to our center between 01/01/2020 and 12/31/2021 were included in the study. Patient files and forensic reports were used to acquire information regarding the age, date of the incident, relationship of the offender, type of incident, usage of weapons, injuries sustained, and if the incident was domestic violence. The ages of 121 cases evaluated ranged from 10 to 88 years, and the mean age was 36.1 (SD=17.6) years. When the mean number of incidents per day was examined, it was shown that cases of domestic violence were most common during the lockdown period. When all cases were considered together, it was shown that the highest mean number of cases occurred in the first days following the restrictions. Violence against women increased during the periods of the pandemic. In cases of domestic violence, as expected, the most significant rise occurred during lockdown periods. The 24-hour period following the lockdown application has been identified as the most intensive time of violence against women during the pandemic.

Keywords: Clinical forensic medicine, violence against women, domestic violence, COVID-19

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Corresponding Author:
Mahmut Şerif Yıldırım
Email: dr.msyildirim@gmail.com

Introduction

Aside from being identified as a public health issue, violence against women is a topic that has been examined and attempted to solve on a global scale [1-3]. Because of the changes in social life caused by COVID-19, which was proclaimed as a pandemic in January 2020, numerous problems were predicted to worsen, particularly due to restrictions imposed to battle the pandemic. The stress burden of being confined on the aggressor, the effects directly related to the disease caused by the pandemic, the economic and social stressors arising from pandemic-prevention measures, and the necessity of being in the same environment as the aggressor and the victim bring additional risks in domestic violence cases, and the necessity of taking precautions on these issues has been widely discussed in the literature [2-11].

Along with papers warning that violence against women, particularly domestic violence crimes, may increase during the pandemic period due to the psychological pressure that was caused by the outbreak of the pandemic and shutdown processes, studies investigating the change in domestic violence by comparing the pandemic period with the pre-pandemic periods have also been published in the period following the COVID-19 pandemic, and it has been shown that violence against women increased during the pandemic [12-17]. Furthermore, the assumption of a substantial pattern change in violent crimes during this period led to the expectation of a pattern change in clinical forensic medicine cases [4]. Domestic violence, which is believed to increase particularly during the lockdown periods, has been studied more thoroughly in these studies. Other forms in the broad definition of violence against women and the change in the number of violence cases during the pandemic period seem to be areas that still need to be investigated in the literature.

In this study, it was aimed to examine the change in violence crimes against women evaluated in a tertiary forensic medicine clinic over a two-year period, including the pandemic period, by focusing on periods of lockdown and domestic violence.

Materials and Methods

Within the scope of the study, cases that admitted to Afyonkarahisar Health Sciences University Hospital and were victims of violence that took place between 01/01/2020 and 12/31/2021 were included. After excluding male cases among 6643 applications between the mentioned dates, 1466 female cases were identified. Among these cases, after excluding cases found to be related to accident, self-harm/suicide and natural diseases and repeated applications for the same incident, it was determined that a total of 121 cases were cases of violence against women and were included in the study population. Patient files and forensic reports were used to acquire information regarding the age, date of the incident, relationship of the offender, kind of incident, usage of weapons in the incident, injuries sustained in the incident, and if the incident was domestic violence.

The data were recorded as two separate data sets. The first data set was collected by documenting the case features on a case-by-case basis, while the second data set was collected by documenting the number of domestic violence and total violence cases admitted on a date-by-date basis. According to the reported dates of the incidents, the cases were separated into four groups. The period between 01/01/2020 and 3/11/2020, when the first case was detected in our country, was designated as group I, the lockdown and quarantine periods as group II, the days immediately following the removal of lockdown period as group IV, and the days in between as group III.

In addition to simple descriptive statistics derived from the case-based recorded data set, Pearson's Chi square test was used to compare violence against women to other instances in terms of injury forms. The date-based data set was evaluated in terms of variations across groups based on daily frequencies. The level of significance in statistical analysis was set at p=0.05. SPSS 22.0 (MA, USA) was used for all statistical analyses.

The study was approved by Afyonkarahisar Health Sciences University Medical Ethics Board with the decision numbered 2022/570 and dated 02.12.2022.

Results

The ages of 121 cases evaluated between the specified dates ranged from 10 to 88 years, and the mean age was 36.1 (SD=17.6) years. Table 1 shows the number of cases by date groups, type of injury, discharge status, scene of incident, injured body part, injury, and whether there is domestic violence or not.

The type of injury, discharge status, scene of the incident and injuries of the cases of domestic violence cases and other cases are shown in Table 2.

No statistically significant difference was found between domestic violence cases and other cases in terms of soft tissue trauma, bone fracture or visceral organ injury.

When the mean number of incidents per day was examined, it was shown that cases of domestic violence were most common during the lockdown period. When all cases were considered together, it was shown that the highest mean number of cases occurred in the first days following the restrictions, and the lowest mean number of cases occurred before the pandemic was declared (Table 3).

Discussion

Violence against women has emerged as an unacknowledged pandemic that cannot be stopped in recent decades around the world. Many studies have been conducted on the

Table 1. Case numbers according to the date group, injury type, discharge status, incident scene, injured body parts, injuries, and presence of domestic violence.

Table 1		**n**	**%**
Date group	*I*	11	9.1
	II	25	20.7
	III	80	66.1
	IV	5	4.1
	Total	121	100.0
Injury type	*Blunt injury*	106	87.6
	Sharp instrument injury	5	4.1
	Firearm injury	7	5.8
	Sexual assault	3	2.5
	Total	121	100.0
Discharge status	*Home discharge*	117	96.7
	Death	4	3.3
	Total	121	100.0
Incident scene	*Home*	55	45.5
	Workplace	1	.8
	Other	65	53.7
	Total	121	100.0
Injured body parts	*No injury*	6	5.0
	Head/neck	71	58.7
	Thorax	15	12.4
	Abdomen/pelvis	18	14.9
	Extremities	36	29.8
Injury	*Soft tissue injury*	116	95.9
	Bone fracture	15	12.4
	Visceral organ injury	7	5.8
Presence of domestic violence	*Yes*	52	43.0
	No	69	57.0
	Total	121	100.0

subject since the COVID-19 pandemic appeared in 2020, especially with the idea that risk factors for domestic violence have increased [2,15,18-20]. The impacts of the COVID-19 pandemic on violence against women have been studied since the outbreak began, with research based on several surveys, hotline call records, criminal records, and health system records [7,10,15,18,19].

The majority of the studies in the literature are studies comparing the pandemic period to the pre-pandemic period. The vast majority of these studies described an increase in cases of violence against women and domestic violence during the pandemic period, with the most dramatic increase occurring in cases of emotional violence [7,15,19,21,22]. Furthermore, it has been demonstrated that there is a substantial rise in domestic violence during lockdowns [23,24]. Our data also revealed an increase in violence against women throughout the pandemic era, as well as an increase in domestic violence during lockdown times. There were no cases admitted to our center owing to emotional violence in our study. The socio-cultural acquis of people, their avoidance of hospital admissions during the pandemic period, and less reflection of emotional violence on judicial authorities can be counted among the possible reasons for this situation.

It has been revealed in the literature that women's help-seeking behaviors have changed during the pandemic process, especially during lockdown periods, and these changes also differ regionally [18,25,26]. One of the reasons for the inability to seek help or the change in help-seeking behavior in domestic violence may be staying in the same house with the aggressor and fearing that seeking help will aggravate the violence. According to a research based on hospital records that used a methodology similar to ours, applications for violence against women

Table 2. Case numbers of injury type, discharge status, incident scene and injuries according to the presence of domestic violence.

		Domestic violence cases		Other cases		Total	
		n	%	n	%	n	%
Injury type	*Blunt injury*	48	45.3%	58	54.7%	106	100.0%
	Sharp instrument injury	3	60.0%	2	40.0%	5	100.0%
	Firearm injury	1	14.3%	6	85.7%	7	100.0%
	Sexual assault	0	0.0%	3	100.0%	3	100.0%
Discharge status	*Home discharge*	50	42.7%	67	57.3%	117	100.0%
	Death	2	50.0%	2	50.0%	4	100.0%
Incident scene	*Home*	47	85.5%	8	14.5%	55	100.0%
	Workplace	0	0.0%	1	100.0%	1	100.0%
	Other	5	7.7%	60	92.3%	65	100.0%
Injury	*Soft tissue injury*	50	43.1%	66	56.9%	116	100.0%
	Bone fracture	4	26.7%	11	73.3%	15	100.0%
	Visceral organ injury	2	28.6%	5	71.4%	7	100.0%

Table 3. Mean violence against women and domestic violence against women case numbers per-day.

		Date group				All days
		I	II	III	IV	
All violence cases	Mean	0.0571	0.2137	0.1641	0.25	0.1642
	SD	0.0234	0.0613	0.0433	0.055	0.0457
Domestic violence cases	Mean	0.0143	0.1111	0.0706	0.05	0.0711
	SD	0.0120	0.0390	0.0278	0.0224	0.0287

reduced during the pandemic period, which was attributed to people's unwillingness to admit to the hospital until the violence reached a very serious level [27]. There are also studies reporting that violence against women and domestic violence decreased during the pandemic period due to the possible lack of reporting [14,25,26]. In our study, when simple soft tissue injuries, bone fractures, and visceral organ injuries were evaluated separately in terms of severity, there was no statistically significant difference in injury severity between domestic violence and other forms of violence against women. This finding suggests that the effect of refraining from reporting due to fear of being closed with the aggressor after reporting the incident is not at a level that will cause a significant difference, and it may also occur as a result of the complex effect of other factors including refraining from admitting to the hospital during the pandemic process. However, it is understood that the dynamics that prevent hospital admissions for emotional violence do not apply to cases of physical violence.

Romito et al., discovered that during lockdown periods, partner violence increased in couples living together but reduced in couples living apart, as expected [7]. In our study, the fact that most of the domestic violence cases occurred during the lockdown period and all but 5 cases (9.6% of domestic violence cases) occurred in the home environment confirms that the necessity of being with the aggressor in a closed environment poses a risk for domestic violence.

Aside from emotional violence, research show a rise in domestic sexual violence incidents [2,15]. Although there were three cases of sexual violence in our study, none of them were cases of domestic sexual assault. It was also worth noting that these three incidents occurred on days other than the lockdown period. It appears more acceptable to credit the fact that assaults in the form of non-consensual sexual intercourse have never been reported, rather than the fact that these incidents did not occur, but were hidden for reasons comparable to those in situations of emotional violence.

It has been observed that in the days following the lockdown measures, people tend to enter social environments more frequently, and traffic and outdoor activities increase [28-30]. Considering this information, the events that occurred within 24 hours after the end of the lockdown measures were considered as a separate group in our study. Although domestic violence is more common during the lockdown period, when all forms of violence against women are evaluated together, it has been determined that the most common daily violence event is in the days following the lockdown. Similar to our findings, there are studies in the literature showing that when all forms of violence against women are evaluated together, there are studies showing that more incidents occur in the interim periods than during lockdown periods [14], but our study reveals that this increase is especially concentrated in the first hours after the lockdown.

Death, the most severe consequence of violence, occurred in four cases in our study. Two of these cases died as a result of domestic violence. An inverse link between the amount of violence and the frequency of reporting appears to corroborate an inverse relationship between the level of violence and the frequency of reporting in a study revealing the impacts of the epidemic on violence against women in Mexico and Colombia [14]. Although it seems possible that data reflecting the population in terms of death numbers can only be revealed as a result of studies to be conducted throughout the country, it is known that violence against women resulting in death in our country increased even before the pandemic [31]. Multicenter and nationwide researches are needed to determine how and how much the pandemic affects this increasing pattern.

One of the notable limitations of our study is its retrospective design. Apart from this, the small number of cases has led to its low adaptability to the whole population and the inability to examine the different types of injury subtypes and broadly defined violence against women separately. There is a need for studies on the subject in which both multicenter and clinical forensic applications, as well as hot-line applications and survey results can be evaluated comparatively.

Conclusions

Similar to the literature, it appears that violence against women has increased during the periods of the pandemic. The 24-hour period following the lockdown application has been identified as the most intensive time of violence against women during the pandemic. In cases of domestic violence, as expected, the most significant rise occurred during lockdown periods. In this period, when pandemic measures have vanished, there is a need for studies that conduct detailed analyses of the pandemic period, and as a result of these studies, there is also a need to determine the measures to be taken to reduce violence against women in future crisis periods.

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Conflict of interest

There is no conflict of interest between the authors concerning the materials or methods used in this study or the findings specified in this paper.

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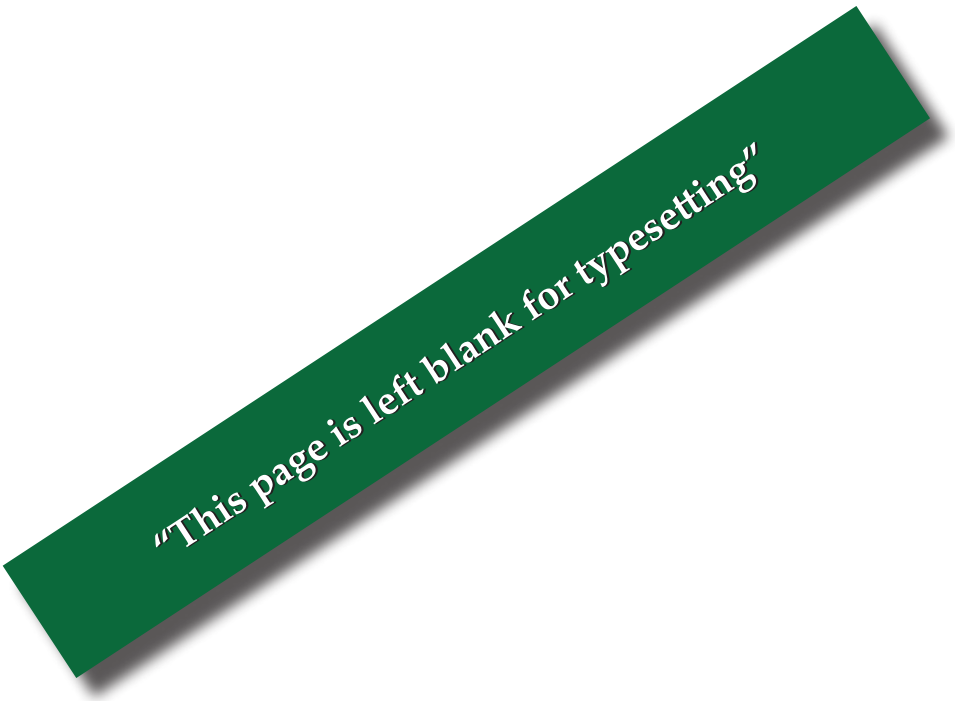
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ORIGINAL ARTICLE

COVID-19 vaccination hesitancy among patients admitted to the immunology and allergy clinic with drug allergies

Elif Haznedaroğlu Benlioğlu[1] **Seda Bayrak Durmaz**[2]
Göksal Keskin[2]

[1] Department of Internal Medicine, Faculty of Medicine, Ankara University. Ankara / Türkiye
[2] Department of Allergy and Immunology, Faculty of Medicine, Ankara University. Ankara / Türkiye

Abstract

The aim of our study was to determine the factors responsible for COVID-19 vaccination acceptance and hesitancy in patients with drug allergies. We prepared a survey to understand the thoughts, hesitancies and experiences about COVID-19 vaccination and COVID-19 infection in patients with drug allergies and statistically examined the results. A survey study was applied to 76 patients who were admitted to Ankara University Internal Medicine Allergy and Immunology Department with drug allergies. 38 patients who were vaccinated and 38 patients who weren't were compared. Among the 38 patients who were vaccinated, 34 (89.5%) chose Biontech vaccine, 4 (10.5%) chose Sinovac vaccine. Among the patients who weren't vaccinated, 28 (73.7%) explained they weren't vaccinated because of drug allergies. Educational statuses were statistically significantly different (p=0.026) among vaccinated and non-vaccinated patients, lower in vaccinated patients. Vaccinated patients thought the vaccine reduced the possibility of COVID-19 infection and complications, which was significantly different (p<0.01). Non-vaccinated group significantly feared the possible allergic reaction to the COVID-19 vaccine, more than the vaccinated group (p=0.028). Fear of the possible side effects of the COVID-19 vaccine (p<0.001) and the thought of the COVID-19 vaccine being associated with unpredictable effects were significantly more evident in the non-vaccinated group (p<0.001). In conclusion, our study analyzed multiple factors in drug allergy patients regarding vaccine acceptance, rejection, and hesitancy for the first time in literature, similar studies with larger samples can also contribute to the literature in the future.

Keywords: COVID-19, COVID-19 vaccines, drug Hypersensitivity, vaccination hesitancy

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Corresponding Author:
Elif Haznedaroğlu Benlioğlu
Email: elifhaznedaroglu9@gmail.com

Introduction

COVID-19 infection, caused by the Sars-CoV-2 virus, emerged in the Wuhan city of China in December 2019 and quickly spread worldwide after a month, causing World Health Organization to declare COVID-19 a pandemic on the 11th of March 2020. As of February 2023, COVID-19 has caused roughly 750 million cases and 7 million deaths worldwide, with 17 million cases and 100 thousand deaths in Turkey [1]. As of February 2023, there are 242 vaccine candidates, 821 vaccine trials and 50 vaccines that have gone through Phase 3 and were approved [2].

Vaccine hesitancy was a very important issue even before the COVID-19 pandemic, so much so that in 2019 World Health Organization added vaccine hesitancies to the ten threats to global health [3]. COVID-19 vaccine acceptance and hesitancy is a complex subject, and its complexity is increased by the new variants and newly developing vaccines. Therefore, identifying factors that induce vaccine acceptance and hesitancy is very important in order to overcome vaccine hesitancy [4]. In a review about COVID-19 vaccine acceptance and hesitancy which was published in July 2022, vaccine motivators were listed as high perception of COVID-19 infection risk (loved ones experiencing COVID-19, chronic diseases, old age), trust for the healthcare system, social responsibility; while factors inducing vaccine hesitancy were listed as low perception of COVID-19 infection risk, poor experiences with other vaccines, disinformation, fear of the vaccine side effects, distrust against vaccine effect [5]. It was also shown in previous literature that among people with allergies, allergic asthma and the families of child-adolescent patients with allergies and allergic asthma, vaccine hesitancy is very common [6]. Therefore, it is particularly crucial to thoroughly and carefully inform these groups about the COVID-19 vaccines in order to raise vaccine extensity and reduce the spread of the COVID-19 pandemic.

In this study, we aimed to understand the thoughts and experiences about the COVID-19 vaccine and determine factors inducing COVID-19 vaccine hesitancy (age, marital status, educational status, chronic diseases, anaphylaxis, COVID-19 infection history, concerns about COVID-19 infection) among patients who were admitted to Ankara University Internal Medicine Allergy and Immunology Department with drug allergies.

Materials and Methods

This study was approved by the Ankara University Faculty of Medicine Human Research Ethics Committee (I05-271-22).

Study Design

This study has been conducted among 76 patients who were older than 18 years and were admitted to the Ankara University Internal Medicine Allergy and Immunology Clinic May 2022 to September 2022. We prepared a survey to analyze demographic information, attitudes and behaviors about vaccines, COVID-19 vaccines, thoughts and experiences about COVID-19 infection. Patients were informed that their participation to our study was voluntary and written informed consent was obtained from patients who participated in this study.

Statistical Analysis

Statistical analyses were conducted with the IBM® SPSS® Statistics Version 25 program. Normal distribution of variables was examined visually (histogram, probability graphs) and analytically (*Kolmogorov-Smirnov*/*Shapiro-Wilk* tests). Descriptive analyses were reported with medians and quartiles for numeric variables which were not normally distributed, and frequency tables for ordinal and categorical variables. For numeric variables which were not normally distributed *Mann Whitney U* test was used, while for categorical variables Chi-Square test or *Fisher* test were used. *P* values below 0.05 were considered statistically significant.

Results

Characteristics and Survey Answers of All Participants

Our study included 76 drug allergy patients. Characteristics and survey answers of all participants are summarized in Table 1.

Table 1: Characteristics, survey answers and statistics of all drug allergy patients, non-vaccinated and vaccinated groups.

	All drug allergy patients (n=76)	**Non-vaccinated patients (n=38)**	**Vaccinated patients (n=38)**	**p value**
Gender*				0.62[a]
Female	52 (68.4)	25 (65.8)	27 (71.1)	
Male	24 (31.6)	13 (34.2)	11 (28.9)	
Age				0.78[b]
Mean±SD	40.6±13.4	40.2±14.1	41±12.7	
Median value	40 (22)	41 (27)	39 (21)	
Age*				0.55[a]
18-25	14 (18.4)	9 (23.7)	5 (13.2)	
26-35	18 (23.7)	7 (18.4)	11 (28.9)	
36-45	15 (19.7)	7 (18.4)	8 (21.1)	
46-65	29 (38.2)	15 (39.5)	14 (36.8)	
Marital status*				0.64[a]
Single	30 (39.5)	14 (36.8)	16 (42.1)	
Married	46 (60.5)	24 (63.2)	22 (57.9)	
Educational status*				**0.026**[a]
Primary school	9 (11.8)	1 (2.6)	8 (21.1)	
Middle school	6 (7.9)	6 (15.8)	0 (0)	
High school	26 (34.2)	13 (34.2)	13 (34.2)	
College	29 (38.2)	16 (42.1)	13 (34.2)	
Masters	2 (2.6)	1 (2.6)	1 (2.6)	
Doctorate	4 (5.3)	1 (2.6)	3 (7.9)	
Working status*				0.11[a]
Unemployed	39 (51.3)	23 (60.5)	16 (42.1)	
Employed	37 (48.7)	15 (39.5)	22 (57.9)	
Chronic disease*				0.49[a]
None	53 (69.7)	25 (65.8)	28 (73.7)	
One chronic disease	14 (18.4)	9 (23.7)	5 (13.2)	
Multiple chronic diseases	9 (11.8)	4 (10.5)	5 (13.2)	
Chronic disease*				0.45[a]
None	53 (69.7)	25 (65.8)	28 (73.7)	
Present	23 (30.3)	13 (34.2)	10 (26.3)	
Which drug group caused the reaction?*				0.51[a]
Analgesic	36 (47.4)	19 (50)	17 (44.7)	
Antibiotic	25 (32.9)	10 (26.3)	15 (39.5)	
Muscle relaxant	8 (10.5)	4 (10.5)	4 (10.5)	
Contrast material	2 (2.6)	2 (5.3)	0 (0)	
Other	5 (6.6)	3 (7.9)	2 (5.3)	
Allergy with antibiotics*	25 (32.9)	10 (26.3)	15 (39.5)	0.22[a]
Allergy with analgesics*	36 (47.4)	19 (50)	17 (44.7)	0.65[a]
Did you experience anaphylactic shock?*				0.43[a]
No	57 (75)	27 (71.1)	30 (78.9)	
Yes	19 (25)	11 (28.9)	8 (21.1)	
How was the drug used?*				0.75[a]
Oral	58 (76.3)	30 (78.9)	28 (73.7)	
Intravenous (IV)	10 (13.2)	5 (13.2)	5 (13.2)	
Intramuscular (IM)	8 (10.5)	3 (7.9)	5 (13.2)	
Allergy with oral drug*	58 (76.3)	30 (78.9)	28 (73.7)	0.59[a]
Allergy with IV drug*	10 (13.2)	5 (13.2)	5 (13.2)	1.00[a]
Allergy with IM drug*	8 (10.5)	3 (7.9)	5 (13.2)	0.71[c]
Were you hospitalized with drug allergy?*				0.81[a]
No	52 (68.4)	27 (71.1)	25 (65.8)	
Yes, inpatient care	11 (14.5)	6 (15.8)	5 (13.2)	
Yes, emergency room	11 (14.5)	4 (10.5)	7 (18.4)	
Yes, intensive care unit	2 (2.6)	1 (2.6)	1 (2.6)	
Hospitalization with drug allergies*	24 (31.6)	11 (28.9)	13 (34.2)	0.62[a]
Have you ever had COVID-19?*	38 (50)	20 (52.6)	18 (47.4)	0.65[a]
If you had COVID-19, were you hospitalized?*, n=38	2 (5.3)	1 (5)	1 (5.6)	>0.99[c]

If you had COVID-19, were you hospitalized in intensive care unit? *, n=38	1 (2.6)	1 (5)	0 (0)	>0.99[c]
If you had COVID-19, did you have a reaction with the medication for COVID-19? *, n=38	2 (5.3)	0 (0)	2 (11.1)	0.22[c]
Have any of the people you know had COVID-19? *				1.00[a]
No	14 (18.4)	7 (18.4)	7 (18.4)	
Yes	62 (81.6)	31 (81.6)	31 (81.6)	
Do you know anybody who died from COVID-19? *				1.00[a]
No	56 (73.7)	28 (73.7)	28 (73.7)	
Yes	20 (26.3)	10 (26.3)	10 (26.3)	
Are you anxious about getting COVID-19? *				1.00[a]
No	50 (65.8)	25 (65.8)	25 (65.8)	
Yes	26 (34.2)	13 (34.2)	13 (34.2)	
Do you think COVID-19 leads to serious complications? *				0.065[a]
No	34 (44.7)	21 (55.3)	13 (34.2)	
Yes	42 (55.3)	17 (44.7)	25 (65.8)	
Do you think you would get really sick if you had COVID-19? *				0.15[a]
No	48 (63.2)	27 (71.1)	21 (55.3)	
Yes	28 (36.8)	11 (28.9)	17 (44.7)	
Are you afraid of getting COVID-19? *				0.34[a]
No	48 (63.2)	26 (68.4)	22 (57.9)	
Yes	28 (36.8)	12 (31.6)	16 (42.1)	
Do you think COVID-19 vaccine reduces the risk of getting COVID-19 or its complications? *				**<0.001**[a]
No	36 (47.4)	28 (73.7)	8 (21.1)	
Yes	40 (52.6)	10 (26.3)	30 (78.9)	
Have you ever had a reaction with a vaccine? (other than the COVID-19 vaccine) *				>0.99[c]
No	75 (98.7)	37 (97.4)	38 (100)	
Yes	1 (1.3)	1 (2.6)	0 (0)	
Do you know anybody who had an allergic reaction to the COVID-19 vaccine? *				0.48[c]
No	67 (88.2)	32 (84.2)	35 (92.1)	
Yes	9 (11.8)	6 (15.8)	3 (7.9)	
Are you afraid of an allergic reaction to the COVID-19 vaccine? *				**0.028**[a]
No	25 (32.9)	8 (21.1)	17 (44.7)	
Yes	51 (67.1)	30 (78.9)	21 (55.3)	
Have you had the COVID-19 vaccine? *				NA
No	38 (50)	NA	NA	
Yes	38 (50)	NA	NA	
If you had the COVID-19 vaccine. which vaccine did you choose? *, n=38				NA
Sinovac	4 (10.5)	NA	NA	
Biontech	34 (89.5)	NA	NA	
Why did you choose the vaccine you had? (written answers)* , n=38				NA
More protective	24 (36.2)	NA	NA	
Less side effects	4 (10.5)	NA	NA	
I trust it more	3 (7.9)	NA	NA	
Physician recommendation	3 (7.9)	NA	NA	
Effective	1 (2.6)	NA	NA	
European recommendation	1 (2.6)	NA	NA	
mRNA vaccine	1 (2.6)	NA	NA	
Live virus vaccine	1 (2.6)	NA	NA	
Did you get the vaccine immediately when it was possible? *, n=38				NA
No	3 (7.9)	NA	NA	
Yes	35 (92.1)	NA	NA	
If you had the vaccine later, what was the reason?*, n=3				NA
Pregnancy	1 (33.3)	NA	NA	
No time	1 (33.3)	NA	NA	
Fear of side effects	1 (33.3)	NA	NA	

What was the positive factor that persuaded you to get the COVID-19 vaccine? (written answers) [*], n=14				NA
Protection	4 (28.6)	NA	NA	
Precaution	2 (14.3)	NA	NA	
People who were vaccinated had a milder disease	2 (14.3)	NA	NA	
Fear	1 (7.1)	NA	NA	
Necessity	1 (7.1)	NA	NA	
Having a chronic disease	1 (7.1)	NA	NA	
High antibody response	1 (7.1)	NA	NA	
To avoid infecting other people	1 (7.1)	NA	NA	
Statements from the government	1 (7.1)	NA	NA	
If you weren't vaccinated, is it because of your drug allergy?[*], n=38				NA
No	10 (26.3)	NA	NA	
Yes	28 (73.7)	NA	NA	
Is it because of another reason? (written answers)[*], n=12				NA
Fear from vaccine side effects[*]	11 (91.7)	NA	NA	
Post-vaccine embolism in family[*]	1 (8.3)	NA	NA	
If you had the COVID-19 vaccine, did you experience an allergic reaction? [*], n=38				NA
No	35 (92.1)	NA	NA	
Yes	3 (7.9)	NA	NA	
Would you get the COVID-19 vaccine once you have been informed thoroughly? [*]				0.16[a]
No	44 (57.9)	25 (65.8)	19 (50)	
Yes	32 (42.1)	13 (34.2)	19 (50)	
Are you afraid of the possible side effects of the COVID-19 vaccine? [*]				**<0.001**[a]
No	21 (27.6)	3 (7.9)	18 (47.4)	
Yes	55 (72.4)	35 (92.1)	20 (52.6)	
Sinovac	4 (10.5)	NA	NA	
Biontech	34 (89.5)	NA	NA	
Why did you choose the vaccine you had? (written answers)[*] , n=38				NA
More protective	24 (36.2)	NA	NA	
Less side effects	4 (10.5)	NA	NA	
I trust it more	3 (7.9)	NA	NA	
Physician recommendation	3 (7.9)	NA	NA	
Effective	1 (2.6)	NA	NA	
European recommendation	1 (2.6)	NA	NA	
mRNA vaccine	1 (2.6)	NA	NA	
Live virus vaccine	1 (2.6)	NA	NA	
Did you get the vaccine immediately when it was possible? [*], n=38				NA
No	3 (7.9)	NA	NA	
Yes	35 (92.1)	NA	NA	
If you had the vaccine later, what was the reason?[*], n=3				NA
Pregnancy	1 (33.3)	NA	NA	
No time	1 (33.3)	NA	NA	
Fear of side effects	1 (33.3)	NA	NA	
What was the positive factor that persuaded you to get the COVID-19 vaccine? (written answers) [*], n=14				NA
Protection	4 (28.6)	NA	NA	
Precaution	2 (14.3)	NA	NA	
People who were vaccinated had a milder disease	2 (14.3)	NA	NA	
Fear	1 (7.1)	NA	NA	
Necessity	1 (7.1)	NA	NA	
Having a chronic disease	1 (7.1)	NA	NA	
High antibody response	1 (7.1)	NA	NA	
To avoid infecting other people	1 (7.1)	NA	NA	
Statements from the government	1 (7.1)	NA	NA	
If you weren't vaccinated, is it because of your drug allergy?[*], n=38				NA

No	10 (26.3)	NA	NA	
Yes	28 (73.7)	NA	NA	
Is it because of another reason? (written answers)*, n=12				NA
Fear from vaccine side effects*	11 (91.7)	NA	NA	
Post-vaccine embolism in family*	1 (8.3)	NA	NA	
If you had the COVID-19 vaccine, did you experience an allergic reaction? *, n=38				NA
No	35 (92.1)	NA	NA	
Yes	3 (7.9)	NA	NA	
Would you get the COVID-19 vaccine once you have been informed thoroughly? *				0.16[a]
No	44 (57.9)	25 (65.8)	19 (50)	
Yes	32 (42.1)	13 (34.2)	19 (50)	
Are you afraid of the possible side effects of the COVID-19 vaccine? *				**<0.001**[a]
No	21 (27.6)	3 (7.9)	18 (47.4)	
Yes	55 (72.4)	35 (92.1)	20 (52.6)	

*n (%), NA: not applicable, aChi-Square, bMann-Whitney U, cFisher's Exact Test

68.4% of all participants were female, 31.6% of them were male. Mean age was 40.6±13.4, median value was 40 (22). Most common drug group that caused reactions among our study group was analgesics (47.4%), and drugs that caused reactions in the study group were most commonly used orally (76.3%).

In our study group, 50% of the drug allergy patients experienced COVID-19 infection, among them 5.3% required hospitalization, 2.6% needed intensive care. 5.3% of the patients had a reaction with COVID-19 medication (favipravir).

Among the 38 patients who were vaccinated, 34 (89.5%) chose Biontech vaccine, 4 (10.5%) chose Sinovac vaccine. Reasons for patients to prefer the indicated vaccine were listed as: more protective (Biontech), less side effects (Sinovac), safety (Biontech), physician recommendation (Biontech), effective (Biontech), European recommendation (Biontech), mRNA vaccine (Biontech), live virus vaccine (Biontech, which is misinformation). 14 of the vaccinated patients answered our question about the positive factor that persuaded them to get vaccinated, and these factors were listed as: Protection, precaution, people who were vaccinated experienced a milder disease, fear, necessity, having a chronic disease, high antibody response, to avoid infecting other people, statements from the government. 92.1% of vaccinated patients didn't experience an allergic reaction after the COVID-19 vaccine.

While 28 (73.7%) of the non-vaccinated patients indicated that they were not vaccinated because of their drug allergies, 10 patients (26.3%) indicated they were not vaccinated because of other reasons. These reasons were indicated as fear from vaccine side effects and familial history of post-vaccine embolism.

Comparison of the Vaccinated and Non-Vaccinated Groups

Comparison and statistics of the vaccinated and non-vaccinated groups are shown in Table 1.

There was no significant difference between non-vaccinated and vaccinated groups in regard to gender (p=0.62), age (p=0.78), marital status (p=0.64), working status (p=0.11), chronic diseases (p=0.45), hospitalization requiring drug allergies (p=0.62), COVID-19 infection history (p=0.65), hospitalization with COVID-19 infection (p>0.99), knowing someone who had COVID-19 infection (p=1.00), knowing someone who died because of COVID-19 infection (p=1.00). Educational status was significantly lower in the vaccinated group (p=0.026)

Vaccinated patients thought the vaccine reduced the possibility of COVID-19 infection and complications, which was significantly different from the non-vaccinated patients (p<0.01). Non-vaccinated group feared the possible allergic reaction to the COVID-19 vaccine, significantly more than the vaccinated group (p=0.028). Fear of the possible side effects of the COVID-19 vaccine (p<0.001) and the thought of the COVID-19 vaccine being associated with unpredictable

effects were significantly more evident in the non-vaccinated group (p<0.001).

Discussion

As a perspective published in New England Journal of Medicine indicated, COVID-19 vaccines emerged as a hope to "give us our world back" [7]. Therefore, vaccination hesitancy is an important topic to be addressed in order to universalize the COVID-19 vaccines and attaining herd immunity. It was established in previous research that families of young individuals with allergies and allergic asthma have COVID-19 vaccine hesitancy, so it is crucial to address concerns of individuals with allergies [6,8,9]. The aim of our study was to determine the factors responsible for COVID-19 vaccination acceptance and hesitancy in patients with drug allergies.

While 28 (73.7%) of the non-vaccinated patients indicated that they were not vaccinated because of their drug allergies, 10 patients (26.3%) indicated they weren't vaccinated because of their fear of vaccine side effects or post-vaccine embolism in their families. Previous research also indicated that fear of vaccine side effects is an important factor for vaccine hesitancy [10]. It is very important to thoroughly explain the side effects of the vaccine, probability of these side effects and risk-benefit ratio of the COVID-19 vaccine. As for vaccine hesitancy due to allergies, it should be shared with patients that Biontech COVID-19 vaccine has an anaphylaxis probability of 4.7 among 1 million cases and there is no mortality with anaphylaxis when patients were observed [11]. In our study, among 38 drug allergy patients who were vaccinated, 3 of them (7.9%) had post-vaccine reaction, but these reactions were skin reactions, and none of these patients had anaphylaxis. European Academy of Allergy and Clinical Immunology (EEACI) stated in 2021 that allergy to drugs, food, insect venoms or inhalant allergens is not a contraindication for COVID-19 vaccines [12].

There was no difference in gender, marital status, working status between vaccinated and non-vaccinated groups. Although older age has been indicated as a factor inducing vaccine acceptance in previous research [13], there was no difference in age between non-vaccinated and vaccinated groups, this may be due to the lack of geriatric individuals among our drug allergy patients.

While in previous literature it was shown that lower educational status was associated with lower vaccination rates [14], in our study educational status was significantly different between non-vaccinated and vaccinated groups (p=0.026), with lower educational status being higher in the vaccinated group. This can be due to the fact that our sample is smaller, or due to the fact that higher educated individuals may have higher vaccination hesitancy because of their more frequent usage of social media, which can lead to misinformation [15,16].

Although it was shown in the literature that individuals with chronic diseases had higher vaccine acceptance rates [13], in our study there was no significant difference in regard to chronic diseases between vaccinated and non-vaccinated groups.

Vaccinated patients thought the vaccine reduced the possibility of COVID-19 infection and complications, which was significantly different (p<0.01). Non-vaccinated group significantly feared the possible allergic reaction to the COVID-19 vaccine, more than the vaccinated group (p=0.028). Fear of the possible side effects of the COVID-19 vaccine (p<0.001) and the thought of the COVID-19 vaccine being associated with unpredictable effects were significantly more evident in the non-vaccinated group (p<0.001). These results were compatible with previous research that vaccine acceptance was highly associated with trust towards the COVID-19 vaccine effectivity and safety [17].

In our study group, patients who chose the inactivated Sinovac vaccine made this decision based on the thought that the vaccine had fewer side effects than the Biontech vaccine. The most common side effect related to the inactivated vaccine is pain at the site of the injection. Fever, headache, fatigue, myalgia were also reported as mild side effects [18]. As for the Biontech vaccine, most common side effects were pain at the site of the injection, fatigue, muscle pain, local swelling, headache, joint pain, fever, lymph node swelling

[19]. In terms of allergic reactions, in a phase 1-2 clinical trial of Sinovac reported only one case of acute hypersensitivity [18], another phase 1-2 clinical trial reported one case of anaphylaxis, which was grade 1 severity [20]. A phase 3 trial of Sinovac conducted in Turkey reported one grade 3 allergic reaction, which required hospitalization but resolved within 24 hours [21]. Among the 17.5 million doses of Biontech and Moderna mRNA vaccines, only 66 anaphylaxis cases were reported, which was interpreted as 4.7 cases per 1 million doses for Biontech vaccine [21]. A study conducted with elderly patients in our country showed that the probability of allergic reactions was similar with Biontech and Sinovac vaccines [22]. Neither Sinovac nor Biontech caused mortal allergic reactions or anaphylaxis cases, all reported allergic reactions mentioned during phase studies or real-life studies resolved uneventfully [18,19].

With our survey study, we analyzed multiple factors regarding vaccine hesitancy among 76 drug allergy patients, for the first time in literature. Most important limitation of our study was the number of participants. Some of our results were incompatible with previous research, this may be due to the participant number, but also can be due to the changes in individuals' experiences, thoughts and behaviors between the beginning of the COVID-19 pandemic to our study timeline, which was two years after the start of the COVID-19 pandemic. Similar studies among drug allergy patients involving multiple centers and larger groups of participants may also contribute to the literature in the future.

Conclusion

In conclusion, our study analyzed multiple factors regarding vaccine acceptance, rejection and hesitancy among drug allergy patients for the first time in literature. Our results show that informing patients with drug allergies thoroughly, answering questions about the side effects and effectiveness of the COVID-19 vaccines are crucial in order to overcome vaccine hesitancy. Similar studies with larger samples and involving multiple centers can also contribute to the literature in the future.

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Conflict of interest

The authors have no competing interests to disclose.

Data availability statement

The authors confirm that the datasets for this article are included within the article, raw data that for our study is available from the corresponding author, upon request.

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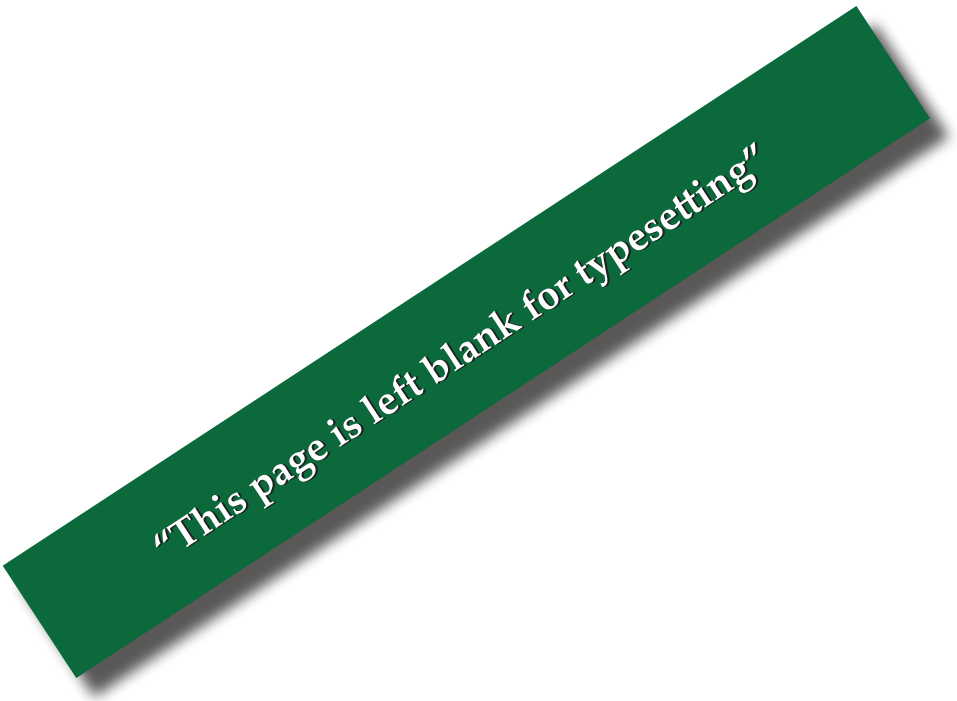
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ORIGINAL ARTICLE

Sultan Mahmud II's diseases and cause of death from the perspective of medical doctor's and current medical literature

Hasan Sultanoğlu[1,2] **İbrahim Topçu**[3] **Raşit Gündoğdu**[4] **Zeynep Salman**[2]

[1] Department of Emergency Medicine, Faculty of Medicine, Düzce University. Düzce / Türkiye
[2] Department of History of Medicine and Ethics, Institute of Hamidiye Health Sciences, University of Health Sciences. İstanbul / Türkiye
[3] Department of History of Medicine and Ethics, Hamidiye Medical Faculty, University of Health Sciences. İstanbul / Türkiye
[4] Department of Social Service and Consultancy, Hamidiye Health Services Vocational School, University of Health Sciences. İstanbul / Türkiye

Abstract

The illness of Sultan Mahmud II, the 30th Sultan of the Ottoman Empire and the 109th Islamic Caliph, started to be discussed after his death. In this study, the possible illnesses of Sultan Mahmud II, his illness process and death were analysed by comparing the claims and explanations made by his physicians during his illness and death. The research includes: the incomplete document of Abdülhak Molla, the chief physician of the period; the book titled Deux Annees de l'Histoire d'Orient 1839-1840 (Two Years in the East 1839-1840) written by Edmond De Cadalvene and Emile Barrault; the book titled Relation Officielle de la Maladie et de la Mort du Sultan Mahmud II (Sultan Mahmud II's Illness and Death) by Mac Carthy and Konstantin Kara Todori. The Illness and Death of Sultan Mahmud II), published in 1841; and, three reports sent by Karl Ambros Bernard to the Austrian government on different dates based on Jakob Neuner. In the light of current medical knowledge, the above-mentioned information and documents about the sultan's illness suggest that Sultan Mahmud II suffered from "lung cancer" and "alcohol withdrawal syndrome". It was concluded that his death was due to sepsis developing as a result of the infection caused by the disease and the deterioration of metabolite balances in the body.

Keywords: Sultan Mahmud II, lung cancer, alcohol withdrawal syndrome

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Corresponding Author:
Hasan Sultanoğlu
Email: drsultanoglu@hotmail.com

Introduction

A Brief Description of Sultan Mahmud II Period

Sultan Mahmud II was the son of Sultan Abdulhamid I and Nakş-i Dil Vâlide Sultan, born on 13 Ramadan 1191/20 July 1785 [1]. Mahmud II, who was only four years old when his father Sultan Abdulhamid I died, was raised by Sultan Selim III. Selim III, during the fourteen-month reign of Mustafa IV, had frequent contact with Mahmud II and had sufficiently instilled everything he had to do when he ascended the throne and adopted his ideas on state administration. Therefore, Sultan Mahmud II learnt the necessary lesson from Selim III's weaknesses and tried not to make the same mistakes [2].

Mahmud II, the 30th Ottoman sultan and 109th Islamic Caliph, ascended the throne during the most troubled years of Ottoman history in terms of political, military and social aspects [3]. His reign, which began on July-28 1808, lasted 31 years without interruption until July-1 1839. In the first years of his reign, he experienced very bloody and intense events in a short period of time. After the Kabakçı Mustafa Rebellion of May-28 1807, which resulted in the dethronement of Sultan Selim III and his replacement by Mustafa IV, Alemdar Mustafa Pasha, the Ayan of Ruse, who came to Istanbul and stormed the palace with his troops and witnessed the murder of Selim III, suppressed the rebellion and brought Prince Mahmud to the throne, but Kabakçı was killed in the janissary revolt that took place a while later [4].

During this period, the Ottoman Empire had already entered a period of rapid decline. While the state was deteriorating financially and economically, factors such as the weakening of the state organisation, the lack of self-renewal in the army and educational institutions, and the lack of transportation and communication facilities were the main reasons that accelerated this process. The problems awaiting Sultan Mahmud II were not only the internal social collapse of the state and the corruption of its institutions. The 1789 French Revolution and the nationalist movements that started to spread in the Ottoman Empire were also major external problems that gradually caused rebellions in the Ottoman Empire and shook the structure of the state [5].

Sultan Mahmud II was an intelligent, capable and prudent ruler who was well-informed of the period. He came to the conclusion that it was necessary to keep up with the period for the maintenance of the Ottoman Empire and that the solution to the problems was to change the structure of the classical period. With the reforms he carried out during his reign, which lasted for about 31 years, he extended the life of the state and enabled it to enter a new era. Mahmud II made changes in almost all institutions of the so-called classical period. Before he embarked on these reforms, he neutralised the elements that could oppose him, namely the ayyān, ulemā and janissaries. Firstly, he broke the political and military power of the ayyān, then he abolished the Janissary Corps in 1826. In the same year, by establishing the Ministry of Evkaf-ı Hümayun and gradually centralising the foundations under this roof, he tied the ulema, the third of the opposition pillars, to the state a little more. It can be said that the process of removing the obstacles to reforms continued until the early 1830s [4]. After creating the infrastructure, he abolished the Janissary Quarry, conducted the first census in 1831 to determine the military potential of the Asāqir-i Mansure-i Muhammadiyya, which was established in its place, and then carried out an estate census to determine the tax opportunities of the country. In the same year, Takvîm-i Vekāyi', the first Turkish newspaper published in Istanbul, was published. From 1834 onwards, he re-established permanent embassies in the capitals of major European states [6]. In order to prevent the spread of infectious diseases, he adopted the quarantine procedure to be applied throughout the country. He took initiatives for a modern postal system and built a postal route from Üsküdar to İzmit. He introduced the passport procedure. He sent students to Europe to train specialists in various fields. He opened the schools of Medicine and Military. The ministries were transformed and new ministries were established.

Mahmud II completely transformed the classical Ottoman system. What was done in the Tanzimat period is related to the details of his reforms. Therefore, if one has to speak of a Tanzimat period, the beginning of this period is not November-3 1839, but the reign of Mahmud II [4]. Sultan Mahmud II, who turned the face of the Ottoman Empire towards the West with the reforms he made during his difficult reign, was exhausted by the troubles he experienced during his 31 years of military and politically turbulent and exhausting reign, and his ailments, which gradually emerged, increased even more towards the end of his life.

Materials and Methods

The research utilised the incomplete document of Abdülhak Molla, the physician of the period; the book Deux Annees de l'Histoire d'Orient 1839-1840 (Two Years in the East 1839-1840) co-authored by Edmond De Cadalvene and Emile Barrault; Mac Carthy and Konstantin Kara Todori's Relation Officielle de la Maladie et de la Mort du Sultan Mahmud II (The Illness and Death of Sultan Mahmud II) published in 1841; and, three reports sent by Karl Ambros Bernard to the Austrian government on different dates based on Jakob Neuner. After the sources were obtained, the events were categorised according to time and place. After the analysis, the data were evaluated in light of current medical knowledge.

Findings

Opinions of the Physicians of the Period about the Sultan's Diseases

In this study, the possible diseases of Sultan Mahmud II, the disease process and the death of Mahmud II will be discussed and analysed by comparing the claims and explanations made by his physicians during his illness and death. The thoughts, claims and determinations of the Sultan's physicians and other physicians who were consulted from time to time will be evaluated from the perspective of current medical knowledge and physicians.

During Sultan Mahmud II's illness, different diagnoses and treatments were proposed, and there were even mutual accusations between the physicians who treated him. The first of these is revealed in the book titled Deux Annees de l'Histoire d'Orient 1839-1840 (Two Years in the East 1839-1840) written by Edmond De Cadalvene and Emile Barrault [7]. Mac Carthy and Konstantin Kara Todori, the physicians they accused, did not delay in responding to these allegations and published a treatise entitled Relation Officielle de la Maladie et de la Mort du Sultan Mahmud II (The Illness and Death of Sultan Mahmud II) in Paris in 1841 [8]. Another document on the subject is the three reports sent to the Austrian government on different dates by an Austrian physician, Karl Ambros Bernard, based on Jakob Neuner. Finally, the incomplete report of Abdülhak Molla, the chief physician of the period, on Mahmud II's illness guides us. Physician Abdülhak Molla wrote a work titled Rûznâme on the course of Mahmud II's illness. However, due to the loss of this work, Abdülhak Molla's view on the subject has remained incomplete until today.

In order to evaluate the symptoms and diagnoses mentioned in the books and documents, it is necessary to start with Hekimbaşı Abdülhak Molla, who closely followed Sultan Mahmud II, especially in the last period, examined him and made the final decision on his treatment, rather than the aforementioned foreign physicians who evaluated the Sultan in a limited way and based only on consultation. In an incomplete report [9] written in the physician's own handwriting, there is brief information about the symptoms and the course of the disease. According to the document, the Sultan had been drinking for a long time, vomiting from time to time, and having diarrhoea to the point of weakness, but hiding these complaints by not telling anyone. When he stopped vomiting, he would fill his stomach with wine again. It is stated that he had inflammation in his lungs and a cough due to this inflammation, that the cough and inflammation started to bother the Sultan from December 1838 (Shawwal 1254) onwards, and that the Sultan stopped drinking for a while because the cough increased in intensity as he drank. Although the sultan drank raw milk for a few days on the advice of those who said that milk would cure his illness, milk consumption

exacerbated his diarrhoea. During this time, he concealed the fact that he had both diarrhoea and bleeding haemorrhoids. In response, Konstantin of Edirne, one of the palace physicians brought in, first stopped the milk and then alleviated his cough with the medication he gave. After ten days of abstinence, the Sultan's appetite was completely lost. The Sultan started drinking again. On the other hand, as a result of the diarrhoea exacerbated by the milk, the Sultan's weakness increased and a white layer formed on his tongue. In the meantime, pus started to come out with the cough, which proves the previous assumption that there was a wound in the lung. After February 1839 (Dhu'l-Hijjah 1254), he stopped drinking again out of necessity and his weakness increased. Abdülhak Molla became chief physician on May-15 1839. He examined the Sultan and observed extreme weakness, exhaustion, loss of appetite, increasing whiteness of the tongue, abdominal fever, pain in the liver and stomach, fever, mild malaria, cough and purulent sputum. Meanwhile, the Sultan hid the fact that he had bloody haemorrhoids even from the physician. Abdülhak Molla gave the patient linseed paste to suppress the bad odour coming from the stomach. He also stimulated his appetite by giving him a certain amount of alcohol in the morning, noon and evening. The Sultan travelled from the palace to Çamlıca in bad and rainy weather. Therefore, his cold recurred, his cough and fever increased. That night, loss of appetite, pus and bloody haemorrhoids increased and the next day he fainted three times. He fell ill in the mosque where he went for the Friday Greeting (the term used in the Ottomans for the Sultan to pray the Friday prayers in a public mosque and the ceremonies held in the meantime). He was taken to Çamlıca and stayed in bed for a day. The following Friday, the Sultan became heavier and was unable to pray. Thereupon, a minbar and a mihrab are placed in the courtyard of the mansion in Çamlıca, and although he tried to perform the Friday prayer, he was unsuccessful. In Abdülhak Molla's words, he "became an angel" and no more water passed down his throat [9]. The document ended here before it was completed (Figure 1).

We learn about Dr Neuner's evaluations and findings about the Sultan's illness from the three reports Dr Bernard sent to the Austrian government. The last report, dated July-28, contains Dr Bernard's assessments of the illness discussed in a meeting with the physician Abdülhak Molla after the Sultan's death. Since the physician's evaluations in this last report are in harmony with his own report discussed above, they are mentioned in this section. According to the physician's statement, Sultan Mahmud II had been ill for a longer time than was known. The disease made itself felt gradually in the last three years of his life, but the critical period the state was going through and the extremely serious political events did not leave the Sultan any time to take care of his illness. Although the Sultan had been suffering from frequent relapses of his illness for three years, it was not possible to wean him from his habitual behaviour. He continued to drink strong liquor irregularly and this played a major role in the relapse of his illness. His drinking habit increased to such an extent that he drank rum, arak and then champagne in the morning. This was repeated three or four times a day. The Sultan denied that he was ill and did not follow the methods and diet recommended for the treatment of the disease. Those around him did not dare to advise him on this matter, which became a fixed opinion [10].

The first of Dr Bernard's reports to the Austrian government is dated June-19. His report begins with the findings that, contrary to the decisions taken in the previous consultation, the physician had tried to treat the Sultan with aromatic herbs using his own authority; that this had impaired the patient's health, that the Sultan continued to drink wine as before, and that those around him did not tell him that he should give up such habits, which were bad for his illness, and that he should follow the diet prescribed. At the consultation held on June-18 at 10 am, the palace physicians, Hekimbaşı Abdülhak Molla, Mac Carthy, Neuner, Konstantin Kara Todori, Stefanaki and Mahmud Efendi attended. The patient's symptoms included high fever, an uncomfortable cough, insomnia due to coughing, and weakness. According to Dr Neuner, the disease was tuberculosis in the second stage. However, he does not despair of the Sultan's

condition if he followed the prescribed diet. He recommended taravacum (a medicine obtained by boiling snails with wild chicory), myosciax [a pill containing henbane (bilsenkraut) extract], an herbal diet to alleviate the cough, and mineral water to be brought from Vienna to reduce the fever. The second report is dated June-22. At the ninth consultation, held at 11 a.m. on Friday June-21, the same physicians attended. In the past three days, the Sultan's condition did not change much. The symptoms of the disease were loss of appetite, vomiting, severe cough with bloody phlegm, insomnia, constipation, high pulse rate (120 per minute), high fever, bitterness in the mouth, lentil-sized white blisters on the tongue and redness in the urine. Despite this condition and all the insistence of the physicians and those around him, the Sultan could not be prevented from going to the Üsküdar Mosque for Friday Greetings [10].

According to the claims of Ed. de Cadalvene and E. Barrault in their works on the controversy surrounding illness, Mahmud II needed medical consultation only twice until the last two years of his life: once in 1828 when he suffered from a severe cold and once in 1837 when he had leeches applied to him for *lumbago* (low back pain). Allegedly, after the abolition of the janissary corps, the Sultan gave himself over to wine. In time, this became a habit and lasted for about ten years until his death. In the last year of his life, the Sultan, who drank every evening, complained of weakness, stomach pain, insomnia and nervous exhaustion. From the winter of 1839 onwards, a cough was added to these. On March-8 1839, a serious attack of coughing occurred and Konstantin Kara Todori was summoned. Kara Todori reported that the Sultan was fine and had a cold. As the complaints continued, Dr Neuner was brought from Austria. In the meantime, it was discovered by chance that he had bloody haemorrhoids, but the Sultan denied it. Anxious, Kara Todori asked for a consultation with the participation of other physicians. Those around him concealed the true nature of the disease from the Sultan. The Greek doctors suggested that the disease was a stubborn pneumonia, and in order to cure it, they boiled flax seeds and make the Sultan drink the water. Then, in April, they started to give milk to the Sultan. These last two medicines disrupted the patient's digestive system and after a while, this treatment was abandoned. Abdülhak Molla, who was of the opinion that it was not right to suddenly cut off the need of the body accustomed to alcohol, defended the idea of giving alcohol to the Sultan in low doses. Although the Greek doctors were against this method of treatment, they did not raise a voice against it. According to the statements of Abdülhak Molla, Ed. de Cadalvene and E. Barrault, as a result of the treatments of "Greek physicians who were half doctors", towards the end of April the patient became more and more severe. In addition to his extreme weakness, the Sultan's behaviour, tastes and habits began to change. He refused his favourite foods and even alcohol. He often daydreamed and sometimes stared at one point for a long time. From time to time, he became too active to sit still and spoke by jumping from topic to topic. He even took a horse ride on the day of an important government meeting. In addition, the Sultan had a clouded mind [11].

Meanwhile, rumours spread that the Sultan had liver weakness and hepatitis. Excessive weakness demoralised his morale, which rose from time to time. On the other hand, bloody haemorrhoids, which continued for 11 days, caused him to lose blood and made him feel weak. On June-14, Dr Neuner attended the consultation. The Sultan was seriously agitated, his pulse was weak and his tongue was covered with yellow rust. There was also loss of appetite, digestive and intestinal disorders and constipation. Dr Neuner diagnosed the patient with stage three *phthysis tuberculosa* (pulmonary tuberculosis). According to him, the patient, who had only a short time to live, could be given emollients (*mucilagineux*) and tranquillisers. At the physician's request, the Sultan was taken to Çamlıca, where the air was fresh. On June-16, Mac Carthy and Ansaldi attended the consultation. These physicians state that the lungs were not as bad as Dr Neuner had thought. On June-21, the patient deteriorated. Despite this and the opposition of those around him, he wanted to attend the Friday Greeting. He rebuked those who wanted to oppose him and then collapsed on the ground because of using all

his strength on this occasion. Even in this state, he went to the Valide Mosque in Üsküdar for the Greeting. On June-23, the fifth consultation was held. On the other hand, Esma Sultan, worried about her brother, sent Julius Michael Millingen, a doctor she trusted, to the palace. On June-27, the sixth consultation was held with the participation of Millingen. Although the Sultan was in a very ill state, he wanted to read and dictate the writings on state affairs himself. However, his answers were not very healthy. While the other doctors were kept waiting in a nearby room, Millingen was taken to the Sultan's room. The patient's lips were dry, the edges of his tongue were red and there was a layer of rust that gradually turns yellow towards the centre. His teeth were also covered with a black layer of soot. The Sultan, whose face showed traces of drunkenness, responded to questions with a blank stare. On Friday, June-28, at about eight o'clock in the morning, it was thought that the Sultan was dead. Millingen was called in again. According to him, there was not much to be done for the Sultan, who was suffering from *delirium tremens* or *erethismus ebriosorum*, a disease caused by excessive use of alcoholic beverages and which causes confusion in the mental faculties. The only thing to do in this case was to alleviate the suffering of the patient. For this reason, he recommended that the Sultan be given the liquid boiled with two parts of valerian and sixty drops of laudanum in two ounces (58 ml) of water every half hour. After drinking half of this liquid, the Sultan, who could not sleep for five days, relaxed and fell into a deep sleep. The Sultan woke up after three hours and felt good. He sat for about an hour, smoked two cigarettes and ate. That night, instead of medication, the patient was given a mixture of linden, orange blossom and thirty drops of laudanum twice. The fever subsided and his pulse became a little more regular. At the Sultan's request, he was given some laxatives, but this was not effective. On Sunday morning, June-30, the effect of the medication waned and the patient began to lose strength. Thereupon, Millingen told Rıza Beg that it was a miracle that the Sultan lived for another twenty-four hours, and Hüsrev and Halil Pashas that if some measures were to be taken for the possible disturbances that might arise upon the death of the Sultan, the time came (Figure 1) [11].

Mac Carthy and Kara Todori wrote a book to clear up the desecration of the Sultan's memory by Ed. de Cadalvene and E. Barrault. Their criticism is based on the diagnosis of delirium tremens. Mac Carthy and Kara Todori argue against this diagnosis, citing the works of the claimants themselves and the reforms made by the Sultan as evidence. Cadalvene and Barrault state in the second volume of their work (p. 62) that the Sultan was an accomplished calligrapher. However, those who suffer from the disease in question cannot engage in the art of calligraphy as their hands would tremble. Therefore, these findings contradict the diagnosis of delirium tremens. On the other hand, another important argument of Mac Carthy and Kara Todori was the reforms made by the Sultan. Because a Sultan who made such important reforms as mentioned above could not have been mentally ill. According to Mac Carthy and Kara Todori, the Sultan suffered from well-known dropsy (goutteuse). He also suffered from a sharp rheumatism in 1835, which they treated themselves. Another ailment was that the Sultan could not lie on his right shoulder. In the illness that was the subject of the discussion, the Sultan suffered from loss of appetite, nausea, vomiting and coughing. The Sultan also suffered from haemorrhoids, for which Kara Todori prescribed leech treatment. The Sultan did not follow the physicians' advice to rest and did not accept his illness. This tied the hands of the physicians. On June-16, the Sultan went to the dykes in Bahçeköy and fainted several times. The next day, Mac Carthy, Etienne Kara Todori (Konstantin Kara Todori's uncle) and Mahmud Efendi consulted the Sultan. The consultation reveals that the Sultan was mentally sound and engaged in the affairs of the cabinet. On June-21, on the Friday before his death, he ignored the warnings given to him not to attend the Greeting ceremony and to pray in his room [12].

Mac Carthy and Kara Todori testified that the patient was suffering from digestive distress at the last examinations. At the consultation on June-23, it was diagnosed that the disease was progressing rapidly and the Sultan

had only a short time to live. On 25 June, another consultation was held. On June-27, a surgeon named Monsieur Millingen attended the consultation. The Sultan's doctors gave him all the data they had and information about the diagnosis and treatment methods. Millingen entered with Neuner and Mac Carthy (Cadalvene states that Millingen examined the patient alone). After a long examination, Millingen stated that the patient was not in such a dangerous and bad condition as described to him, that the disease was a simple liver burn and stomach pain, and that he could recover in a few days with a light diet. He prescribed a stomach relaxant and flaxseed poultice as medicine. These explanations caused happiness in the palace. Thereupon, all physicians except Kara Todori were sent home, with the condition to meet again on Saturday June-29. Millingen suddenly became the favourite of the palace and the Sultan's saviour. He was asked to come back the following day. On the night of June-28 Friday, the patient's palpitations intensified and his discomfort increased. Kara Todori observed that the Sultan's face was white, his tongue was black as coal, and his skin was cold even though there was a fever inside, and informed the chamberlain. Millingen was summoned again. Millingen said that the patient had *delirium tremens* and that he should be given some opium. Thus, the disease he had diagnosed as a simple stomach and liver disorder turned into *delirium tremens* in one night. He recommended two moxibustions for the legs and *laudanum* for internal use. After drinking the opium liquid, the patient fell into a deep sleep. Stating that the patient would wake up completely cured, Millingen went further and suggested that the physicians be sent home. On Saturday morning, June-29, Monsieur Millingen and Kara Todori visited the patient. When Kara Todori tried to dress the moxibustion, the Sultan was hurt and expressed "Konstantin, you are hurting me". This is the reaction of a patient diagnosed with delirium tremens 48 hours before his death. In other words, the Sultan recognised people and addressed them by their names. After that day, no doctor examined the Sultan. Until the last minutes, the dose of opium water recommended by Millingen was increased and given to the Sultan. Millingen continued to assure the chamberlain that the patient would recover. However, when he arrived at the palace on Monday morning, July-1 1839, he did not see much activity. He heard sad weeping sounds accompanying the voice of the imam: Sultan Mahmud passed away (Table 1) [12].

In the book written by Kara Todori and Mac Carthy, in his last four days, the Sultan had symptoms such as redness of the face, intense fever, rapid pulse (140 beats per minute), headache, severe pain in the liver and abdomen, bloody cough, haemorrhagic discharge, dirty and bloody urine and fear of light. The patient was not delirious and did not tremble in his hands. Kara Todori and Mac Carthy conclude from these data that there were no symptoms of delirium tremens. Kara Todori and Mac Carthy state that although they had been the Sultan's physicians for several years, their role in the field of illness was no more than a bystander and that they had been relegated to a secondary role. Chief Physician Abdülhak Molla and Dr Neuner also receive their share of criticism. According to their claims, if the recommendations they had submitted to the physician had been fulfilled day by day, at least the progression of the disease could have been stopped. On the other hand, they were of the opinion that Neuner had diagnosed third-degree pulmonary tuberculosis (*phthisis tuberculosa*) based on pathological findings such as blood coming from the mouth and nausea, and that this diagnosis was insufficient [12].

Discussion

In this section, the symptoms, complaints and habits that caused Sultan Mahmud II's illness in his last period, as written in books, mentioned in documents and described in the report, are evaluated. Firstly, we will start with the report of Dr Bernard dated July-28 1839 about the illness of Sultan Mahmud II during his meeting with Chief Physician Abdülhak Molla after the Sultan's death and the information in the incomplete document written by Chief Physician Abdülhak Molla. The report mentions that Sultan Mahmud II had been suffering from frequent relapses of the disease for three years, that he had consumed too much alcohol in recent years, and that he did not follow the diet. This

situation shows that the Sultan's illness was not acute, but that he was suffering from a chronic disease. Increasing his alcohol consumption, smoking and not following the diet caused his illness to worsen. The acute onset of the disease and the presence of triggering factors suggest a "rapidly progressing lung cancer".

Today, the reasons that increase the risk of lung cancer include advancing age, heavy smoking history, nutritional disorders, family history and genetic factors [13]. It is thought that Sultan Mahmud II's history of smoking and not paying attention to his diet (excessive drinking) prepared the ground for cancer. Lung cancer incidence and mortality rates increased markedly during most of the 20th century, first in men and then in women [14]. The overall 5-year relative survival rate for lung cancer is 25.4% despite treatment. Lung cancer survival is lower in men compared to women [15]. 5-year survival rate is low despite current treatment protocols. In the 19th

Table 1. Sultan Mahmud II's consultations and findings according to sources.

Source	Consultation and/or Examination Dates	Findings/Events	Consultant Physician/s
Incomplete document of Hekimbaşı Abdülhak Molla	December 1838 (Shawwal 1254)	The Sultan's cough increases	Abdülhak Molla
	10 days after December 1838 (Shawwal 1254)	Increased diarrhoea, haemorrhoidal bleeding and loss of appetite	Konstantin of Edirne
	February 1839 (Dhu al-Hijjah 1254)	Extreme weakness, exhaustion, loss of appetite, white tongue, pain in the liver and stomach, fever, cough and purulent sputum	Abdülhak Molla
	May 1839 (Rabi al-Awwal 1255)	Abdülhak Molla becoming the chief physician	
Dr Bernard's three reports to the Austrian government	18 June 1839	High fever, irritating cough, cough-related insomnia and weakness	Chief Physician Abdülhak Molla, Mac Carthy, Neuner, Konstantin Kara Todori, Stefanaki and Mahmud Efendi
	21 June 1839	Vomiting, severe cough with bloody sputum, associated insomnia, constipation, tachycardia, high fever, white blisters on the tongue and haematuria	Chief Physician Abdülhak Molla, Mac Carthy, Neuner, Konstantin Kara Todori, Stefanaki and Mahmud Efendi
	28 July 1839	Dr Bernard's interview with the Chief Physician Abdülhak Molla about the disease after the Sultan's death	
Deux Annees de l'Histoire d'Orient 1839-1840, written jointly by Ed. de Cadalvene and E. Barrault	1828	Severe influenza	-
	1837	Lumbago	-
	8 March 1839	Severe cough	Kara Todori
	14 June 1839	Bradycardia, discolouration of the tongue, loss of appetite, digestive disorders and constipation	Neuner
	16 June 1839	Deterioration in the patient's condition	Mac Carthy and Ansaldi
	23 June 1839	No changes in the patient's condition	Chief Physician Abdülhak Molla, Mac Carthy, Neuner, Konstantin Kara Todori
	27 June 1839	Millingen joins the consultation at the request of Esma Sultan	
	28 June 1839	The sultan is presumed dead and falls into a coma.	
	30 June 1839	Millingen gives the Sultan 24 hours to live	
Mac Carthy and Kara Todori's book	1835	Gout diagnosis	Mac Carthy and Kara Todori
	16 June 1839	Syncope	Mac Carthy, Etienne Kara Todori and Mahmud Efendi
	23 June 1839	Digestive distress	Mac Carthy and Kara Todori
	25 June 1839	Deterioration in the patient's condition	
	27 June 1839	Mac Carthy and Kara Todori are accompanied by Millingen	
	28 June 1839	Comatose state, Millingen diagnoses "delirium tremens"	
	1 July 1839	Sultan Mahmud passed away	

century, the survival rate was probably lower than today's conditions. In the report sent by Dr Bernard to the Austrian government, the fact that he stated in his interview with Chief Physician Abdülhak Molla that his disease had recurred in the last three years supports the diagnosis. Lung cancer patients show symptoms such as cough (75%), weight loss (68%), shortness of breath (60%), chest pain (49%), haemoptysis (bloody cough 35%), fever (20%), bone pain, vena cava superior syndrome (flushing of the face due to vascular compression), weakness, difficulty in swallowing [16]. The fact that Sultan Mahmud II showed symptoms such as cough, weight loss, body aches, intense fever and redness of the face in his last periods supports our opinion about the disease. Some of the cancer patients have problems with blood production. Anaemia is the most common. The change in the colour of the Sultan's tongue and his pale appearance in the following periods may be due to anaemia.

Cancer disease weakens the immune system, metastasises to other parts of the body (cancer spreading to other tissues) and predisposes to many diseases, especially infections. Neuner's diagnosis of pulmonary tuberculosis may have been due to a weakened immune system. The fact that he was said to be suffering from hepatitis and that haemorrhage from haemorrhoids occasionally became active suggests the possibility of metastasis to the liver, which produces bleeding factors. Bloody urination may also occur in renal failure or renal metastasis due to low fluid consumption, primarily in cancer patients.

As for Millingen's claim that the patient had *delirium tremens*, this claim does not meet current medical diagnostic criteria. However, alcohol withdrawal syndrome (AWS) does explain Sultan Mahmud II's experiences at the time. Chronic alcohol use can result in alcohol use disorder (AUD) and approximately 50 per cent of people with AUD may experience AWS when they reduce or stop alcohol consumption [17]. In addition, changing the drink and not being able to adjust the dose in the new drink may also lead to the emergence of withdrawal symptoms. Convulsions and *delirium tremens* (DT), which are life-threatening complications, may occur in 3-5% of those who develop AWS [18]. Withdrawal symptoms are likely to occur if alcohol is abruptly discontinued after prolonged use of alcohol in large quantities (more than two weeks). Depending on individual differences, withdrawal symptoms begin 6 to 24 hours after the last alcohol intake.

Alcohol withdrawal affects the central nervous system, autonomic nervous system and cognitive functions [18]. After reduction or cessation of alcohol use, it is considered that the development of AWS occurs if two of the following symptoms are present: Autonomic hyperactivity (sweating, tachycardia); increased hand tremor, insomnia, nausea or vomiting, transient visual, tactile, auditory hallucinations or illusions; psychomotor agitation, anxiety, or tonic-clonic seizures. If AWS is not treated or not treated appropriately, DT may occur [18]. In the light of the above information, it can be concluded that Sultan Mahmud II did not have DT based on the findings stated in the documents and sources.

Conclusion

In the light of current medical knowledge, the above-mentioned information and documents about the sultan's illness suggest that Sultan Mahmud II suffered from "*lung cancer*" and "*alcohol withdrawal syndrome*". The fact that he showed problems in various parts of his body suggests that the disease had metastasised, and the deterioration of the Sultan in the last three years is consistent with the survival rate of lung cancer. Sepsis developing as a result of infection caused by this disease and deterioration of metabolite balances in the body can also be considered as the cause of death.

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Conflict of interest

The authors have no conflicts of interest to report.

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Appendices

Incomplete Report of Chief Physician Abdulhak Molla on II. Mahmud's Illness

(Transcript of Assoc. Dr. Raşit GÜNDOĞDU)

Sultân Mahmûd'un zuhûr ve iştidâd-ı marazına dâ'ir Hekîmbaşı Abdülhak Efendi'nin hatt-ı destiyle muharrer nâ-tamâm makâledir.

(Mizâc-ı Velîni'met Mahmûd Han Efendimiz)

"Hayli müddet îş ü işret ile me'lûf olup sûi'l-kınye gibi hâzim-i hazm (هظم حضم) ve aralık aralık kay dahi vâki' olmuş iken ketm ederek takarrür etmiş ve kay' vâki' olup nûş olunan ervâh mi'deden çıkarıldığı an yine rûh ve ba'dehû hamr ile mi'de imlâ olunup yine kay gelirse minvâl-i mezkûr üzere yine nûş olunarak hazm za'îf olup ri'ede dahi hafîfce bir iltihâb ile suâl olmuş idi. Bu kalîlü'l-bizâ'a hekîmbaşılıktan azlolunup nâ-halef birisi hekîmbaşı olmuş ise de mizâc-ı şâhâneye aslâ müdâhale etmeyip resmî hekîmbaşı olmuş ve iki yüz elli dört senesi Şevvâl-i şerîfinde yine iltihâb-ı ri'e ile bir öksürük vâki' olup ziyade iz'âc ve işret olundukça öksürük dahi müştedd olup çâr ü nâ-çâr işret külliyen terk olunmuş ve yirmisine kadar ilâc olunmayıp ketm olunmuş ise de bazıları "süt içmek nâfi'dir" deyu ta'rîf etmeleriyle birkaç gün ham süt isti'mâl olunup çend gün sonra süt tezyîd olunup basura dokunmuş olmağla amel verip on gün kadar amel müştedd olarak kan dahi gelmiş ise de ketm olunup Sarây-ı Hümâyûna memûr Edirneli Kostantin celb ve mu'âleceye şurû' olunmuş sütü kat' edip birkaç gün mu'âlece olunarak öksürüğe hiffet gelmiş on gün

kadar perhîz olunup iştihâ külliyen sâkıt olmağla arak nûş olmayarak işrete mübâşeret olunmuş yine evvelki usûl üzere muâmele olunarak ilâcdan kesilip iştihâ munkatı‘ olarak işrete devam olunmuş, sütten olan ishâl mümtedd olup küllî za‘f gelmiş ve derecesiz iştihâ kat‘ olup lisana pas ve öksürük dahi irin ile beraber olup ri’ede yara olmak ihtimâli isbât olmuş, bu hal ile Zilhicceden sonra yine işret kat‘ olunup za‘f ziyâde olmakta olarak Muharrem ve Safer geçip Rebîülevvelde hekîmbaşı olmak nasip oldu. Efendimizi gördüğümde ziyade hüzâl gelip dilinde ziyâde pas ve iştihâ kat‘ olunmuş ve karnında harâret ve karaciğerde salâbet ve veca‘ ve mi‘dede veca‘ ve hummâ-yı dıkiyye (حمای دقیه) ile hafifçe sıtma ve öksürük ve balgam ile beraber kıh var idi. Demli basur dahi olduğu sonradan keşfolunmayıp mektûm imiş. Mi‘dede olan ufûnet-i redîe def‘ olunmak içün keten tohumu lu‘âbı verilip onuncu günü sekiz dirhem bâde ale’s-sabah ve on iki dirhem bâde öylede on sekiz dirhem bâde ahşamda verilip mi‘denin za‘fı bununla def‘ olup oldukça iştihâ gelmiş idi. Ancak tabîb olacak hâin bâdenin kesreti olur da yine evvelki gibi olup deyü men‘ etmişler. Muhâlefet edemeyip gizlice “Hekîmbaşı Efendi bak ne diyor” diye etrafa işâ‘a edip bâdeden istikrâh ettim. “İçemem” buyurdular, gerçek zanneyledim. Her ne hal ise birkaç gün içilip mi‘de yoluna girmiş olmağla tabîb “işte ufûnet gitti, hemen perhîz olmak lâzımdır” deyip birkaç gün bu hal üzere gidip çubuk içmek niyet olunmağla Çamlıca’ya nakle karar verildi idi. Nakl-i hümâyûn olup mizâc-ı şâhâne oldukça yolunda iken Kapudan Paşanın hareket edeceği musammem ve zâiçesi dahi yapılmış olmağla hava be-gâyet bozuk ve yağmurlu ve bayağı kış havası gibi iken sefîneye gitmeğe niyet ettiler. Her ne hal ise men‘ olunup gemi vakt-i muhtârda hareket edip ol gün Sâliha Sultan haz-retleri dahi nâ-mizâc olmağla beni istifsâr-ı hâtır içün irsâl ettiler. Ben Sâliha Sultanda iken hemen mâbeyn-i hümâyûndan hareket buyurup ol murdâr havada zevrak-süvâr olarak teşrîf etmişler. Ben dahi Sâliha Sultandan hareket ve Nâfiz Paşa hazretlerini ziyârete gidip Müneccimbaşı Efendi’yi Nafiz Paşa’da bulup “gemi hareket etti, ancak ba’de’l-hareke efendimiz teşrîf etti” dedi. Her ne kadar münâsib değil ise de ne çâre teşrîf olunmuş, “Allah hayırlı eyleye” dedim. Hemen kahve içerken Mahmûdiye’den bir başka çifte kayık ile bir hademe gelip “Mahmûdiye’den taleb buyurdular” deyü Nâfiz Paşa’dan hareket edip sefîneye gittim idi. Gördüm ki hava fenâ teşrîf etmişler, ne çare hayrola deyip hayret el verdi. Sefineden sâat onda hareket olunup yağmur yağarak teşrîf ettiler. Ama nezle yeniden nüksedip öksürük ziyâde ve harâret gelip bayağı hasta oldular idi. Ol gece müştedd olup harâret ve lisânda pas, adem-i iştihâ ve öksürük ve balgam yerine yine irin gelip dem-i basur dahi ziyade olup yeniden evvelki za‘fın üzerine bir kat daha ziyâde oldu. Bir iki gün sabrolunup hamâma girdiler. Ertesi gün bu hal ile bend-i cedîde teşrîf olunup yolda iki defa bayılıp bir kere dahi bendde bayıldı. Ne hal ise avdet olunup bin belâ ile Çırağan’a teşrîf ve ondan sahil-saraya gelindi. İllet bir kat daha müştedd olup artık yatmağa başladılar. Ertesi gün Hüsrev Paşa hazretlerinin câmiine gitmek niyet olunup gitmek bir vechile câiz olmadığından bin belâ ile Kuleli Câmiine, ondan dahi bir hareket ile Çamlıca›ya teşrîf ettiler. Zira ertesi günü Tersâne’de gemi nüzûl olacak imiş. Ona dahi teşrîf ederek ertesi Çamlıca’ya çıkacak idi. Bir hareket-i Cuma ile Çamlıca’ya teşrîf olunup illet dahi ziyâde olmağla bir çare bulunmaz derecede iken ertesi Cuma günü câmie gidilip hemen ye’s-i tâmm geldi. Câmiden teşrîf olunup bir gün kadar sabrolunup döşekten çıkmadılar. Ertesi Cuma günü be-gâyet ağırlaşıp hemen hâlet-i nez‘ derecesine girip Cumayı kılmağa tâkat kalmayıp Çamlıca’da köşkün havlısına minber ve mihrâb vaz‘ olunup namazı edâ edemediler. Hemen melek hükmüne girip boğazından su dahi nüfûz etmeyip”

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ORIGINAL ARTICLE

Evaluation of the readability levels of patient information leaflets of frequently prescribed drugs in rheumatology practice

Adem Ertürk

Department of Internal Medical Science, Division of Rheumatology, Faculty of Medicine, Afyonkarahisar Health Sciences University. Afyonkarahisar / Türkiye

Abstract

The development and use of new drugs have accelerated in proportion tothe increase in understanding of the pathogenesis of rheumatological diseases. In the treatment of rheumatological diseases, regular and proper use of drugs prevents disease progression and protects the patient from potential exacerbations and complications. The readability of patient information leaflets (PILs) increases treatment compliance. In this study, it was aimed to evaluate the readability levels of PILs of frequently prescribed drugs in rheumatology practice. A total of 182 frequently prescribed medications in rheumatology practice were randomly selected. The PILs of these drugs were scored according to Ateşman and Bezirci-Yılmaz readability scales and their readability levels were thus determined. It was determined that the PILs could be read with 11-12 years of education and high school education on average according to Ateşman and Bezirci-Yılmaz readability scales respectively. Considering the fact that the mean schooling level in Türkiye is 6.5 years, the readability levels of the PILs of frequently prescribed medications in rheumatology practice are well above this level. It is suggested that the current readability of the PILs is adjusted in accordance with the patients' level of understanding and education and arrangements to increase the readability levels are made.

Keywords: Rheumatology, patient information leaflet, readability level

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Corresponding Author:
Adem Ertürk
Email: drademerturk@hotmail.com

Introduction

Rheumatological diseases are chronic inflammatory diseases that cause loss of function at different levels and decrease in quality of life and may increase morbidity and mortality. In the treatment of these diseases, the aim is to achieve an early and permanent reduction in disease activity and, if possible, remission [1,2]. Disease-modifying anti-rheumatic drugs (DMARD) form the basis of the treatment of rheumatological diseases. The introduction of biological (b) DMARD agents afterconventional synthetic DMARDs (csDMARDs) has started a new era in the treatment of inflammatory arthritis. bDAMRDs work through specific cytokines and pathways involved in the pathogenesis of diseases or through mechanisms directed against cellular targets. The efficacy and safety of many bDMARDs such as anti-TNF agents (adalimumab, etanercept, infliximab, golimumab, certolizumab), B-cell blockers (rituximab), T-cell blockers (abatacept), IL-6 blockers (tocilizumab), IL-17 blockers, IL-12 and IL-23 blockers, JAK-kinase inhibitors (tofacitinib, baricitinib) have been well demonstrated in rheumatological patients. Biosimilar agents of originator drugs have also started to be used after bDMARDs [3-7]. bDMARDs and biosimilar agents are important treatment options in resistant patients who cannot be treated with medications within the csDMARD category [5,8]. Anakinra and canakinumab are Interleukin-1 (IL-1) antagonist drugs for the treatment of autoinflammatory diseases such as Familial Mediterranean Fever (FMF) [9]. Used in systemic lupus erythematosus (SLE), belimumab is a monoclonal antibody against BLys that blocks B-cell growth factors [10]. Cyclophosphamide, azathioprine, mycophenolate mofetil and calcineurin inhibitors (cyclosporine, tacrolimus) are immunosuppressive drugs prescribed in many rheumatic diseases such as connective tissue diseases and vasculitis, especially in the presenceof life-threatening organ involvement [11]. Steroids can be used both as immunosuppressive and like DMARDs at low doses as in rheumatoid arthritis. Colchicine is still an effective and current medicationemployed in gout arthritis and FMF. Colchicine supplied from abroad may also be used before anti-IL-1 treatments when locally-supplied colchicine is insufficient or cannot be tolerated. Allopurinol and febuxostat, which are inhibitors of xanthine oxidase, are prescribedin gout arthritis as uric acid lowering drugs (ULD) that work by reducing uric acid synthesis [12]. Non-steroidal anti-inflammatory drugs (NSAIDs) are used in many diseases in rheumatology practice, especially in spondyloarthropathies. Although fibromyalgia is not an inflammatory rheumatological disease, it may be comorbid with rheumatic diseases, and patients with fibromyalgia can present to rheumatology outpatient clinics with complaints of pain, and rheumatologists can prescribe drugs for fibromyalgia. Osteoporosis may occur during the course of rheumatological diseases or develop due to the use of medications, and treatment of osteoporosis is also often included in rheumatology practice.

Some patients may be willing to learn the side effects, method of use, and dose of the drugs they are prescribed in detail from the patient information leaflets (PILs). Some other patients stop taking the medication or change the dose without informing the physician after theyhave read the PIL. PILs should thus be understandable by patients.

The degree of understandability of a written text by the reader is assessed based on the text's readability level [13]. Readability level of a written text is determined through the use of some scales whose power is demonstrated with scientific studies. These scales calculate the readability score by using parameters such as the number of sentences, words, and syllablesin the text. Ateşman and Bezirci-Yılmaz readability scales are often utilized for Turkish texts [14,15].

This study aims to measure the readability levels of PILs of frequently prescribedmedications in rheumatology practice and determine the age and education level to which these PILs are appropriate.

Materials and Methods

This study was carried out according to the decision of Afyonkarahisar Health Sciences University Clinical Research Ethics Committee dated 30.02.2023 and numbered 2023/74.

A total of 182 frequently prescribed drugs in rheumatology practice were randomly selected. The readability scores of the PILs of these drugs were calculated. These medications were divided into 8 groups: conventional synthetic DMARDs (csDMARDs), biologic DMARDs (bDMARDs), targeted synthetic DMARDs (tsDMARDs), immunosuppressive drugs, NSAIDs, FMF-gout arthritis drugs, fibromyalgia drugs, and osteoporosis drugs.The mean readability levels of these drug groups were evaluated within and among the groups.The readability levels of the PILs were measured based on the text that remained after the headings and authorization details at the end had been removed.

Many scales are utilized to determine the readability level of a text. These scales provide a mean score based on parameters such as the number of words, sentences, and letters in the text. In this study, the readability levels of the PILs of the relevant drugs were evaluated by using Ateşman and Bezirci-Yılmaz readability scales.

In Ateşman readability scale, the score is between 0 to 100. Scores closer to 100 are defined as easier to read while those toward 0 are more difficult to read. Ateşman readability score calculation formula: RS=198.825-(40.175 x X1)-(2.610 x X2)

RS: readability score

X1: Total syllable number/Total word number

X2: Total word number/Total sentence number

Table 1. Atesman readability scores and relevant required education level.

Readability Score	**Education Level**
90–100	Can be read by a person with education up to the 4th grade of primary school.
80–89	Can be read by a person with education at the 5th or 6th-grade level.
70–79	Can be read by a person with education at the 7th or 8th-grade level.
60–69	Can be read by a person with education at the 9th or 10th-grade level.
50–59.	Can be read by a person with education at the 11th or 12th-grade level.
40–49	Can be read by a person with education at the 13th or 15th-grade level.
30–39	Can be read by a person with education at the undergraduate level.
≤29	Can be read by a person with education at the graduate level

Table 1 shows Ateşman readability scores and relevant required education level.

On the other hand, Bezirci-Yılmaz readability scaleconsiders a text difficult to read as the readability score increases while texts receiving lower scores are deemed easier to read. Bezirci-Yılmaz readability score calculation formula:

RS= √OKS x ((H3 x 0,84) +(H4x1,5) + (H5x3,5) + (H6x26,25))

RS: readability score

OKS: mean word number

H3: mean 3-syllable word number

H4: mean 4-syllable word number

H5:mean 5-syllable word number

H6: mean +6-syllable word number

Table 2 shows Bezirci-Yılmaz readability scores and relevant required education level.

The software developed by Bezirci-Yılmaz was utilized to calculate readability scores with the formulas.

Statistical Analysis

Categorical variables were presented as percentage and frequency. Continuous variables were provided as mean and standard deviation. ANOVA test was used to compare continuous variables between groups. Statistical analyses were performed with SPSS 26.0 package program. All *p* values were two-sided and values with $p<0.05$ were considered statistically significant.

Results

A total of 182 PILs were used in the study. The mean readability score of these PILs was58.42±7.62 according to Ateşman readability scale. On average, these PILs require 11-12 years of education. The score was 9.95±2.52 when calculated with Bezirci-Yılmaz readability scale. The corresponding education level is the secondary school (high school) (Table-3).

Table 2. Bezirci-Yılmaz readability scores and relevant required education level.

Readability Score	**Education Level**
1-8	Primary school
9-12	Secondary school (High school)
13-16	Undergraduate
16+	Graduate

Table 3. Mean readability scores of frequently prescribed drugs in rheumatology practice based on Ateşman and Bezirci-Yılmaz scales and corresponding education levels.

	Number	**Minimum**	**Maximum**	**Mean (Standart Deviation)**	**Educational Status**
ATEŞMAN	182	40.54	78.94	58.4238±7.62	11-12 years
BEZİRCİ-YILMAZ	182	5.10	15.71	9.9595±2.52	Secondary School (High School)

These medications were divided into 8 groups: csDMARDs (n:20), bDMARDs (n:32), tsDMARDs (n:3), immunosuppressive drugs (n:26), NSAIDs (n:45), FMF and gout arthritis drugs (n:7), fibromyalgia drugs (n:18), and osteoporosis drugs (n:31).

Among these groups, the ones that required the lowest education level to be read and understood were osteoporosis drugs and targeted synthetic DMARDs according to Ateşman readability scale and targeted synthetic DMARDs according to Bezirci-Yılmaz readability scale. According to the Ateşman readability scale, the education levels required for reading and comprehension of the drug groups other than osteoporosis drugs and targeted synthetic DMARDs are at the 11th or 12th grade level. According to the Bezirci-Yılmaz readability scale, the education levels required for reading and comprehension of the drug groups other than targeted synthetic DMARDs are at the Secondary School (High School).

Figure 1 and 2 present the mean scores of the above-mentioned drug groups according to Ateşman and Bezirci-Yılmaz readability scales along with their comparison. Table 4, on the other hand, provide corresponding education levels for the mean scores of the drug groups.

Discussion

A written text's value is determined by how much of it can be understood by the reader as much as it depends on the contents. The meaning of a written text is only as much as the reader understands. Since the beginning of 1950, many readability scales have been developed to determine text's understandability by readers. Flesch Reading Ease Score and the Gunning Fog

Table 4. Corresponding education levels for the mean scores of the drug groups frequently prescribed in rheumatology practice.

	Bezirci	**Ateşman**
Osteoporosis Drugs	Secondary School (High School)	At the 9th or 10th-grade level.
NSAIDs	Secondary School (High School)	At the 11th or 12th-grade level
Conventional Syntetic DMARDs	Secondary School (High School)	At the 11th or 12th-grade level
Biologic DMARDs	Secondary School (High School)	At the 11th or 12th-grade level
Targeted Synthetic DMARDs	Primary School	At the 9th or 10th-grade level
Immunosuppressive Drugs	Secondary School (High School)	At the 11th or 12th-grade level
FMF-Gout Arthritis Drugs	Secondary School (High School)	At the 11th or 12th-grade level
Fibromyalgia Drugs	Secondary School (High School)	At the 11th or 12th-grade level

Index are some examples. These scales use the number of sentences, words, and syllables in a text and their proportion to each other in order to determine the readability level [16].

Each language has unique characteristics, and languages thus are different from each other. Works on readability scales for Turkish texts started in the early 1990s. Ateşman and Bezirci-Yılmaz readability scalesare the most common alternatives for Turkish texts. Ateşman defined readability as texts being easy or difficult to be understood by the reader [14,15].

Patient information leaflets are written texts providing information about medications to patients. Patients may sometimes misunderstand PILs or they may be confused due to insufficient and missing information.

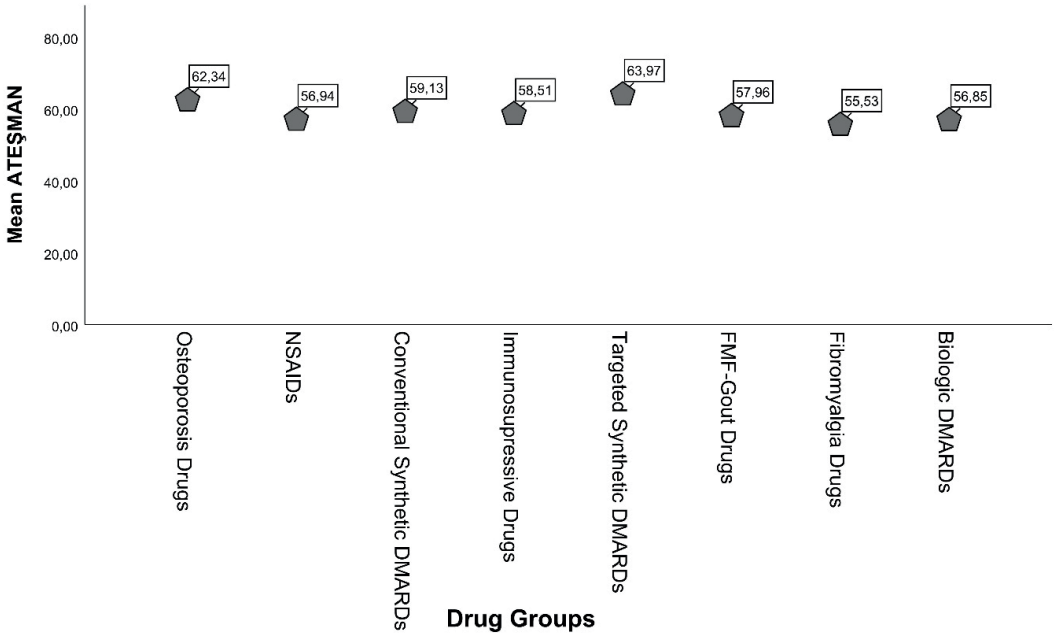

Figure 1. Mean scores of the drug groups according to Ateşman readability scale.

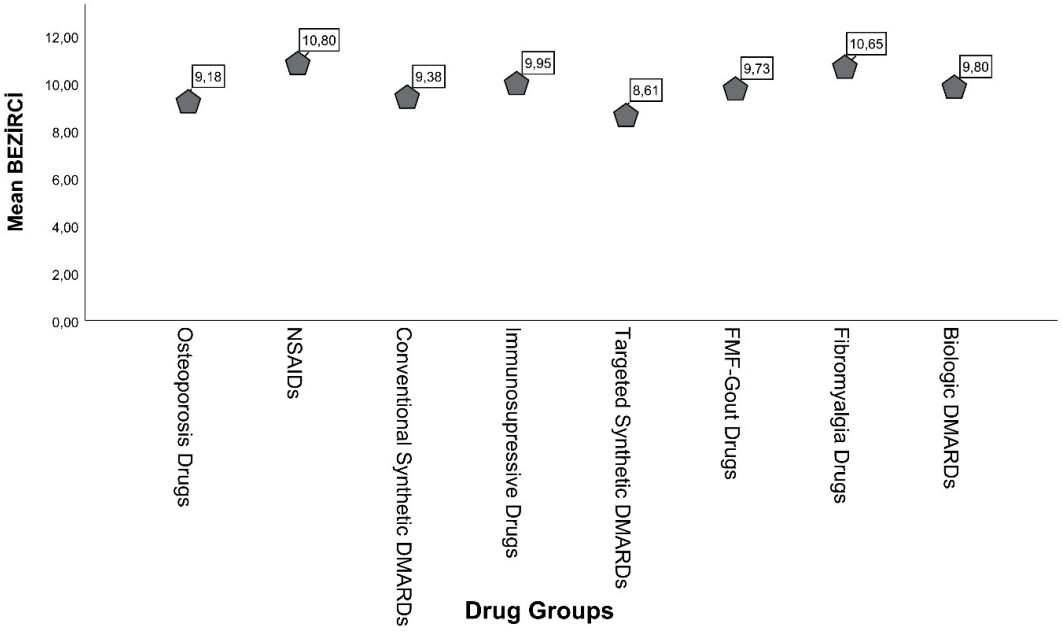

Figure 2. Mean scores of the drug groups according to Bezirci-Yılmaz readability scale.

A study by Sayın Kasar K. et al., where antihypertensive medication errors in elderly individuals were examined showed that 57% of the patients made medication errors.The medication error rate was significantly higher in women, people taking three and more drugs, people using other drugs in addition to theantihypertensive, and people that don't read the PILs of the drug they are taking. 32% of those who don't read the PILs said that it is because they can't understand what is in the PILs [17]. As demonstrated also with this study, the more difficult it is to understand PILs, the less the patients benefit from them and the higher the likelihood of medication error by the patients.

A study by Sarı A. et al., where they evaluated the readability levels of PILs of antihypertensive drugsdetermined that an average of 11-12 years of education, i.e. high school education, is required in order to read and understand the PILs of antihypertensive drugs. This study proved that PILs of drugs for hypertension, which is a quite common condition insociety, are prepared for a higher education level than the average level of education in Türkiye [18].

The literature review for this research did not provide a Turkish study on the readability levels of PILs of drugs used in rheumatology practice.In the oral presentation at the National Rheumatology Congress in 2021, Tazegül G. et al., evaluated the readability levels of informed consent forms prepared by the Turkish Rheumatology Association (TRD) for 26 different drugs and stated that TRD informed consent forms required 11-14 years of education to be understood by the reader and that the readability of the current informed consent forms must be increased. Also in the oral presentation titled "Turkish readability levels of informed consent forms used for biological treatments of autoimmune diseases" by Tazegül G. et al., at the 8th Fırat RheumatologySymposium in 2021, eight informed consent forms created for anti-TNF group drugs, anakinra, baricitinib, belimumab, rituximab, tofacitinib, and vedolizumab were evaluated and found to require at least graduate level education, and the authors suggested thatthe readability of the current informed consent forms must be enhanced.

In a study by Pires C. et al. with 63 individuals including physicians, pharmacists, and potential users,participants' accessibility to, and comprehensibility of, the PIL for diclofenac 12.5 mg tablets was evaluated according to the readability guideline of the European Medicine Agency (EMA). Despite the fact that almost all (85%) of the 20 potential users were educated above the 9th grade, the majority of them (95%) had, at least, one PILs interpretation issue, mainly related to the comprehension of technical terms; regarding the readability assessment of the PILs for diclofenac 12.5 mg tablets, the authorsconcluded that the method proposed in the EMA guidelines might not be as effective as expected and could be enhanced for safer use [19]. In a study by Arandy D.A. et al., in which they compared PIL contents of locally-supplied and imported NSAIDs, the researchers evaluated the PILs for a total of 35 NSAIDs, 18 locally-supplied and 17 imported, containing 9 different active ingredients. It was demonstrated in the study that the PILs of the locally-supplied NSAIDs provided less information in comparison with imported NSAIDs, and it was therefore suggested that both the Palestinian authorities and the manufacturers make appropriate arrangements to improve the content and quality of the information in PILs of locally-supplied NSAIDs [20]. In our study, we determined that the PILs of NSAIDs that we frequently use in rheumatology practice required 11-12 years of education, i.e. high school education. NSAIDs are medications that may have serious side effects and are common in society. When patients use NSAIDs at inappropriate doses or in conditions when NSAIDs are contraindicated or in combination with drugs such as warfarin and acetylsalicylic acid that may amplify the side effects of NSAIDs. Our study found that the PILs of NSAIDs that are used by people of all ages and for many different reasons required knowledge well beyond the average education level in Türkiye.

In a survey by Oton T. et al., where they assessed the experiences and needs of patients receiving methotrexate, their general treatment, and the quality of the information provided by their rheumatologist, 80% of the respondents said they had read the PILs and 62% of them found it

helpful while only 15% of all respondents did not find the PILs functional [21]. In our study, we also found that the level of readability of the PILs of csDMARDs such as methotrexate, leflunomide, and sulfasalazinecorresponded to the education level of 11-12 years, *i.e.* high school education. We may face life-threatening conditions due to methotrexate intoxication when patients don't have a sufficient understanding of how to use the medication that should be taken every week. Rheumatologists provide information to patients about teratogenic drugs such as methotrexate and leflunomide; however, patients turn to the PILs to get information when physicians cannot allocate enough time to patients at outpatient clinics because of intense working conditions, and we thus believe that this may lead to problems due to insufficient understanding of the PILs of these drugs since a complete and thorough understanding of these PILs requires an education level beyond the average education level in Türkiye.

In a study by Masri H.E. et al., where they analyzed calls by patients taking csDMARDs and bDMARDsto an Australian national medicine call center, patients' most common problem about both csDMARDs and bDMARDs was found to be inadequate information with 44% [22].

Mean years of schooling and expected years of schooling give information about the education level of countries and regions. In their 2016 study, Yeşilyurt M. et al., calculated the average schooling year in Türkiye as 6.51 years while the expected schooling year was 11.03 years [23]. The readability levels of PILs of all drug groups examined in our study are above the actual schooling years in Türkiye. This level should be taken into account while preparing written texts targeting the whole society. The limited level of health HL is one of the important issues in Turkey [24]. Patient readability and comprehensibility of patient information leaflets may also be related to f health literacy (HL), comprehensive studies are needed on this subject.

Conclusion

In conclusion, we determined in our study that on average 11-12 years of education, *i.e.* high school education, is necessary to read and understand the PILs of drugs commonly prescribed in rheumatology practice. Considering that the mean years of schooling in Türkiye is 6.51 years, the said education level is too high. The readability levels of PILs should be in accord with the mean years of schooling in Türkiye. Since patients will thus benefit more and get better information from PILs, we believe that medication errors will be decreased, medication error-related complications may be prevented, or disease exacerbations or activation due to inadequate use may be avoided. We also think that patient adherence to treatment will increase when PILs are understandable by patients. In this study, it was determined that the readability levels of PILs of medications frequently prescribed in daily rheumatology practice were low by patients compared to the average education level in Türkiye. The current readability of the PILs should be adjusted in accordance with the patient's level of understanding and education and arrangements to increase the readability levels of PILs should be introduced.

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Conflict of interest

There is no conflict of interest.

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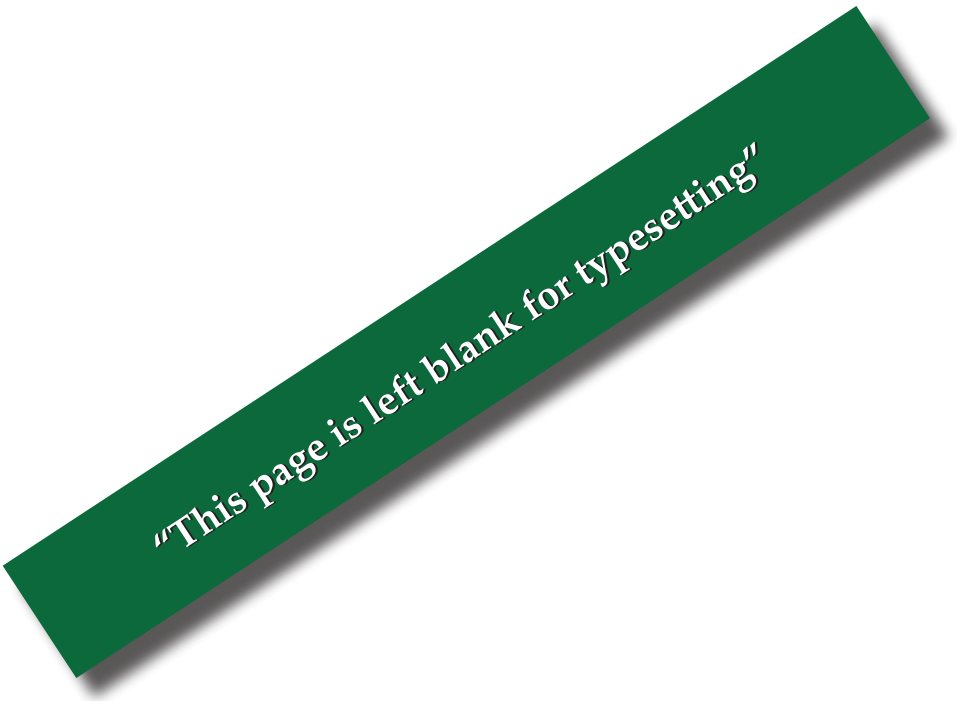
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ORIGINAL ARTICLE

Effect of labor pain on placental gene expressions

Evrim Suna Arıkan Söylemez[1] **Dağıstan Tolga Arıöz**[2]
Mariam Chkhikvadze[3]

[1] Department of Medical Biology, Faculty of Medicine, Afyonkarahisar Health Sciences University. Afyonkarahisar / Türkiye
[2] Department of Obstetrics and Gynecology, Faculty of Medicine, Afyonkarahisar Health Sciences University. Afyonkarahisar / Türkiye
[3] Department of Gynecology, American Hospital. Tbilisi/ Georgia

Abstract

A close relationship between labor and the placenta is known. The study of gene expression profiles describing the effects of labor on placental tissue has accelerated in recent years. This study aims to compare the expression levels of *GDF15, ADM, SERPINE1, NOS3, IL-6, TNF-α* genes in placental tissues discarded after vaginal deliveries with labor pain and elective cesarean deliveries before the onset of labor pain. For this purpose, placental tissues of vaginal deliveries with labor pain (n=9) and elective cesarean deliveries without labor pain (n=9) were collected immediately after births. RNA extracted from tissues (umblical cords and deciduas). Gene expression analyzes were performed by Real-time PCR method. *TNF-α* gene expression levels in decidua and umblical cord tissues in vaginal deliveries with labor pain were higher than in elective cesareans without labor pain, and *NOS3, ADM, SERPINE1* gene expression levels were low. *GDF15* and *IL-6* gene expression levels were high in the umblical cord tissues and were low in the decidua in vaginal deliveries with labor pain compared to elective cesareans without labor pain. The high level of *GDF15* gene expression in the vaginal deliveries with labor pain umblical cord tissues was significant ($p<0.05$). Changes in gene expression between different types of birth may help us to understand how labor pain affects gene expression levels. These results suggest that labor pain affects different tissues in different ways. The "birth experience" of a placenta that has experienced pain stress is absolutely different to others process. Since birth pain is a natural stress, it can be a light in determining the effects of the differences in cesarean section on the baby and the mother. Gene expression alterations may cause labor starting and progressing, or just be an result of labor.

Keywords: Labor pain, *SERPINE1*, *GDF15*, *ADM*, *NOS3*, *IL-6*, *TNF-α*

Abbreviations: Adrenomedullin (*ADM*); glyceraldehyde-3-phosphate dehydrogenase (*GAPDH*); growth differentiation factor 15 (*GDF15*); interleukin 6 (*IL-6*); nitric oxide synthase 3 (*NOS*); serpin family e member 1 (*SERPINE1*); tumor necrosis factor-α (*TNF-α*).

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Corresponding Author:
Evrim Suna Arıkan Söylemez
Email:arikanmt@gmail.com

Introduction

The onset of labor is characterised by changes in the uterus, including softening and ripening of the cervix, activation of the amniotic and decidual membranes, and transformation of the uterine smooth muscle from quiescent to contractile [1]. Wang et al., reported that there was a significant differences in gene expression between vaginal and cesarean placentas [2]. On the contrary to this Churchill [3] and Cui and Churchill [4] have suggested that there was a slightly difference in gene expression at birth compared with nonlaboring placentas.

Hypoxia of the placenta caused by uterine contractions during labor may be the reason for the differences of gene expression in the placenta depending on the mode of delivery. Labor is in connection with deep uterine contractions that may result in intermittent blood flow to the placenta in contrast to elective cesarean delivery [5,6].

The processes that initiate spontaneous labor may explain the differences between laboring and non-laboring placentas. Noting that these processes are not fully understood, inflammation is one of the important pathways proposed to initiate labor [7,8]. In addition, it is also possible that the conditions leading to the choice of elective cesarean delivery over vaginal delivery are related to gene expression in placental tissue alone. It is believed that labor and its associated pain affect a pregnant woman in a special way.

Women experience a lot of stress during pregnancy and childbirth, and the biggest stressor is labor pain [9]. On average, labor before birth (including the first and second stages) can last 9-18.8 hours for nulliparous women and 6-13.5 hours for multiparous women [10]. At the peak of contractions, the uterine pressure can reach 80-100 mmHg. There can be up to 5-6 contractions in 10 minutes [11]. It has been suggested that labor, in conjunction with uterine contractions and labor pain, has important physical and biochemical effects on the mother, baby and placenta [12].

It is reported that, during physiological or pathological events, gene expression profiling provides comprehensive information about the molecular mechanisms of cellular function in specific tissues. Human labor is a complex biological process with interactions between neurological, hormonal, mechanical stretch and inflammatory factors. In general, it has been reported that alterations of genes expressions involved in exacellular matrix elements, immune pathways, inflammatory processes and hormones is important during labor [12].

GDF15 protein acts as a pleiotropic cytokine. It is involved in cellular damage stress response. It is reported that, protein levels increased in case of tissue hypoxia, acute injury, inflammation and oxidative stress [13]. *SERPINE1* encodes a member of the serine proteinase inhibitor superfamily. The protein also functions as a component of innate antiviral immunity and high concentrations of the gene product are related to thrombophilia [13]. *ADM* is a pre-hormone and involved in vasodilation, regulation of hormone secretion, promotion of angiogenesis and antimicrobial activity. In fetoplacental tissues, *ADM* has been proposed to control vascular tone at the local level to regulate uteroplacental-fetal circulation [14]. *IL-6* is a marker and its expression is known to be increased in preterm labor, premature rupture of membranes and labor. *TNF-α* accumulation has been associated with an increase in markers of inflammation, fibrotic response, vascular remodeling and proteins that facilitate lipid deposition in the placenta [15]. *NOS3*, nitric oxide, is a reactive free radical that acts as a biological mediator in various processes including neurotransmission and antimicrobial and antitumoral activities. It has been reported that ovarian excretion also occurs in the placenta [13].

During normal labor, uterine contractions may create stress for the fetus by affecting fetal oxygen saturation and may lead to slow fetal heart rate, hypoxia and even death [16]. Other pathways that are differentially expressed between birth types include immune pathways and inflammatory. Given the stress and inflammation known to occur with both childbirth [12] and major surgery [17], these pathways warrant further investigation due to their importance. Epigenetic changes in the genome that occur during labor have been

described in one study. More specifically, there is increased DNA methylation in leukocytes from cesarean-born babies compared to vaginally-born babies. Whether these epigenetic changes have lasting effects on both mother and child is not yet known [18]. Kothiyal et al., identified differential gene expression between different birth delivery modes. Enrichment of antimicrobial peptide (*AMP*) pathways in vaginal delivery is of particular interest. It is reported that, the PI3 gene (*AMP*), showed a twofold increase in vaginal delivery compared to cesarean section [19].

It is suggested that, contractions and labor can influence oxidative and inflammatory stresses that may trigger changes in placental gene expression. The effects of labor may therefore be the cause of some of the changes observed in the placenta. The contractions of the uterus during labor affect the uteroplacental blood flow, which temporarily reduces the maternal perfusion of the placenta. This intermittent perfusion may be the cause of ischaemia-reperfusion injury to the placenta. Therefore, delivery may serve as an in vivo model of acute ischaemia and reperfusion injury [20]. There is strong evidence that intrauterine cytokine upregulation is related to both on-time labor, preterm labor, and a number of key aspects of labor [21-23].

Peng et al. identified novel genes and several signaling pathways involved in inflammatory and immune pathways with additional diverse biological functions, in addition to several known genes regulated in the maternal-fetal-placental compartments during birth. Interestingly, overexpressed genes were found to be different when compared maternal blood, placental tissues and cord blood [12].

In this study, the expression levels of *GDF15, ADM, SERPINE1, NOS3, IL-6, TNF-α* genes in placental tissues discarded after vaginal deliveries with labor pain and non-painful elective cesareans before the onset of labor were determined.

Materials and Methods

Sample Collection and Ethics

This study has been approved by Afyonkarahisar Health Sciences University Ethical Board with decision number 33 of 07/01/2022/1. All patients have given their written consent for the use of their placentas.

Eighteen patients who underwent giving birth between January-March 2022 were chosen for the study. All the placentas from the 9 mothers with vaginal delivery (with labor pain) and from 9 mothers with elective cesarean delivery (without labor pain) (aged 18-45) were collected from the polyclinic of the Afyonkarahisar Health Sciences University, Faculty of Medicine, Department of Obstetrics and Gynecology.

RNA Extraction and Real-Time PCR Analyses

Total RNA from placenta tissues (umblical cords and deciduas) was isolated according to the PureZole isolation kit protocol steps (Biorad, USA). cDNA was obtained from 1 µg of total RNA by using iScript Reverse Transcription Supermix (Biorad, USA). Real-time PCR analysis was performed using Rotor Gene-Q (Qiagen, Hilden, Germany) by using iTaq Universal SYBR Green Supermix (Biorad, USA) to analyse *SERPINE1*, *GDF15*, *ADM*, *NOS3*, *IL-6* and *TNF-α* mRNA levels (Table 1).

Oligonucleotide primers were designed Oligomere Biotechnology (Ankara, TURKEY). PCR protocol for *SERPINE1, GDF15, ADM, NOS3, IL-6, TNF-α* and *GAPDH:* 95°C for 30s initial denaturation followed by 40 cycles of 95°C for 5s and 60°C for 30s.

Statistical Analysis

REST 2009 V2.0.13 and SPSS v.19 Software [24] were used for assessing the relative expression results.

Results

We evaluated the gene expression changes between diferent delivery birth modes. Changes in related mRNA levels of placenta tissues with labor pain were analysed according to the mRNA levels of laboring painless placenta tissues.

mRNA Analyses of *GDF15, ADM, SERPINE1, NOS3, IL-6,* and *TNF-α* Genes

TNF-α mRNA levels were increased in umblical cord and decidua tissues of vaginal deliveries with labor pain compared to those of elective cesarean deliveries without pain (1.126-fold

and 1.424-fold, respectively) (p>0,05). *NOS3*, *ADM*, *SERPINE1* gene expression levels were decreased. *NOS3* mRNA level decreased 0.352 fold in umblical cord tissue and 0.355 fold in decidua tissue. *ADM* mRNA level decreased 0.933 fold in umblical cord tissue and 0.562 fold in decidua tissue. *SERPINE1* mRNA level decreased 0.768 fold in umblical cord tissue and 0.691 fold in decidua tissue (p>0,05). *GDF15* and *IL-6* gene expression levels were increased (2.009-fold p<0.05, 1.153-fold, respectively) in umblical cord, whereas they were decreased (0.623-fold, 0.619-fold, respectively) in decidua compared to elective cesarean section related tissues (Figure 1, and Figure 2) (fold changes are shown in Log10 level).

Discussion

A close relationship between labor and the placenta is known. But little is known about the gene expression profiles describing the effects of labor on placental tissue. Gene expression profiling is a powerful tool that enables the study of changes in gene expression to study complex biological processes such as the labor process [25].

In this study, the expression levels of *GDF15*, *ADM*, *SERPINE1*, *NOS-3*, *IL-6*, *TNF-α* genes were determined in placentas discarded as a result of vaginal delivery with labor pain and placentas discarded as a result of elective cesarean delivery without labor pain before the onset of labor and contractions. The expression of the related genes differed between the two modes of delivery. Lee et al., suggesting a large diversity of gene expression changes and an overall complexity in the birth process [20].

In addition, a surgical procedure can induce relevant gene expression changes that can cause adverse outcomes. For example, a study examining changes in gene expression after major thoracoabdominal surgery showed that genes related to innate immunity and inflammation

Table 1. Primer sequences.

Gene	Primer sequences
GDF15-F	5'-GCAAGAACTCAGGACGGTGA-3'
GDF15-R	5'-TGGAGTCTTCGGAGTGCAAC-3'
ADM-F	5'-ATGAAGCTGGTTTCCGTCG-3'
ADM-R	5'-GACATCCGCAGTTCCCTCTT-3'
SERPINE1-F	5'-CCTCCAGCAGCTGAATTCCT-3'
SERPINE1-R	5'-GGGTTTCTCCTCCTGAAGTTCT-3'
NOS-3-F	5'-AACAGCATCTCCTGCTCAGA-3'
NOS-3-R	5'-CACTGAGCGGATTGTAGCCT-3'
IL-6-F	5'-ACAGCCACTCACCTCTTCAG-3'
IL-6-R	5'-CCATCTTTTTCAGCCATCTTT-3'
TNF-α-F	5'-CCCGAGTGACAAGCCTGTAG-3'
TNF-α-R	5'-GATGGCAGAGAGGAGGTTGAC-3'
GAPDH-F	5'-CATTGCCCTCAACGACCACTTT-3'
GAPDH-R	5'-GGTGGTCCAGGGGTCTTACTCC-3'

were upregulated and genes related to adaptive immunity were downregulated after surgery [17]. In placental tissue, delivery increases the expression of genes related to placental oxidative stress, inflammatory cytokines, angiogenic regulators and apoptosis [26]. It also regulates genes involved in placental hormone metabolism [27,28]. *TNF-a* and *IL-6* gene expressions were found to be higher in umblical cords in vaginal delivery compared to cesarean delivery. Similarly *TNF-α* gene expression was higher in decidua, whereas *IL-6* gene expression decrease. Placental and extraplacental membranes are also known to secrete many cytokines and chemokines [29]. The onset of labor at term causes an increase in amniotic fluid concentrations of interleukin *IL-1β*, *IL-6*, *IL-8* and tumor necrosis factor *TNF-α* [30]. Normal labor is associated with an up-regulation, although not significant, of cytokine expression in the amnion and chorionic villi, as shown by cDNA array studies [31].

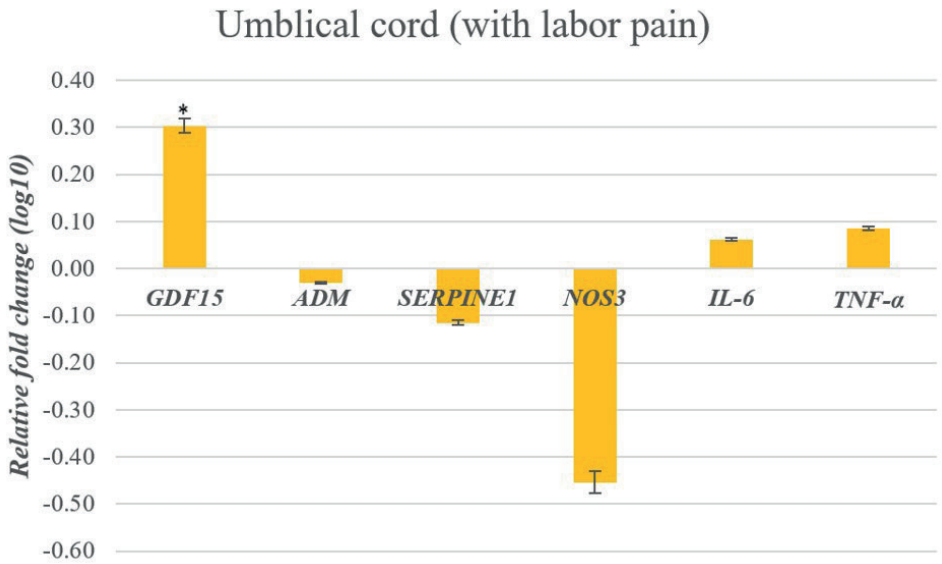

Figure 1. Umbilical cord gene expression alterations in vaginal deliveries with labor pain compared to elective cesarean deliveries without labor pain. *GAPDH* was used as a reference gene for normalization. * $p<0.05$.

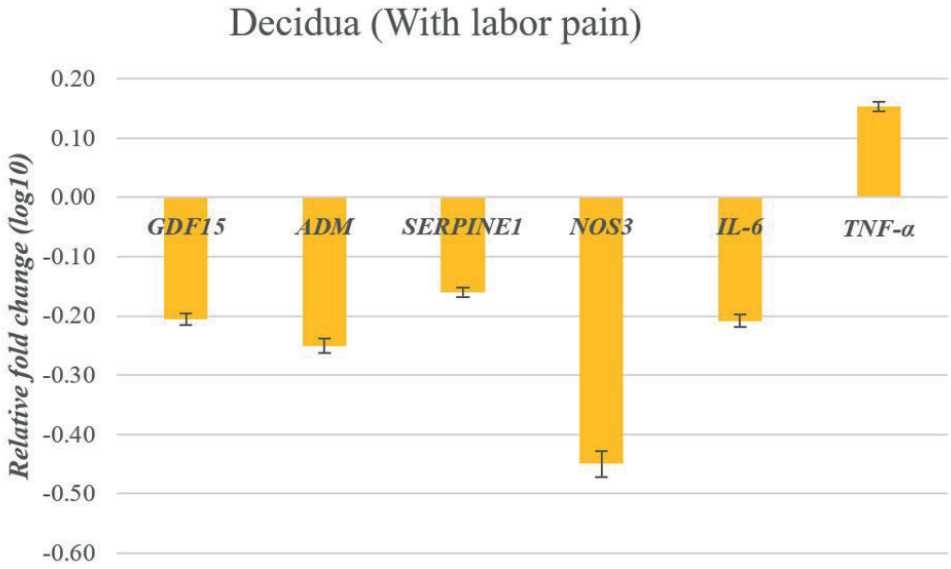

Figure 2. Decidua gene expression alterations in vaginal deliveries with labor pain compared to elective cesarean deliveries without labor pain. *GAPDH* was used as a reference gene for normalization.

NOS3 has been reported to be overexpressed in the placenta [13]. In our study, there was almost a 3-fold difference in *NOS3* gene expression levels in cesarean section tissues without labor pain compared to vaginal delivery tissues with lobor pain. This indicates that this free radical is triggered more during cesarean section operation.

ADM is involved in the biological process of fluid and electrolyte homeostasis [32]. In fetoplacental tissues, *ADM* has been suggested to control vascular tone at the local level to regulate uteroplacental-fetal circulation [33]. In our study, *ADM* gene expression level was found to be higher in both placental tissues in the cesarean group compared to vaginal delivery. Considering that anesthesia in cesarean section affects fluid and electrolyte homeostasis during the operation, this increase in *ADM* gene expression may be necessary to maintain the related homeostasis.

It has been reported that there was no significant difference in the distribution or intensity of *GDF15* staining in placentas with and without labor [34]. On the contrary, Peng et al. suggested that *GDF15* has a role in the regulation of this labor process in their observations by microarray and Western blot [20]. In our study, *GDF15* gene expression level in cord tissues of placentas from vaginal delivery with labor pain was significantly higher compared to cord tissues from cesarean delivery. To clarify the role of *GDF15*, further studies are needed.

SERPIN1 gene expression level was found to be lower in both cord and decidua tissues of placentas of vaginal delivery compared to cesarean section tissues. It is also high in tissues belonging to the cesarean section group. Considering that high concentrations of the *SERPIN1* gene product increase the risk of thrombophilia, the high level of gene expression in cesarean placenta draws attention to the risk. More detailed analyses are required to determine the relationship between this situation in cesarean with thrombophilia.

Conclusion

These results suggest that labor pain affects different tissues in different ways. The fact that we cannot fully disentangle the effect of labor, associated pain or stress on the different gene expression profiles in the maternal-fetal-placental compartment is a limitation of this study. However, it is clear that both labor pain/stress and labor itself underlie gene regulation during labor. The "birth experience" of a placenta that has experienced pain stress is absolutely different to others process. Since birth pain is a natural stress, it can be a light in determining the effects of the differences in cesarean section on the baby and the mother. These changes in gene expression may cause labor to start and progress, or simply be an effect of labor.

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Conflict of interest

The authors declare that there are no conflicts of interest.

Data availability statement

The authors confirm that the data supporting the findings of this study are available within the article.

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ORIGINAL ARTICLE

The relationship between 18F-FDG PET/CT parameters and histopathological-immunohistochemical properties in breast cancer

Ali Ozan Öner[1] **Şenay Yıldırım**[2] **Evrim Sürer Budak**[3] **Arsenal Sezgin Alikanoğlu**[2]

[1] Department of Nuclear Medicine, Faculty of Medicine, Afyonkarahisar Health Sciences University. Afyonkarahisar / Türkiye
[2] Department of Pathology, Antalya Training and Research Hospital. Antalya / Türkiye
[3] Department of Nuclear Medicine, Antalya Training and Research Hospital. Antalya / Türkiye

Abstract

In this study, it is aimed to determine the correlation between histopathologic-immunohistochemical factors, tumor subtypes and fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG PET/CT) parameters such standardized uptake value (SUVmax), metabolic tumor volume (MTV), total lesion glycolysis (TLG) in breast cancer (BC). Initial PET/CT examination of 110 histopathologically proven BC patients (age ranging 27-92, mean age 56.18 ± 14.59) were included in this retrospective study. The relationship between histopathological-immunohistochemical factors, tumor subtypes and PET/CT parameters were analyzed by regression analysis. The mean SUV max value of 110 breast tumors was 7.73 ± 5.62 (range 1.4 - 34.15). Histological subtypes were; invasive ductal carcinoma (n:94, 85.5%), invasive lobular carcinoma (n=6, 5.5%) and other types (n=10, 9.1%). The distribution of BC subtypes was as follows; Luminal A (Lum A) (n=38; 34.5%), Luminal B (Lum B) (n=56; 50.9%), HER2-positive (n=3; 2.7%) and Triple Negative (TN) (n=13; 11.8%). Univariate regression analysis revealed significantly higher SUV max values in ductal carcinomas than lobular carcinomas (p=0.03). SUVmax values of the Lum B, HER2 positive and TN groups were higher than Lum A group (p=0.03, p<0.001, p<0.001 respectively). Univariate regression analyses also showed that the MTV and TLG values of TN group were significantly higher than Lum A group (p=0.011, p=0.007, respectively). In multivariate regression analyses, no significant difference was observed in above mentioned groups. MTV, TLG and SUVmax values significantly correlated with histopathological-immunohistochemical factors and tumor subtypes in BC. So that, these parameters can be used to predict the tumors' behavior.

Keywords: Breast cancer, 18F-FDG PET/CT, standardized uptake value (SUVmax), metabolic tumor volume (MTV), total lesion glycolysis (TLG)

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Corresponding Author:
Ali Ozan Öner
Email:draliozanoner@hotmail.com

Introduction

Breast cancer (BC) is one of the most common cancers in women and its incidence has increased in recent years [1]. Despite it's increasing incidence, early diagnosis by using new imaging techniques and the effective treatment modalities have reduced mortality rates in BC. An accurate initial staging is very important in the management of an effective personalized treatment and to predict the prognosis. Some of the prognostic factors are histological type, tumor size, presence of vascular, lymphatic and perineural invasion, proliferation rate and receptor status [2]. The relation of the BC subtypes such Luminal A (Lum A), Luminal B (Lum B), HER2 positive and triple negative (TN) with the prognosis is also known [3,4].

In BC, the use of fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG PET/CT) for initial staging becomes increasingly crucial [5,6]. It provides essential contributions to the clinical practice in therapy planning, assessing therapy response and recurrence determination [5,7]. There are many studies in the literature focused on the relationship between SUVmax and histopathological-immunohistochemical factors in BC [8-12]. The relationship between histopathological-immunohistochemical factors and PET/CT parameters such as metabolic tumor volume (MTV) and total lesion glycolysis (TLG) are also recently mentioned in the literature [13].

In this study, we aimed to determine the relationship between the histopathologic-immunohistochemical factors, tumor subtypes (lum A, lum B, HER2 positive, TN) and 18F-FDG PET/CT parameters (SUVmax, MTV, TLG) in BC patients.

Materials and Methods

Patients: A total of 110 biopsy proven BC patients who had undergone PET/CT examination for initial staging in the Antalya Training and Research Hospital Nuclear Medicine Clinic were included in this retrospective study. Sixty-three patients were operated after initial staging. Patients with additional malignancy and received treatment before PET/CT examination were excluded.

PET/CT Imaging: After 4 hours fasting, a dose of 0,1 mCi/kg F18-FDG was injected intravenously to the patients with blood glucose levels less than 180 mg/dL. All patients underwent whole-body PET/CT imaging with a Philips Gemini TF 16 PET/CT scanner (3 mm CT slice thickness, 110 mAs, 120 kV, 3 min PET per bed) 60 minutes after injection. PET, CT, and fusion PET/CT images were examined visually and semiquantitative measurements (SUVmax, MTV and TLG) were all performed by the same nuclear medicine physician. The SUVmax value was calculated automatically by drawing the three-dimensional region of interest (ROI) on the hypermetabolic breast tumour. MTV was obtained from attenuation-corrected FDG PET/CT images by drawing the boundaries of the whole mass. MTV was defined as the sum of the metabolic volumes of the primary tumor. The threshold value for the SUVmax was assumed to be 40% of SUVmax, and the tumor's boundaries were automatically drawn (Extended Brilliance Workspace, Philips). TLG was also calculated using attenuation-corrected FDG PET/CT images by the same way. The 40% of the primary tumor's SUVmax was considered as a threshold value and the contours of the mass were drawn automatically. The SUVmean value of the area within these contours was calculated. Then MTV and SUVmean values of this area were multiplied and TLG value was obtained.

Histopathologic and Immunohistochemistry Analyses: 110 patients had diagnosis by core biopsies; 63 of these underwent surgery after diagnosis. Final histopathological examination of opereated patients was based on these mastectomy specimens. Histological type, histological and nuclear grade, Ki-67 proliferation index, receptor status (ER, PR, HER2), subtypes (Lum A/B, HER2 positive and TN), presence of invasion (vascular, lymphatic and perineural) and axillary lymph node status were evaluated. Histologic grade (HG) was evaluated using *Elston–Ellis* modification of the *Scarff–Bloom–Richardson* grading system, based on tubular score (TS), nuclear pleomorphism score (PS) and mitotic score (MS). Expression of ER, PR, HER2 and Ki-67 proliferation index of tumor tissue was examined by standard avidin-biotin complex immunohistochemical staining

methods. Positive ER and PR staining is accepted when nuclear staining was demonstrated in more than 10% of tumor cells. Ki-67 expression is evaluated by calculating the percentage of immunoreactive tumor cells showing nuclear staining at X10 amplification. HER2 membrane immunostaining was scored from 0 to 3; Score 3+ was accepted as positive while Score 0 and 1+ was negative. Score 2+ cases were tested by Fluorescence in situ Hybridization (FISH) method for final determination of HER2 status.

Subtyping: BCs were divided into four subtypes according to 12th International Breast Conference recommendations:

Lum A: ER (+) and /or PR (+), HER2 negative, Kİ-67 <14%

Lum B: Lum B(-); ER (+) and /or PR (+), HER2 negative, Kİ-67 ≥14% or Lum B(+); ER (+) and / or PR (+), HER2 positive, Ki-67 expression independent

HER 2 Positive: ER (-), PR (-), HER2 (+)

Triple Negative (TN): ER (-), PR (-), HER2 (-)

Statistical Analysis

Statistical analysis was performed with the IBM Statistical Package for Social Sciences v20 (SPSS Inc., Chicago, IL, USA). *Kolmogorov-Smirnov* test was applied to check the normal distribution of the quantitative data. Parametric tests (Independent-samples t-test) were used to evaluate the data of normal distribution, and non-parametric tests (*Mann–Whiney U*-test) were used to evaluate the data of questionably normal distribution. *Pearson* chi-square test was applied to compare the distribution of categorical variables in both groups. The determinants were explored using multiple logistic regression analysis. All results are presented as mean±SD. Statistical significance was accepted as $p<0.05$.

The study was approved by the Antalya Training and Research Hospital Ethics Committee (2018-159).

Results

The mean age of the 110 female patients included in the study was 56.18 ± 14.59 (ranging 27-92) years. Patient characteristics are shown in Table 1.

Table 1. Histological and immunohistochemical characteristics of tumour.

	NUMBER OF PATIENTS (%)
	ER status
No	18 (16.4%)
Yes	92 (83.6%)
	PR status
No	32 (29.1%)
Yes	78 (70.9%)
	HER2 status
No	93 (84.5%)
Yes	17 (15.5%)
	KI-67
<%14	43 (39.1%)
≥%14	67 (60.9%)
	Histology
Ductal	94 (85.5%)
Lobular	6 (5.5%)
Other	10 (9.1%)
	Histologic grade
1	6 (5.5%)
2	34 (30.9%)
3	70 (63.6%)
	Nuclear grade
1	6 (5.5%)
2	74 (67.3%)
3	30 (27.3%)
	Mitosis
1	69 (62.7%)
2	39 (35.5%)
3	2 (1.8%)
	Score
1	22 (20%)
2	79 (71.8%)
3	9 (8.2%)
	Vascular invasion
Negative	43 (60.6%)
Positive	28 (39.4%)
	Lymphatic invasion
Negative	36 (50.7%)
Positive	35 (49.3%)
	Perineural invasion
Negative	48 (67.6%)
Positive	23 (32.4%)
	Axillary lymph node
Negative	35 (56.5%)
Positive	27 (43.5%)
	Subtype
Luminal A	38 (34.5%)
Luminal B	56 (50.9%)
HER2 positive	3 (2.7%)
Triple negative	13 (11.8%)

The mean SUVmax value of 110 breast tumors were 7.73±5.62 (range 1.4-34.15). The mean SUVmax value in invasive ductal carcinomas was 8.33±5.81 and in invasive lobular carcinomas was 3.49±1.52. Univariate regression analysis showed that the SUVmax values of ductal carcinoma were significantly higher than lobular carcinomas (p=0.03). Mean SUVmax values of LumA, Lum B, HER2 positive and TN subtypes were 5.28±3.24,

7.44±4.24, 18.38±9.43, and 13.71±8.44, respectively (Figure 1).

In univariate regression analysis, SUVmax values of the Lum B (p=0.03), HER2 positive and TN groups (p<0.001, for both) were significantly higher than Lum A group. However, significant results could not be obtained in multivariate analyses. In univariate regression analyses, ER and PR positivity had significantly correlated with lower SUVmax values than negative status (p<0.001). In multivariate analyses, no significant difference was observed between both ER positive/negative and PR positive/negative cases. SUVmax values of HER2 positive cases were significantly higher in univariate analyses than HER2 negative cases (p=0.013). However, any significant difference was not observed in multivariate analyses. In univariate regression analyses, SUVmax values were significantly lower in tumors with Ki-67 proliferation index <14% than those with ≥ 14% (p=0.007); significant values were not obtained in multivariate analyses. Also, in univariate analyses, significant increases were observed in SUVmax values as the mitosis, and score parameters were increased, but these significant increases were not present in multivariate analyses. The relation between SUVmax and aksillary lymph node status was also not significantly correlated. The detailed results of univariate and multivariate linear regression analysis showing the relationship between SUVmax values and histopathologic-immunohistochemical factors are shown in Table 2.

Mean MTV values of Lum A, Lum B, HER2 positive and TN subtypes were 6.93±4.84, 17.78±42.94, 72.49±93.14 and 69.35±200.22, respectively. When the relationship between MTV of tumors and histopathological-immunohistochemical data was examined (Table 3), univariate regression analyses showed that negative ER and PR status had significantly correlated with higher MTV values than positive ER and PR status (p=0.013, p=0,034, respectively). However, in multivariate regression analyses, no significant results were observed for both ER and PR status. In univariate regression analysis with subtypes; The MTV values of the TN group were significantly higher than those of the Lum A group (p=0.011). There was no other significant relationship between other subtypes.

Mean TLG values of Lum A, Lum B, HER2 positive and TN subtypes were 23.88±29.53, 92.3±232.44, 903.29±1278.43 and 991.1±3186.57, respectively. In univariate regression analysis between TLG and histopathologic-immunohistochemical characteristics of the tumor (Table 4); ER–negative and PR–negative cases were found to have significantly higher TLG values (p=0.005, p=0.036, respectively) than positive ones. Triple-

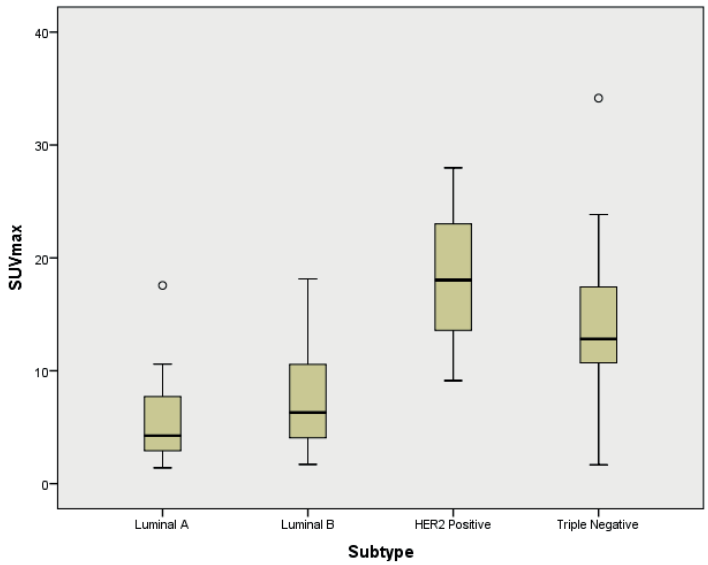

Figure 1. Mean primary tumor maximum standardized uptake value (PT SUVmax) according to tumor subtypes (Luminal A; Luminal B; HER2 positive; Triple negative).

negative tumors were found to have significantly higher TLG values than Lum A tumors (p=0.007). However, in multivariate regression analyses, no significant correlation was observed between TLG values and tumor histopathologic-immunohistochemical characteristics.

Discussion

In BC, therapy response and prognosis significantly depends on histopathological-immunohistochemical characteristics and subtypes. For this reason, in recent years, adjustment of treatment protocols by considering histopathological-immunohistochemical features and subtypes has been recommended [2].

18F-FDG PET/CT is a hybrid imaging technique which enables to observe metabolism and anatomical properties of tumor. In BC, it is

Table 2. Results of univariate and multivariate linear regression analysis for SUVmax.

	SUVmax	Univariate analysis		Multivariate regression analysis	
		Parameter estimate	*p* value	Parameter estimate	*p* value
Age		0.107	0.266		
Size		0.460	<0.001	0.269	0.023
ER status					
No	13.52±8.58				
Yes	6.6±4.03	-0.457	<0.001	-0.036	0.879
PR status					
No	10.96±7.69				
Yes	6.41±3.85	-0.37	<0.001	0.025	0.874
HER2 status					
No	7.17±5.15				
Yes	10.83±7.15	0.236	0.013	0.115	0.344
Kİ-67					
<%14	5.93±3.92				
≥%14	8.89±6.24	0.258	0.007	-0.379	0.223
Histology					
Ductal	8.33±5.81	1			
Lobular	3.49±1.52	-0.197	0.038	-0.198	0.061
Other	4.65±2.53	-0.189	0.046	-0.173	0.125
Histologic grade					
1	5.85±3.02	1			
2	5.96±3.75	0.009	0.966		
3	8.75±6.3	0.249	0.219		
Nuclear grade					
1	5.33±2.13	1			
2	7.81±6.14	0.208	0.302		
3	8.01±4.68	0.214	0.29		
Mitosis					
1	6.1±3.78	1			
2	10.3±7.12	0.359	<0.001	0.138	0.283
3	14.08±4.73	0.19	0.036	0.018	0.868
Score					
1	5.01±2.64	1			
2	8±6.04	0.24	0.023	0.007	0.96
3	12.04±3.88	0.344	0.001	-0.043	0.806
Vascular invasion					
Negative	7.11±5.6				
Positive	7.64±5.51	0.047	0.695		
Lymphatic invasion					
Negative	7.68±6.6				
Positive	7.28±4.59	-0.036	0.766		
Perineural invasion					
Negative	8.2±6.02				
Positive	5.5±3.84	-0.23	0.053		
Axillary lymph node					
Negative	7.16±5.76				
Positive	7.37±5.69	0.018	0.889		
Subtype					
Luminal A	5.28±3.24	1			
Luminal B	7.44±4.24	0.193	0.033	0.514	0.144
HER2 positive	18.38±9.43	0.381	<0.001	0.333	0.158
Triple negative	13.71±8.44	0.486	<0.001	0.673	0.054

used widely for staging and evaluating therapy response and also predicting prognosis [6,14].

In the literature, SUVmax was shown as one of the most commonly used PET/CT parameter correlating with histopathological features, receptor status, stage and prognosis in BC. As compatible with the literature, in our study invasive ductal carcinomas showed significantly higher primary tumor (PT) SUVmax values than invasive lobular carcinomas [10,12,13,15]. We observed the highest SUVmax values in HER2 positive group. While some of the studies were compatible with our results [16], most of them were conflicting with us. The highest SUVmax values were observed mostly in TN group in the literature [8,10,12,13,15,17].

Has Şimşek et al., analyzed BC subtypes as we grouped and SUVmax values in 436 patients

Table 3. Results of univariate and multivariate linear regression analysis for MTV.

	MTV	**Univariate analysis**		**Multivariate regression analysis**	
		Parameter estimate	*p* value	Parameter estimate	*p* value
Age		0.001	0.991		
Size		0.491	<0.001	0.415	0.001
ER status					
No	62.64±172.54				
Yes	13.59±33.93	-0.237	0.013	0.111	0.67
PR status					
No	45.87±130.28				
Yes	11.67±35	-0203	0.034	0.125	0.445
HER2 status					
No	20.43±81.73				
Yes	28.15±44.46	0.036	0.706		
Kİ-67					
<%14	8.92±7.92				
≥%14	29.77±97.94	0.133	0.167		
Histology					
Ductal	23.56±83.16	1			
Lobular	5.12±1.86	-0.055	0.574		
Other	13.29±11.35	-0.039	0.691		
Histologic grade					
1	12.87±22.01	1			
2	9.69±15.27	-0.019	0.926		
3	28.16±95.45	0.096	0.643		
Nuclear grade					
1	10.51±8.61	1			
2	26.02±93.09	0.095	0.638		
3	13±18.3	0.014	0.943		
Mitosis					
1	13.54±37.77	1			
2	35.79±118.9	0.139	0.152		
3	23.94±22.63	0.018	0.851		
Score					
1	8.88±12.21	1			
2	25.72±90.35	0.099	0.369		
3	16.76±16.17	0.028	0.798		
Vascular invasion					
Negative	15.71±46.99				
Positive	14.64±33.35	-0.013	0.917		
Lymphatic invasion					
Negative	21.44±57.98				
Positive	8.12±5.92	-0.161	0.181		
Perineural invasion					
Negative	18.75±50.34				
Positive	8.07±9.36	-0.12	0.318		
Axillary lymph node					
Negative	9.64±11.66				
Positive	14.69±33.88	0.106	0.414		
Subtype					
Luminal A	6.93±4.84	1			
Luminal B	17.78±42.94	0.071	0.495	0.096	0.461
HER2 positive	72.49±93.14	0.139	0.149	0.133	0.464
Triple negative	69.35±200.22	0.263	0.011	0.199	0.488

and reported that SUVmax values of ER and PR negative patients were significantly higher than those with ER and PR positive patients (p=0,001 for both group) [16]. In this study, the lowest SUVmax levels were observed in Lum A group followed by the Lum B, TN group, respectively, and the highest SUVmax values were observed in the HER2 positive group similar with our study. Koo et al., grouped 552 patients similar with our study as Lum A, Lum B, HER2 positive and TN and evaluated the relationship between PT SUVmax values and subtypes [10]. In this study, Lum A group formed the majority by number while it was lum B group in our study. ER and PR negativity was also similarly correlated with high PT SUVmax values in their study (p<0.001 for both group). The significant correlation between high SUVmax values

Table 4. Results of univariate and multivariate linear regression analysis for TLG.

	TLG	Univariate analysis		Multivariate regression analysis	
		Parameter estimate	*p* value	Parameter estimate	*p* value
Age		-0.008	0.932		
Size		0.434	<0.001	0.256	0.031
ER status					
No	867.51±2730.98				
Yes	65.82±184.69	-0.263	0.005	0.104	0.668
PR status					
No	549.33±2059.54				
Yes	52.46±179.29	-0.2	0.036	0.202	0.19
HER2 status					
No	185.27±1207.82				
Yes	261.2±574.24	0.024	0.801		
Kİ-67					
<%14	36.76±52.48				
≥%14	299.85±1444.12	0.114	0.236		
Histology					
Ductal	226.35±1222.57	1			
Lobular	9.82±5.19	-0.044	0.653		
Other	33.42±27.78	-0.049	0.612		
Histologic grade					
1	62.14±127.29	1			
2	46.58±122.17	-0.006	0.975		
3	281.62±1412.25	0.094	0.651		
Nuclear grade					
1	30.79±31.28	1			
2	257.96±1375.22	0.095	0.639		
3	79.89±150.15	0.019	0.923		
Mitosis					
1	61.21±194.2	1			
2	435.42±1873.98	0.159	0.101		
3	232.86±256.36	0.02	0.832		
Score					
1	32.6±67.34	1			
2	250.77±1332.33	0.087	0.428		
3	126.92±136.58	0.023	0.835		
Vascular invasion					
Negative	86.23±247.23				
Positive	119.77±443.36	0.049	0.684		
Lymphatic invasion					
Negative	154.11±465.05				
Positive	43.87±57.1	-0.165	0.168		
Perineural invasion					
Negative	131.26±403.8				
Positive	33.07±60.34	-0.138	0.252		
Axillary lymph node					
Negative	59.36±102.18				
Positive	120.11±451.67	0.099	0.443		
Subtype					
Luminal A	23.88±29.53	1			
Luminal B	92.3±232.44	0.03	0.768	0.127	0.297
HER2 positive	903.29±1278.43	0.127	0.185	0.314	0.069
Triple negative	991.1±3186.57	0.277	0.007	0.321	0.234

and ER and PR-negativity was commonly demonstrated in the literature [9,12,13,15,17]. In the study of Ekmekcioğlu et al., involving 140 BC patients, ER-negative patients were found to have significantly higher PT SUVmax values (p=0.004), but no significant differences were found between PR negative and positive patients (p=0.211) [11]. Despite the difference in BC patient numbers involved in the studies, ER and PR negativity are strongly correlated with PT SUVmax.

In the literature, results for the correlation between SUVmax and ER/PR status were substantially similar while it was conflicting for HER2 overexpression. In literature, some studies reported the highest SUVmax values in the HER2 positive group as in our study [10,13,16,18], while some had reported no correlation between them [11,12,17]. In Ugurluer et al., in the study, higher SUVmax values were detected in HER2 positive patients whereas the difference between the groups was not statistically significant (p=0.308) [15].

As compatible with our results, there is a positive association between PT SUVmax values and Ki-67 expression [10,11,16,19]. Ki-67 is a prognostic marker reflecting cell proliferation rate and tumor aggression. Ideal cutoff value for Ki-67 is still challenging. Different cut-off values are accepted in the literature. In this study we accepted 14% as a cutoff value as it was recommended in international Ki-67 in Breast Cancer Working Group [20].

In our study, as the mitosis score increased, a significant increase in PT SUVmax values were observed. This is an expected result and is similar to the findings of previous studies [16]. However, no significant differences were observed between PT SUVmax values and histologic grade, nuclear grade or invasion patterns.

There are recent studies investigating the correlations between tumor phenotypes, immunohistochemical profile and FDG PET/CT volumetric parameters like MTV and TLG. MTV and TLG have been reported to be capable of comprehensively reflecting glucose uptake within the whole tumor rather than a single-pixel value of 18F-FDG activity. Groheux et al., classified 171 stage 2 and 3 BC patients into three subgroups (TN, HER2 positive and ER-positive/HER2 negative) in their retrospective study [13]. There was no significant difference between the three groups regarding MTV values (p=0.089), but they reported significantly smaller MTVs in ER positive and in PR positive tumors than ER and PR negative tumors (p<0,03). TLG significantly differed among the three phenotype subgroups. Similarly, Chen et al., indicated that, TLG values were significantly different in group comparison (p=0.007), while MTV values were not (p=0.175) [21].

In our study, univariate regression analyses showed that those with negative ER and PR status had significantly higher MTV and TLG values than those with ER and PR positive status. The MTV and TLG values of TN patients were significantly higher than those of the Lum A group.

In our study, we investigated the potential efficacy of PET/CT parameters such as SUVmax, MTV and TLG in predicting the histopathological features and subtypes in BC patients. However, we have some limitations. We could not examine the association of PET parameters with survey because of inadequate data. Also, although our distribution of patients among subtypes is similar to the literature, there are very few patients in the HER2 positive group.

Conclusion

In this study, it was observed that SUVmax value was significantly correlated with histopathological-immunohistochemical factors and tumor subtypes in BC cases. In the literature, the relation between histopathological-immunohistochemical factors and MTV-TLG values are not commonly referred in BC patients. However, we've seen that these parameters might be higher in ER and PR-negative cases than in positive ones according to our results. We also observed that, higher MTV and TLG values are seen in TN patients compared to Lum A group. Further studies with larger patient groups are needed to provide more reliable statistical results.

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Conflict of interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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ORIGINAL ARTICLE

Physician migration through the lens of patient and physician rights: A qualitative evaluation from the Turkish Parliament

F. Gülsüm Önal

[1] Department of History of Medicine and Ethics, Faculty of Medicine, Trakya University. Edirne / Türkiye

Abstract

Physician migration, which maintains global importance in terms of health ethics, is a phenomenon that has gained momentum in Türkiye throughout the recent years. However, there are limited studies on this subject, and no research has been found that addresses the issue in terms of health ethics and rights. In this regard, this study is likely to contribute to a better understanding of Türkiye's physician migration. Furthermore, draw some attentions for solutions and health policies through the lens of physician and patients' rights. The population of the retrospectively designed study consists of research proposals related to physician migration in the Turkish Grand National Assembly and the statements of members of parliament in the general assembly proceedings during the same period. Data obtained from transcripts that were searched using keywords such as "physician," "doctor," "health," "migration," and "foreign countries" were coded and subjected to content analysis using a qualitative method. Multifaceted findings emerged in the context of physician and patient rights in the categories of "reasons," "consequences," and "solutions". It was observed that certain rights were more affected by the process, that rights were interdependent, and that structural regulations in the healthcare system were necessary for their fulfillment. There is a need for legislation that would concretely demonstrate physician rights in a legal status. In the context of physician rights, the prominence of "reasons" and the emphasis on patient rights in the "consequences" category also point to a significant ethical dilemma. The dilemma between the autonomy of the physician and the principle of justice, which is central to the ethical debate about physician migration, has been confirmed, indicating a need for further in-depth research on this topic. The purpose of this study is to evaluate how physician migration, which has recently increased in Türkiye, is addressed by members of the Turkish Grand National Assembly in terms of physician and patient rights.

Keywords: Physician migration, health ethics, patient rights, physician rights

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Corresponding Author:
F. Gülsüm Önal
Email: fgulsumonal@trakya.edu.tr

Introduction

The purpose of this study is to evaluate how physician migration, which has recently increased in Türkiye, is addressed by members of the Turkish Grand National Assembly (TGNA) in terms of physician and patient rights. While the phenomenon of migration, which holds great significance for healthcare ethics, has ancient roots in human history, its relevance has been progressively expanding in our century. In order to understand migration, an inevitable feature of modern societies, different definitions have been proposed and theories have been developed in the literature. Migration can simply but effectively be defined as "the voluntary or mandatory departure of an individual or a community from their geographical and sociocultural environment, to settle permanently or semi-permanently in another environment" [1,2]. On the other hand, brain drain, a noteworthy development in recent years, is considered a separate category. It refers to qualified individuals with higher education, creative and research capacities, leaving their home country to settle temporarily or semi-permanently in other countries and practicing their professions for the benefit of the host country [1,3,4].

Over the last two decades, there has been a considerable growth in physician migration, making medicine one of the most active sectors while also facing the most severe labor shortage among highly trained professionals. The number of foreign-trained physicians working in Organisation for Economic Co-operation and Development (OECD) countries has increased by 50% between 2006 and 2016 [5]. The escalation of medical brain drain in vulnerable and disadvantaged nations has worsened crucial staff shortages, resulting in inequity in access to essential healthcare services, raising ethical issues, and yielding an abundance of literature [6,7]. While some bioethicists argue for restrictions on physicians migrating from impoverished countries [8], some believe that such restrictions would interfere with physicians' professional autonomy [9].

Furthermore, the positive aspects of medical brain drain have been highlighted in World Health Organization (WHO) document "Addressing the International Migration of Health Workers". It maintains that besides addressing professional shortages in some countries, migration also has positive factors to it as enhancing individual skills, career opportunities, and living standards. However, the WHO is also working on regulating the ongoing acceleration through future projections and generating novel rules [10].

Physician migration from Türkiye to abroad has also gained momentum in recent years. According to data from the Turkish Medical Association (TMA), the number of physicians applying for the Good Standing Certificate, which is mandatory to practice abroad, was around 40 in the early 2010s, but it started to rise by 2021. The number reached 1403 in 2022 and 1649 in the first 7 months of 2023, with 288 applications in July, reaching the highest monthly number to this date [11].

In today's world, patient rights, which have gained legal status in many countries, are defined as "the rights guaranteed by international treaties, constitutions, laws, and other regulations to individuals in need of healthcare services simply because they are human beings" [12]. Additionally, this definition does not ensure the implementation of these rights, and patient rights are frequently confused with various other types of rights. A more comprehensive description of patients' rights that provides a more specific framework for identifying responsible parties is "as patients we gain rights from the moment we seek care at a healthcare facility". This definition indicates separate responsibilities for the state, healthcare institutions, healthcare administration, and healthcare workers [13].

In terms of legal regulations concerning patient rights in Türkiye, several steps have been taken in line with global developments. Before 998, relevant provisions were scattered across various legislations such as the Law on the Practice of Medicine and Medical Arts (1928), Medical Deontology Regulation (1960), General Public Health Law (1930), Law on Socialization (1961), Decree on the Organization and Duties of the Ministry of Health (1983), Basic Health Services Law (1987), Code of Obligations, Turkish Criminal

Code, Turkish Medical Association Law, and so forth. The 1998 Patient Rights Regulation consolidated fundamental concepts and concretely outlined patient rights. It identified many detailed rights under the categories such as "Equality in Access to Services," "Respect," "Request for Information," "Choosing and Rejecting Treatment," "Confidentiality," "Security," and "Selecting and Changing Professionals" [14].

Regarding Physician Rights, the relevant provisions are still scattered across various regulations, as was the case with patient rights in earlier stages. Laws and regulations that include these rights encompass the Constitution, Law on the Practice of Medicine and Medical Arts, Medical Deontology Regulation, Treatment Services Regulation, and State Civil Servants Law. Particularly, the Medical Deontology Regulation that came into effect in 1960 in Türkiye includes aspects related to both patient and physician rights. For instance, the following statement emphasizes physician autonomy: "Physicians and dentists shall act in accordance with their conscience and professional opinion, without succumbing to any influence or pressure, and they are free to determine the treatment they will apply" [15].

The TMA has published the "Physician Rights Declaration," which this study focuses on, to demonstrate the components of physician rights and consolidate them into a single document. This declaration is based on two main axes: "Physician's Rights Regarding the Individuals and Society to Whom Health Services are Provided" and "Physician's Rights Regarding the Institutions Where Health Services are Produced, Provided, and Financed."

Under the axis of "Physician's Rights Regarding the Individuals and Society to Whom Health Services are Provided," physicians have rights such as the ability to withdraw from providing services in cases of violence, the ability to refer patients to other establishments when conditions are not favorable, and the right to decline requests based on scientific knowledge and the benefit of the patient/society, within the framework of professional independence and autonomy.

The "Personal Rights," classified as "Rights Regarding Employment," include the right to request payment and achieve a sufficient income, rights concerning working hours, on-call duties, rest, and leave, the right to enhance professional knowledge and skills, the right to seek consultation, the right to refuse participation in criminal executions, the right to abstain from giving testimony, and the right to seek legal assistance [16]. Based on this general information, it can be expected that the implementation of both physician and patient rights could have an impact on physician migration.

The dynamics of the recent physician migration in Türkiye have been changing, an intricate phenomena that needs further research to be understood. Moreover, studies on this topic are quite limited, and there has been no research that addresses the issue from the perspective of healthcare ethics and rights. The purpose of this study is twofold: firstly, to present the recent migration factors in Türkiye from the perspective of the Turkish Grand National Assembly (TGNA); and secondly, to evaluate the implications of migration on physician and patient rights from a healthcare ethics standpoint. This study will contribute to the understanding of the phenomenon of migration, creating solutions to the problems it poses, and shaping healthcare policies related to rights. One of the significant developments of our era is the evolution of new rights in healthcare, particularly the increasing importance of patient rights. Therefore, evaluating the potential impacts of the migration process on patient and physician rights could be of strategic importance.

Materials and Methods

The scope of this retrospectively designed study comprises research proposals related to physician migration submitted to the TGNA and the minutes of general assembly sessions during the same period. The reason for selecting the TGNA as the data source is the limited availability of official sources related to the subject and the fact that parliamentary documents are the only reliable public data. The general assembly minutes and research proposals are openly accessible on the TGNA website. Research data were collected online through

the website by conducting searches using keywords such as "physician," "physicians," "health," "migration," and "abroad" within the documents. The first proposal addressing physician migration was submitted on December 13, 2021, and research proposals and general assembly minutes covering the period from that date until the start of this study on June 01, 2023, were coded and subjected to content analysis using consecutive numbers (T.1, T.2, T.3, *etc*.).

Although there are documents related to brain drain in the TGNA, they were excluded from the scope of this study as they do not directly address physicians and do not contain data related to healthcare ethics.

Content analysis, a method frequently used for evaluating qualitative research data, is employed to categorize recurring concepts or common themes and present data in a more comprehensible format for readers. In line with this major objective, the qualitative data obtained were analyzed in four stages: (1) Data coding, (2) Identification of themes, (3) Organization of codes and themes, and (4) Identification and interpretation of findings [17,18].

Key questions asked while scanning the minutes were approached from an exploratory perspective, and the opinions expressed by members of parliament were categorized under three main categories: "reasons for physician migration," "problems caused by physician migration," and "proposed solutions to halt migration." The researcher conducting the qualitative evaluation examined meaningful data related to healthcare ethics and rights in the texts, identified recurring concepts, and highlighted the physician and patient rights relationship indicated by these concepts.

Ethical standards were maintained throughout the research process. Ethics Committee approval was not required as all data were collected from publicly available sources. In the study, the principles of confidentiality and respect for the issues discussed in the parliamentary minutes were adhered to, and no personal or sensitive information was included in the analysis.

Results

The first research proposal related to physician migration in the TGNA was submitted on December 13, 2021, followed by three additional research proposals in 2022. The period between December 13, 2021, and June 1, 2023, corresponds to the 5th and 6th legislative years of the 27th Term of the TGNA. Out of a total of 163 minutes, 26 minutes that were relevant to the context of physician migration were coded and included in the analysis. The sessions in which the suggestions were submitted, as well as those that took place during the Medical Day celebrations on March 14, 2022, were the dates and times allocated for the context of physician migration being most fully addressed within the General Assembly. Furthermore, the context of physician migration was brought up by Members of Parliament during periods when verbal and physical violence incidents against physicians occurred. In a significant portion of the statements, discussions revolved around the rates of migration increase, critical assessments, and proposed solutions.

The rationale behind the proposals was to highlight the increase in physician migration rates and emphasized that if this trend is not reversed, it could lead to adverse and serious consequences. During the General Assembly sessions, the reasons for the increase and proposed solutions were more extensively discussed. The opinions of Members of Parliament regarding "causes of physician migration," "consequences of migration," and "proposed solutions" were ranked based on the frequency of statements and presented in Table-1.

TGNA Members' Evaluations on Physician Migration and the Context of Rights

When the statements related to the categories of causes, consequences, and solutions of physician migration in the TGNA general assembly minutes are considered within the context of physician and patient rights, multiple findings related to rights for both physicians and patients emerged. These findings are presented in Table-2.

Table 1. Evaluations and opinions of members of the Turkish Grand National Assembly on physician migration.

1.1. Reasons for physician migration
▪ Poor working conditions, staff shortages, excessive workload, and long working hours ▪ Occupational safety and health issues in the workplace, cases of violence and mobbing, impunity for violence ▪ Inadequacy of legal regulations protecting healthcare workers' professional rights ▪ Low wages leading to poverty and affecting quality of life, inflation affecting livelihood ▪ Loss of reputation and its impact professional status, language that marginalizes healthcare workers ▪ Lack of merit and failure to recognize achievements ▪ Malpractice lawsuits, compensation, and complaints to Presidency of the Republic of Türkiye Communication Center ▪ Difficulty in working during retirement, unequal and low salaries ▪ Career expectations, concerns about the future, promises from abroad as an attractive factor ▪ Alienation from the profession causing mental health problems, burnout syndrome ▪ Neoliberalism, impact of problematic health policies, such as performance-based systems and weak welfare state, on the healthcare system ▪ Insufficient time allocated for proper care of patients ▪ Challenges in the domains of freedom and democracy, pressure on professional organizations
1.2. Challenges caused by migration
▪ Shortages, vacant positions in certain specialties, surgical restrictions, and public health issues ▪ Low patient satisfaction with healthcare services, loss of qualified services ▪ Lack of access to services for patients, difficulty in obtaining appointments through the Central Physician Appointment System (MHRS) ▪ Discrediting or negative opinions about healthcare service providers or institutions, increased violence in healthcare settings ▪ Challenges in medical education, regression in education quality ▪ National economic costs due to loss of physicians and increased health problems ▪ Increase in foreign doctors and language barriers ▪ Disruptions in cancer patients' treatments ▪ Insufficient focus on elderly health and care ▪ Problems affecting health tourism due to difficulties in healthcare services

1.3. Proposed solutions
▪ Comprehensive legal regulations to improve rights and prevent reputation loss ▪ An effective and deterrent law to prevent violence in healthcare ▪ Salary increase, gradual increase of additional indicators, determination of salary scale based on education level, years of service, and professional risk factors ▪ Increase in on-call payments, utilization of post-call leaves without causing economic loss ▪ Regulations regarding retirement rights and occupational hazard pay ▪ Termination of subcontracted and contracted services, secure employment under a single umbrella (in accordance with OECD average) ▪ Comprehensive legislation on occupational diseases, recognition of healthcare workers who lost their lives due to Covid-19 as martyrs, recognition of Covid-19 as an occupational disease ▪ Ending mobbing and antidemocratic practices, participation of labor and professional organizations in decision-making mechanisms ▪ Functioning medical faculties aligned with their purpose - quality medical education ▪ Priority given to preventive healthcare services and implementation of referral chain ▪ Cancellation of fees collected under names like "contribution fee" or "prescription fee" Equal, accessible, and free healthcare services addressing structural problems instead of populism

Table 2. Ethical and rights-related dimensions of physician migration.

Physician rights
▪ Right to practice the profession while adhering to ethical principles ▪ Right to protect one's own health by avoiding professional risks ▪ Right to request an increase in income ▪ Right to participate in decisions related to the profession ▪ Right to allocate sufficient time to patients ▪ Right to receive necessary training for the profession ▪ Right to preserve dignity and intellectual identity
Patient rights
▪ Right to access healthcare services and receive quality health care ▪ Right to benefit from medical innovations ▪ Right to respect for one's time ▪ Right to safety and quality standards ▪ Right to receive respect and recognition

The statements of Members of Parliament within the context of physician rights included: "Right to protect one's own health by avoiding professional risks," "Right to request an increase in income level," "Right to receive necessary education for the profession," "Right to participate in decisions related to the profession," "Right to allocate sufficient time to patients," "Right to practice the profession while adhering to ethical principles," "Right to preserve dignity and intellectual identity," and "Right to utilize modern and scientific methods."

Prominent rights in terms of patient rights include the "Right to access and receive quality healthcare services," "Right to safety and quality standards," "Right to respect for one's time," "Right to dignity," and "Right to benefit from medical innovations."

Factors causing physician migration are generally classified in the literature as "push" and "pull" factors. In the minutes, the increase in migration is predominantly attributed to "push factors." Many Members of Parliament made comparisons between the number of physicians per capita in Türkiye and OECD data, highlighting the inadequacy of the number of physicians and the potential risks. For example, following were stated: "More physicians want to go abroad than the number of graduates produced by the country's best faculties in a year" (T.3), "Türkiye has the lowest number of physicians per capita - these are global statistics - and the highest number of patients per physicians is also in Türkiye" (T.13), "The migration of tribes has ended in these lands, and the migration of physicians has begun" (T.15), "We cannot retain our physicians in Türkiye, this is the largest migration of physicians abroad in the history of our nation" (T.23).

On the other hand, different less prevalent perspectives that highlight attractive offers from abroad as "pull factors" and view them positively: "They say from abroad, 'Come running, I'll improve your well-being and opportunities. Among the reasons are the facilitation of the difficulties that Europe used to impose on physicians, and the increased trust in Turkish physicians" (T.15).

Findings Related to Physician Rights

In the TGNA minutes, causes of physician migration included issues related to healthcare workers, especially violence against healthcare professionals, as well as problems related to working conditions and the professional rights of physicians. Discourses using "othering language" were extensively addressed: "Physicians who are forced to go abroad due to working conditions in Türkiye mostly complain about overwhelming workloads, decreasing returns on overtime, serious loss of respect for the profession in recent times, losses in professional and retirement rights, and increasing violence in healthcare" (T.14), and "Pushed to the wall, they are seeking for solutions abroad" (T.23).

When the statements of Members of Parliament are evaluated within the context of physician rights, the "Right to protect one's own health by avoiding professional risks" encompassed issues such as violence against physicians and the impunity for such violence: "Approximately two-thirds of healthcare workers experience violence at least once in their professional lives. About one-third of the perpetrators are not held accountable, one-third are superficially detained and released, and the remaining one-third escape this situation with non-deterrent penalties" (T.14).

Under the umbrella of professional risks, the need for comprehensive legislation regarding occupational diseases, including Covid-19 and other hazardous situations, was also emphasized multiple times: "We need comprehensive legislation on occupational diseases, especially for Covid-19 and other work-related illnesses" (T.21).

The adverse effects of problematic working conditions on physicians' health, particularly on their mental health and "Burnout Syndrome" were highlighted. "at least 100 physicians with Burnout Syndrome leave our country every month" (T.3), "The problem is not just about money. The issue is the discomfort and unhappiness our physicians experience" (T.14), and "They feel alone and unsupported" (T.21).

While the decision of physicians to migrate is not solely based on economic reasons, low salaries

and the high cost of living were frequently cited factors. This issue, related to "the right to request an increase in income level," within the context of physician rights, was expressed by Members of Parliament in statements like: "Healthcare workers are not getting the value of their efforts. When the hours they work are considered, their salary is the lowest hourly wage in Türkiye" (T.8), and "They are leaving due to income levels that have regressed to the poverty line and problems related to their professional rights" (T.9).

Economic factors leading to migration also included inter-institutional salary inequality and retirement-related problems as a separate category: "It is essential to make arrangements to address salary inequality" (T.14), and "Regulations are needed regarding seniority bonuses, and there are serious issues for physicians in retirement" (T.15). Here, the problems arising from Türkiye's departure from being a welfare state were discussed, while commentaries regarding young physicians concerns about their career expectations and education-related problems were made: "They leave the country because they cannot progress" (T.2), and "In desperation, they seek a future in other countries" (T.11).

"The right of physicians to receive the necessary education for their profession," was addressed in accordance with challenges in medical schools and specialty training: "The main task of medical faculties is not just to treat patients but to train physicians. The deterioration of the quality of education due to the migration of faculty that would train specialist physicians is a major wound" (T.15).

In this context, the references to intergenerational differences and the "gerontocratic" attitudes, which means the dominance of older generation in leadership roles were found to be significant: "Our young people believe they are not understood by the leaders; they have lost so much hope that they choose to leave" (T.15).

Moreover, the right to "Participation in decisions related to one's profession," which is a fundamental right not only for young physicians but for all generations, was emphasized: "It is necessary to ensure the participation of labor and professional organizations in the decision-making mechanisms regarding the planning and delivery of health services" (T.14).

In the context of physician rights and professional ethics, another important finding was the statements related to the right to "devote adequate time to patients": "They say they cannot adequately and appropriately care for their patients due to the intensity of working conditions" (T.14). "Preventing violence in healthcare and ensuring patient satisfaction cannot be achieved by conducting patient examinations every five minutes" (T.15).

The inadequacy of the examination duration was associated with patient dissatisfaction and violence in the minutes. However, it is also within the scope of the physician's right to "practice the profession in accordance with ethical principles," due to its connection to the principles of "beneficence" and "non-maleficence" in medical ethics. There were direct statements in the minutes regarding this right: "They are troubled by not being able to perform their professions in a manner consistent with professional ethics" (T.15). Additionally, opinions concerning the physician's right to "preserve respectability and intellectual identity" can be evaluated in this context: "Physician respectability has disappeared, the right to a humane life is not granted" (T.7).

Statements were also uttered in the context of the right to "apply contemporary and scientific opportunities," which is significant given the rapid developments in science in our century: "We see that physicians and healthcare personnel are alienated from their work, and the spirit of research has almost disappeared" (T.14). "Scientists who are subjected to mobbing and humiliation by administrators" (T.16).

In this context, problems related to meritocracy and pressures in the workplace together with recruitment processes were particularly highlighted: "Immediate cessation of antidemocratic practices such as unwarranted appointments, investigations, and mobbing is demanded" (T.14). "Incompetent managers make the situation even more difficult to handle" (T.15).

Findings Related to Patient Rights

The TGNA transcripts include statements that assess the impact of physician emigration on healthcare services within the context of patient rights. Members of the parliament have expressed concerns primarily about the "right to access services and receive healthcare" and have framed the situation as a public health issue: "This is why Türkiye is facing a very deep public health problem. And a physician's shortage is awaiting" (T.3). "It will lead to a situation that will also affect public health" (T.4).

In this context, problems related to preventive healthcare services and structural issues in the healthcare system were specifically mentioned: "It is necessary to prioritize services that focus on preventive healthcare" (T.14). "Primary care is disappearing, people are getting sick" (T.23).

Within the transcripts, the commercialization of healthcare services was also mention within the context of the right to access services: "The healthcare fees collected under names of "contribution," "participation fee," and "prescription fee" should be abolished" (T.14). "If you have money, go to a private hospital; otherwise, wait for months or even years" (T.22).

Another frequently mentioned issue related to access to services was the Central Hospital Appointment System and the inability to obtain appointments: "Our citizens cannot get appointments on time, appointment dates extend from six months to two years" (T.14). "Hospitals are without physicians, people cannot find appointments for examinations and treatments" (T.20).

On the contrary, these problems are also related to the "right to respect for the patient's time and right to their dignity." Not only the inability to access services but also problems related to the quality of services were mentioned. In this regard, the patient's "right to security and quality standards" comes into play. Criticisms have been expressed, particularly against attempts to fill the physician gap with immigrant physicians: "What is important is to produce quality service and be able to provide it. It is not about increasing the number of Syrian physicians who even have difficulty speaking Turkish and enter medical faculties without exams" (T.22).

In the views of members of parliament, problems related to the quality of services were also associated with a loss of quality in medical education: "There are no physicians at the level of professors. Just as we lost our trained physicians, the number and quality of future physicians in Türkiye are also at serious risk" (T.15).

This issue is also related to the patient's "right to benefit from innovations in medicine." Especially due to medical malpractice cases and defensive medicine, it was mentioned that there will be more physician shortages in certain specialties, and the situation will deteriorate: "Some specialties don't even attract newly graduated physicians. Our physicians are afraid of these specialties due to the high workload and responsibility" (T.14).

Additionally, within the context of patient rights, issues related to specific groups, such as cancer and elderly patients, were highlighted: "Imagine what will happen if the treatment of cancer patients is disrupted" (T.17). "The brain drain of self-sacrificing physicians and nurses who will provide health and care services to our elderly going abroad" (T.15).

Discussion

There are limited studies regarding the recently increasing emigration of physicians from Türkiye, and no study has evaluated the aspects related to physician and patient rights. However, there are studies in the literature that generally discuss migration factors. The findings were evaluated in light of rights-related legislation along with these studies. Among the reasons for physician emigration stated by Members of Parliament, the prominence of "push" factors and the presence of a multifactorial process have been noted, which was also supported by studies conducted in Africa, the Middle East, South Asia, and Eastern Europe [19-24].

Dimensions Related to Physician Rights

When the statements of Members of Parliament regarding physician rights are evaluated, the prominent right mentioned was the "right to protect one's own health by avoiding professional risks." In this regard, the opinions

are consistent with both the TMA's Physician Rights Declaration and the Medical Deontology Regulation (TDR). Physicians have the right to protection against risks such as infection, radiation, and violence that they may encounter during their professional practice. Taking these risks into account and making arrangements for the protection and support of physicians in working conditions is a prerequisite for practicing medicine in our era [15,16,25].

Article 15 of the TDR states, "Physicians should make an effort to adhere to hygiene and protection rules, even at the cost of refusing to continue treatment when necessary, in other words, it is both a right and an obligation to protect their own health and the health of those around them." Thus, alongside the right, the regulation also imposes a responsibility on the physician.

One of the problems that may arise when this right is not fulfilled is Burnout Syndrome, which was raised by numerous members of parliament. The most widely accepted definition of this syndrome and the scale developed regarding it was by Maslach, who describes it as follows: "A syndrome observed in individuals who are required to work face-to-face with people and encounter intense emotional demands, characterized by physical exhaustion, prolonged fatigue, feelings of hopelessness and helplessness, and reflected in negative attitudes towards work, life, and other people" [26]. Maslach emphasizes organizational factors such as "workload, control, rewards, justice, and values" more than individual factors in its formation. Maslach suggests the "Workplace Civility and Respect" approach as an intervention strategy for this syndrome, stating that the same approach should be applicable during the medical faculty education process [26].

To overcome Burnout Syndrome, it is essential for physicians to work in conditions where they can apply the knowledge acquired in medical schools. This right, defined as the "right to apply modern and scientific opportunities," has been frequently mentioned in records. In fact, the Basic Health Services Law also refers to this right. According to Article 3/I of the Law, in order to achieve the desired level of healthcare nationwide, it is stated that "modern medical knowledge and technology should be brought to the country and be encouraged for" [27].

The issue of bringing contemporary medical knowledge and technology to the country undoubtedly should begin with the medical education process. In this regard, another issue observed among the reasons for physician emigration and its negative consequences is the "right to receive necessary education for their profession." This educational process, which concludes with completing medical school, is not a discontinuous process and is applicable not only during specialized training but also throughout continuous medical education after graduation. Parallel to the speed of medical knowledge production, physicians should be enabled to continuously sustain their professional development through continuous education without any interruptions [25].

On the other hand, fulfilling these rights undoubtedly requires the allocation of necessary time in addition to technical resources to keep up with scientific developments, thus necessitating the regulation of working hours accordingly. For public health workers, Article 99 of the Civil Servants Law, titled "Working Hours," generally sets the weekly working hours at 40 hours. However, with the amendment made in 2018, the phrase "different working hours may be determined in consideration of the characteristics of institutions and departments, through this law, special laws, presidential decrees, or regulations based on them" was added to the law [28]. The provision of different durations for public service health workers in the law and the absence of an upper limit for daily working hours can be subject to abuse, particularly to the disadvantage of consultants. The impact of long working hours for physicians and the issues faced by consultants on the decision to emigrate have been emphasized by members of parliament. The violation of these rights is also contrary to the regulations in the "Regulation on the Operation of Inpatient Treatment Institutions." Especially under Article 41/e titled "Principles of On-Call Duty," regulations regarding rest periods and compensation after on-call duties have been

established, and violations in this regard are frequently mentioned in records [29].

Considering the training that healthcare workers receive, the professional risks they undertake, and the effort they invest, it is widely accepted that they have a natural right to receive sufficient and satisfactory compensation [30]. From this perspective, regardless of who the recipient of the healthcare workers' demand for wages is, it is emphasized by members of parliament that the wages they receive should be sufficient; the "right to request an increase in income" is frequently discussed. Many situations mentioned in records regarding working hours and wages within the context of employment rights, which can actually be intertwined with the "right to preserve one's dignity," which implies the physician's and other healthcare workers' right to receive respect from patients and to allocate adequate time for themselves and their families.

Another right that is significant from a healthcare ethics perspective and is heavily emphasized is the "right to practice the profession while adhering to ethical principles." According to the TMA Physician Rights Declaration, when a physician encounters ethical dilemmas where legal, political, societal, aesthetic, and economic values conflict while practicing their profession, they should have the right to make free and independent decisions. Article 6 of the TDR states that a physician should act according to their conscience and professional judgment while practicing the art and profession of medicine, and they are free to choose the treatment they will apply, emphasizing physician autonomy and guaranteeing the right to choose the method of treatment. Furthermore, every physician is not only obliged to adhere to medical ethical principles themselves but also has the right to demand that their colleagues adhere to these principles. This right is explicitly stated in Articles 38 and 39 of the TDR [15,16].

Another dimension frequently mentioned in relation to practicing the profession while adhering to ethical principles while also related to patient rights is the "right to allocate sufficient time to the patient." It is expected that a physician should show necessary care to their patients, maintain good record-keeping of information and documents, and provide the patient with information regarding their illness. In accordance with this, the professional organization recommends regulating the daily patient load and time allocated to each patient in compliance with international standards, suggesting an average of 20 patients per day with a consultation time of 20 minutes. A study conducted by compiling national and international sources on the subject has concluded that outpatient examination times should not be less than 10 minutes, and this time should be even longer for complex medical conditions [31]. The study also highlights the need for a detailed analysis of the time allocated for outpatient visits in both primary and secondary healthcare services in Türkiye, suggesting that ideal timeframes should be determined and shared with the public based on this data.

In the context of physician rights, another important dimension expressed in records is the democratic rights outlined in the Physician Rights Declaration, including the right to seek solidarity and cooperation among colleagues, the right to organize, and the right to participate in and oversee administrative and department-related decisions within the institutions where they work. The "right to participate in decisions related to the profession" is frequently emphasized by members of parliament. Physicians have the right to contribute to decisions in the institutions where they work and in administrative matters related to the country, as well as to express their opinions on healthcare legislation. This right is based on both their active and influential role in the institutions they serve and their respected status as educated individuals in society due to the nature of their occupation. Additionally, the ability to "exercise control," allowing individuals to use initiative in their work, giving them a sense of agency and empowerment, is also protective against Burnout Syndrome [26].

The utilization of democratic rights is also interconnected with the physicians' "right to preserve an identity as an intellectual." A physician has the right to practice their profession without being under pressure and to avoid situations that conflict with their values. It

should be noted that the identity of a physician is shaped by a demanding and arduous learning process that begins with entering medical school. Throughout the evolutionary development of medicine, one of the reasons for the prominence of physicians has been their "intellectual" qualities. Both globally and in our country, there are many historical and contemporary examples of physicians being initiators, directors, or shapers of social and political movements [25].

It has also been extensively discussed in the records that there are pressures on professional associations, physicians, and all healthcare workers regarding their right to organize, while obstacles to the pursuit of rights should be removed in today's environment of increased violence and challenging working conditions. However, research indicates that the professional and union organization of physicians is not at the desired level. The most significant reasons for this are both the inadequacy of these organizations in meeting the demands of their members and the pressures on healthcare workers who engage in organizational activities within the institutions where they work [32].

Aspects Related to Patient Rights

In the World Medical Association's Declaration of Patient Rights, while explaining the logic of rights, emphasis is placed on the need for physicians to maintain their professional independence, especially when determining what is best for the patient. It is highlighted that one of the indirect paths to patient rights goes through the "autonomy of the physician" [13,33]. Indeed, physician rights and patient rights in healthcare are mutually influential rights under the same umbrella. The findings related to patient rights in our study also confirmed this. The dimensions of physicians' rights expressed in the statements in the TGNA records correspond to patient rights. For instance, the right of physicians to provide qualified healthcare services corresponds to the right of patients to "access and receive quality healthcare services," and this correlation was frequently emphasized. In the Patient Rights Code (PRC), the right to "Benefit from Services in a Just and Fair Manner" (Article 6) [14] obliges not only the healthcare workers but also all institutions and organizations in the healthcare services to provide it in accordance with the principles of justice and fairness. Therefore, it references not only physicians but also the entire healthcare system. When we pay attention to the other problems expressed in the records, difficulties in accessing services, physician shortages, and similar issues are not only mentioned in relation to patient rights but reference the healthcare system in general. For example, a frequently mentioned concrete issue raised in the records is patients' inability to secure appointments and long wait times. This issue can be interpreted in the context of the right of "Respect for Patients' Time," which is included in the Patient Rights Code implicitly and mentioned explicitly in the European Charter of Patients' Rights Basis Document (Rome, November 2002, Article 7). In this article, it is stated that "The determination of waiting times is the responsibility of healthcare services. If healthcare services cannot be provided within the predetermined time, the use of alternative services of the same quality should be ensured, and the resulting expenses should be reimbursed to patients within a reasonable period. Physicians should allocate sufficient time to inform their patients, including the time for information sharing." These statements signify both the right of physicians to allocate time to patients and the necessity for these rights to be regulated by the healthcare system.

Similarly, Article 11 of the PRC regulates the right to "Diagnosis, Treatment, and Care in Accordance with Medical Necessities." According to this, "patients have the right to request their diagnosis to be made, treatment to be conducted, and care to be provided in line with the requirements of modern medical knowledge and technology." The fulfilment of this right inherently necessitates ensuring the physician's right to follow contemporary scientific developments. Thus, it requires structural adjustments within the healthcare system. The right to "Safety and Quality Standards" for patients, regulated in Article 37 of the PRC, can also be approached in this manner.

Another implication of the healthcare and physician shortages caused by migration,

frequently emphasized in the records, pertains to the patient's freedom of choice. This is in line with the "Right to Choose and Change Healthcare Facility" (Article 8) and the "Right to Recognize, Choose, and Change Personnel" (Article 9) in the PRC.

Beyond all these rights from a perspective of healthcare ethics and values, the "Right to Preserve Dignity and Respect," which is included in all regulations regarding patient and physician rights deserves special attention. This right has been emphasized by almost all members of parliament who spoke on the issue of physician migration. This finding not only supports legislation related to rights but also numerous Constitutional norms, especially the right to protect and enhance one's material and spiritual existence [34].

Conclusion

In this study, we evaluated how the increasing physician migration in Türkiye is addressed in the TGNA in the context of physician and patient rights. It was observed that brain drain in healthcare, which is inherently value-driven, has consequences in terms of ethical values and rights. Firstly, physician rights and patient rights are mutually influential and that fulfilling these rights requires structural adjustments within the healthcare system. Secondly, there is a need to consolidate physicians' rights, scattered throughout regulations, in a legislation that concretely demonstrates their components, and thus to establish legal status. Lastly, we discussed physician migration within three main categories: "causes," "consequences," and "solutions."

Physician rights predominantly fall under the "causes" category, while patient rights are highlighted in the "consequences" category, indicating an important ethical dilemma. In the literature, the central ethical dilemma in the discussions of physician migration in relation to medical ethical principles revolves around the autonomy of the physician and the principle of justice. While our findings also demonstrate a similarity in terms of rights, further in-depth research is needed in this regard. In conclusion, comprehensive studies evaluating the both "push and pull" factors and implementations that can be taken for the future of Türkiye's healthcare system are needed.

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REVIEW

Discussion of International Association for the Study of Pain (IASP) pain definition: What has changed in 2020?

Buket Özkara Yılmaz[1] **Emre Aydın**[2]

[1] Department of Neurology, Faculty of Medicine, Sanko University. Gaziantep / Türkiye
[2] Department of Neurology, Faculty of Medicine, Bandırma On Yedi Eylül University. Balıkesir / Türkiye

Abstract

International Association for the Study of Pain (IASP) assigned a committee for setting a definition of pain, in year 1979. Despite many criticisms and suggestions, the definition introduced in year 1979 has been kept almost unchanged, except for the slight changes made in years 1986, 1994, and 2011. Since the criticisms from various philosophical and scientific disciplines increased in the recent period, the association assigned a team of 14 researchers and clinicians, who were at the forefront in their disciplines, in year 2018 to revise the definition. Slight modifications were suggested for the definition and explanation in year 2020. In this paper, the definition of pain suggested in year 2011 is examined first. Then, the alternative definitions and criticisms from the scientific and philosophical actors are discussed and, finally, the criticisms addressing the definition proposed in 2020 are reviewed after assessing the definition.

Keywords: International, pain, definition, criticism

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Corresponding Author:
Buket Özkara Yılmaz
Email: buketozkara4188@hotmail.com

Introduction

Everybody knows the pain as a feeling however, when it was wanted to define exactly, it doesn't seem as easy as before. International Association for the Study of Pain (IASP) was formed in 1975, and started to work on a definition for pain that many scientists from different sub-disciplines can be agree on. The definition was criticized from many different points of view. In this article the definition of pain suggested in year 2011 is examined first, after discussing the main topics, it is pointed why a revision is needed and finally some clarifications will be made.

Definition and Explanation of Pain in 2011

Pain

An unpleasant sensory and emotional experience associated with actual orpotential tissue damage, or described in terms of such damage.

Note

Pain is always subjective. Each individual learns the application of the word through experiences related to injury in early life. Biologists recognize that those stimuli which cause pain are liable to damage tissue. Accordingly, pain is that experience which we associate with actual or potential tissue damage. It is unquestionably a sensation in a part or parts of the body but it is also always unpleasant and therefore also an emotional experience. Experiences which resemble pain, eg, pricking, but are not unpleasant, should not becalled pain. Unpleasant abnormal experiences (dysaesthesiae) may also be pain but are not necessarily so because, subjectively, they may not have the usual sensory qualities of pain. Many people report pain in the absence of tissue damage or any likely pathophysiological cause; usually this happens for psychological reasons. There is no way to distinguish their experience from that due to tissue damage if we take the subjective report. If they regard their experience as pain and if they report it in the same ways as pain caused by tissue damage, it should be accepted as pain. This definition avoids tying pain to the stimulus. Activity induced in the nociceptor and nociceptive pathways by a noxious stimulus is not pain, which is always a psychological state, even though we may well appreciate that pain most often has a proximate physical cause.

When the main definition can be dissected to two parts for analyzing, it can be achived that the first parts are the same but the second parts are different sentences.

1) Unpleasant emotional and sensory experience + related with actual or potential tissue damage

2) Unpleasant emotional and sensory experience + can be defined in terms of actual or potential tissue damage

The first parts of the sentences indicate that the pain is a subjective state of consciousness, whereas the second parts defines if it is related with any actual or potential tissue damage. It can be understood that the pain is a subjective state of consciousness that incorporates actual or potential tissue damage or pain is experienced similar to those experienced by individuals having tissue damage. For IASP, the main point of view the definition can be accepted as its subjectivity [1].

The term "sensory" in the definition refers to a subjective consciousness experience arising from pain-specific neural system structures (different from other sensory experiences), having a specific *sui generis* qualitative character different from the other sensorial states such as sight and touch senses, and generally localized to a specific region of the body. The term "unpleasant" indicates the hedonic part of the experience. It is emphasized that all the consciousness states have a hedonic value (pain, neutral, pleasure) and the pain experience is an unpleasant experience. The term "emotional", as widely used in psychology, is accepted as the organism's complex response, which consists of subjective behavioral and physiological components, to internal and external stimulants. In case of pain, it can be considered that the emotional response determined by neurophysiological changes in tissue damage is experienced in an unpleasant way.

First sentence above successfully defines the classical pain experiences arising from actual tissue damage. It can be seen that the main purpose of the second sentence is to explain the pain experiences that can not be physically related to tissue damage. Majority of the explanation

following the definition aims to explain the relationship of pain with tissue damage. To sum up, explanation part emphasizes that;

Pain is a subjective experience,

It has specific qualitative characteristics (unpleasant, sensory, and emotional),

This experience is not necessarily related with tissue damage,

This experience does not have to be verbally expressed,

Other experiences, which are similar to the pain but do not have the qualitative characteristics that are specific to the pain, can not be defined as pain,

Even if it is related with physical and nociceptive system, it can not be degraded to them,

A person, who states that he/she has pain, should be considered to have pain.

Criticisms and alternative definition suggestions

The criticisms addressing the pain definition made in 2011 can be clustered under several main topics: firstly, philosophic criticisms asserting that the definition creates a fictious mental-physical duality, and eliminates the necessity of pain experience's mental origin from physical processes; secondly cognitive-linguistic criticisms alleged the pain experience requires, as a preliminary assumption, high levels of consciousness and linguistic skills; thirdly some thinks, it is ignored that pain experience have the social determinants and evolutionary origins; and finally, criticisms advocating that some terms in the definition ("unpleasant", "related", "can be defined in terms of") have no clear meaning or do not clearly represent the importance of experience.

In philosophical criticisms, it is asserted that the definition creates a mental/physical dualism by focusing on the subjective consciousness states. Statements *'... many individuals report pain when there is no tissue damage or any possible pathophysiological reason'* in the explanation and the statement *'... or can be defined in terms of this damage'* in the main definition prioritize the subjective experience for the pain experience and it suggests that the accompanying physical situations are contingent for the experience. According to the philosophical thought system called Cartesian Dualism, the realm of existence consists of non-spatial thinking existence/essence (res cogitans), main characteristic of which is the thought, and material existence/essence (ras extansa), main characteristic of which is to occupy a place [2].

Even if not as naiive and concrete as Descartes emphasized, the philosophers adopting the Dualist (duality of mind and body) thought define the mind and body as different from the aspect of existence. Although how to define the relationship between two realms of existence has not been clearly identified, it is advocated that there must be a relationship between them. The definition of pain expresses this relationship from the possibility (not mandatory) aspect and this situation causes problems from the perspective of the dualist philosophical approach. Materialist-reductionist philosophical perspective, however, claims that all the phenomena, including the mind, can be explained by reducing them into physical processes (reductive) Accordingly, the definition defining the relationship between pain experience and physical processes (tissue damage) from the possibility perspective is problematic also from the aspect of physical philosophical theories.

Even if IASP attends mostly on the subjectivism, the definition doesn't reject the pain is realized by the neurobiological system. It can be thought that, differing from the previous explanations, the relationship between physical processes and experience stated in definition can be re-assessed by considering the mechanistic pain classification introduced by IASP in year 2011. According to this classification, all the pains can be clustered under 4 titles (the vast majority in the first three of them); nociceptive pain, neuropathic pain, nociplastic (algopathic) pain, and pains with (yet) unknown reasons [3,4,5]. It can be stated that nociceptive pains originate from actual or potential damage of non-neuronal tissues or stimulation of nociceptors, whereas neuropathic pains originate from lesions or diseases affecting the somatosensory neural system, and nociplastic pains can be defined as the change of the sensitivity of nociceptive system without

a lesion or stimulus affecting the nociceptors or somatosensory system. It can be stated that, if it is possible to examine many pain experiences, which cannot be related to a physical disorder stated in the definition, in detail, they can be assigned to one of the pathophysiological pain classes introduced by IASP and, in case of an increase in clinical competence in future, there will be no pain experience that cannot be related to physical processes and philosophical criticism will not create a problem for the definition of pain.

Another criticism addressing the definition is that pain experience requires high level of cognitive and lingual skills [6]. For instance, asserted that, not having the ability to express themselves, the newborns, toddlers, mentally retarded individuals, those having dementia, those having lingual limitations, and primate and non-primate animals cannot meet the lingual and cognitive criteria specified in the definition [7,8]. Aydede stated that the sentences *"... many individuals report pain when there is neither tissue damage nor potential pathophysiological reason."*, *"... if the subjective expressions are considered, then there is no way to distinguish the experiences generally originating from the tissue damage."*, and *"...if an individual considers his/her experience as pain and defines it the same as the pain arising from the tissue damage, then it should be considered as pain."* in the definition are the main points addressed by the lingual-cognitive criticisms. Aydede alleged that the individuals asserting the criticisms misinterpreted these sentences and they accept the presuppositions that it is possible to express the hypothesis *"if it is expressed verbally* ***(p)*****, then** *there is pain experience* ***(q)****"* as *"if it is not verbally expressed* ***(-p)*****, then** *there is no pain experience***(-q)***"*. However, Aydede emphasized that these presuppositions incorporate a fundamental logical error; the hypothesis that "if p, then q" cannot be interpreted as "if –p, then –q". It can be claimed that, since there is no sentence in the definition that the presence of a connection between pain experience and lingual processes is compulsory, the connection is possible but, even if it is not verbally expressed, it is possible to experience pain [9].

Some of the thoughts advocating the biopsychosocial model in social sciences and health sciences argue that pain diagnosis considers the experience disconnected from the social and cultural aspects. They highlight the pain can be experienced via the mediation of the environment, the opponents addressing this criticism may assert that it cannot be denied that all the consciousness experiences, including the pain, should be examined within the social and cultural environment but it's necessary but not the sufficient condition. They use an example of a pain experience in the desert, that social aspect is not a fundamental necessity for the pain experience So, besides the social and psychological conditions, many other factors can affect the pain experience and such far causal factors should not necessarily be included in a general definition [10].

The criticisms arguing that some terms in the definition ("unpleasant", "related", "can be defined in terms of") have no clear meaning, the term 'unpleasant' makes many acute and chronic pain experiences, which are clinically severe, tend to be perceived unimportant [7], whereas the term "related" expresses the relationship between experience and physical processes loosely. For instance, in the unpleasant dentist anxiety, which is related with a childhood trauma, can meet the relatedness criteria specified in the definition [11-13]. Addressing these difficulties, Aydede suggested the use of the term *"paradigmatically occurring as a result of…"* (paradigmatically arising from actual or potential tissue damage), which is claimed to better emphasize the mental and physical causality, instead of the term "related". Here, the author points out the compulsory relationship between tissue damage and experience by using "paradigmatic" instead of "related". For the cases with no tissue damage, by referring to the subjective similarity of experience, it was recommended to use the term *"similar to or the same type of current experience"* (paradigmatically occurring as a result of an actual or potential tissue damage or the same or similar to the current experience) instead of "*can be defined in terms of*" [9].

Results

In conclusion, pioneering researchers studying the definition of pain and remarking the subjects mentioned above proposed alternative definition suggestions to the definition by IASP;

Some think that the definition misses the emphasis of evolutional origins, Wright proposed the definition below;

"Unpleasant sensation that has evolved to motivate the behavior to avoid or minimize the tissue damage or promotes recovery."[13].

Arguing that the term 'unpleasant' trivializes the importance of pain experience and does not sufficiently emphasize the psychosocial aspect of the definition, Williams and Craig suggested the definition;

"Pain is a distressing experience associated with actual or potential tissue damage with sensory, emotional, cognitive and social components." [7].

The definition is critized that there is no clear idea about the body-experience distinction and the term 'unpleasant' does not reflect the existential importance of pain, Cohen proposed the definition;

"Mutually recognized somatic experience that reflects aperson's apprehension of threat to their bodily or existential integrity" [10].

Generally advocating that the definition by ISAP is sufficient, Aydede proposed changing some of terms, meanings of which cause uncertainty according to his thought;

"Unpleasant sensory and emotional experience that paradigmatically results from actual or potential tissue damage or is of the same kind or similar to such an experience." [9].

After the analyzing the criticisms from various disciplines and suggestions of leading researchers, IASP proposed a preliminary definition in July 2019 on its website and the feedbacks were received between 7th August 2019 and 11th September 2019. The preliminary definition of pain that was provided for the public feedback;

Pain

A distressing sensory and emotional experience typically associated with, or resembling that associated with, actual or potential tissue damage

Notes

1) Pain is a subjective experience that is always affected by biological, psychological, and social factors to various degrees.

2) Pain and nociception are different phenomena: pain experience cannot be degraded into activity in sensory pathways.

3) Individuals learn the pain concept and its implications through their life experiences.

4) If a person expresses that his/her experience is a pain, then it is respected and accepted.

5) Even though pain generally serves for an adaptive role, it might have negative effects on functional, social, and psychological wellbeing.

6) Verbal description is only one of several behaviors expressing the pain; inability to establish a communication does not eliminate the possibility of a human or non-human animal to experience pain.

Etymology

Medieval English, from Anglo-French peine (pain, sorrow), Latin poena (punishment), and Greek poine (payment, punishment, indemnity). *Montreal Declaration, which is a document published on 3rd September 2010 in the 1st International Pain Summit, states that "Access to pain management is a fundamental human right".

The Committee, which assessed 808 feedbacks from 46 countries, determined 4 major principles to be used in setting the final form of definition; 1) definition of pain should be simple and practical to be translated to other languages. 2) definition should better specify the personal pain experience. 3) definition should offer more specificity about various components of pain. 4) pain should refer to tissue injury and be more compatible with modern conceptualizations. As a result of the feedbacks that the Committee received, it was stated that the term "distressing" is not easily understood and not easy to translate and unlike the term "unpleasant", it reminds the motivational aspects besides the hedonic aspect,

the old term should be used. Considering the recommendation of drawing less attention to the tissue damage in accordance with modern pain concepts, it was suggested to use the term "related with" from the old definition instead of "typically originating from" proposed in the draft definition. No change was proposed for the explanation. Then, IASP finalized the definition and published it in year 2020 [14,15].

2020 Revised Pain Definition and Notes (Notes Were Unchanged)

Pain

An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage.

Discussion

Discussion of the New Definition

It can be stated that IASP generally noted the lingual-cognitive and biopsychosocial model criticisms and made several additions to the notes part of the new definition. Unsympathetic long paragraph of note is shortened and rewritten systematically. As the main point of the definition, pain is accepted as a subjective experience which has specific characteristics. Beside this it can be claimed that the question of how to distinguish the pain experience which are no pain but similar to pain, is the main problem that the definition has difficulty in answering [9]. It seems hard to determine why many different types of pain such as sore, throat, migraine are considered as pain but many experiences that are similar but not pain [12]. The definition by IASP addresses this point by stating that the qualitative characteristics of experiences in cases of actual or potential tissue damage should be defined as pain. When the definition can be examined by dividing into two parts; the first part defines the experience and has the 1st-person epistemology, while the second part defines the physical damage and has the 3rd-person epistemology. It is aimed to define distinctive characteristics of experiences in the 1st-person epistemology by making use of the physical damage terms in the 3rd-person epistemology. At this point, it can be claimed that the definition involves an epistemological dilemma. To solve this problem, the first option is to loosen the link between the first and second parts of definition in order to include all the types of pain in the large pathophysiological scale, whereas the second option is to keep the link between the first and second parts solid in order to better define the limits of pain. It can be stated that IASP in the preliminary draft definition in 2019 and Aydede in the alternative definitions he proposed, aimed to put the second option in practice. The terms Aydede suggested to add into the definition aim to emphasize the physical processes and to define the limits of pain more clearly. The term "distressing" proposed in the preliminary draft in 2019 instead of the term "unpleasant" aims to better define the pain experience. Since IASP aims to offer a wide description involving all the types of pain as a general principle, it can be seen that it preferred using the terms, which keep the link between physical processes and pain experience looser. Given the last sentence of definition, it can be said that the phrase "resembling that associated with" considers the relationship of subjective pain experience with the tissue damage looser when compared to the term proposed by Aydede.

Conclusion

As the main point of the definition, pain is accepted as a subjective experience which has specific characteristics. Besides this, it can be claimed that the question of how to distinguish the pain experience which are no pain but similar to pain, is the main problem that the definition has difficulty in answering.

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Conflict of interest

The authors declare no conflict of interest in preparing this article.

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Text Box 1. IASP Definition of Pain (2011)

Pain

An unpleasant sensory and emotional experience associated with actual orpotential tissue damage, or described in terms of such damage.

Note

Pain is always subjective. Each individual learns the application of the word through experiences related to injury in early life. Biologists recognize that those stimuli which cause pain are liable to damage tissue. Accordingly, pain is that experience which we associate with actual or potential tissue damage. It is unquestionably a sensation in a part or parts of the body but it is also always unpleasant and therefore also an emotional experience. Experiences which resemble pain, eg, pricking, but are not unpleasant, should not becalled pain. Unpleasant abnormal experiences (dysaesthesiae) may also bepain but are not necessarily so because, subjectively, they may not have the usual sensory qualities of pain. Many people report pain in the absence of tissue damage or any likely pathophysiological cause; usually this happens for psychological reasons. There is no way to distinguish their experience from that due to tissue damage if we take the subjective report. If they regard their experience as pain and if they report it in the same ways as pain caused by tissue damage, it should be accepted as pain. This definition avoids tying pain to the stimulus. Activity induced in the nociceptor and nociceptive pathways by a noxious stimulus is not pain, which is always a psychological state, even though we may well appreciate that pain most often has a proximate physical cause.

Text Box 2. Revised IASP Definition of Pain (2020)

Pain

An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage.

Note

1)Pain is a subjective experience that is always affected by biological, psychological, and social factors to various degrees.

2)Pain and nociception are different phenomena: pain experience can not be degraded into activity in sensory pathways.

3)Individuals learn the pain concept and its implications through their life experiences.

4)If a person expresses that his/her experience is a pain, then it is respected and accepted.

5)Even though pain generally serves for an adaptive role, it might have negative effects on functional, social, and psychological wellbeing.

6)Verbal description is only one of several behaviors expressing the pain; inability to establish a communication does not eliminate the possibility of a human or non-human animal to experience pain.

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