

# Cost of Healthcare-associated Infections Developing After Endourologic Surgery and the Efficacy of Control Measures in a Turkish University Hospital

Türkiye'deki Bir Üniversite Hastanesinde Endoürolojik Cerrahi İşlem Sonrası Gelişen Hastane Enfeksiyonlarının Maliyeti ve Kontrol Önlemlerinin Etkisi

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## What's known on the subject? and What does the study add?

Besides posing a big threat to patient safety, healthcare-associated infections (HAI) cause serious additional costs and they are important cause of mortality in developed countries. While it is not possible to prevent all the cases of HAIs, it is probable to decrease HAI frequencies, high extra costs, high levels of mortality and lengthy bed-days through continuous monitoring and feedback of HAI, use of simple but extremely effective, evidence-based infection control systems and education and trainings. Therefore, the current study will provide additional information to the literature and will guide the surgeons willing to reduce HAIs.

## Abstract

**Objective:** The study aimed to determine additional costs of healthcare-associated infections (HAIs) in patients undergoing endourologic surgery. It also aimed to evaluate the effect of infection control measures on costs of HAIs.

**Materials and Methods:** This interventional study carried out in patients admitted to the Department of Urology at Osmangazi University Hospital between January 2014 and October 2015. All surgeries were examined in the pre-intervention period for six months and then, a prevention package and education period, which intended to reduce hospital infections, were implemented. In the post-intervention period, all endourological operations were examined for 2 months.

**Results:** The prevalence of HAIs in the pre-intervention and post-intervention periods was 10.1% and 4.9%, respectively. Patients who had healthcare-related infections before or after the intervention had higher costs compared to those who did not get infections. It was found that HAIs decreased by 51% after the intervention (relative risk: 0.49, 95% confidence interval: 0.28-0.86). Thus, an additional cost of 146.332.8±139.29 TL was saved.

**Conclusion:** It is concluded that monitoring and reporting of HAIs regularly by using a simple but effective and evidence-based infection control practices and education programs could decrease the frequency of infection, high additional costs and length of hospital stay.

**Keywords:** Cost, Healthcare-associated infections, Control measures, Türkiye

## Öz

**Amaç:** Bu çalışma endoürolojik cerrahi girişim yapılan hastalarda oluşan sağlık hizmeti ilişkili enfeksiyonların (SHİE) getirdiği ilave maliyetleri belirlemek ve yapılan müdahale ile alınan enfeksiyon kontrol önlemlerinin maliyet üzerine etkisini değerlendirmek amacı ile yapılmıştır.

**Gereç ve Yöntem:** Çalışma Eskişehir Osmangazi Üniversitesi Hastanesi Üroloji Anabilim Dalı Dalında, Ocak 2014-Ekim 2015 tarihleri arasında yürütülen bir müdahale araştırmadır. Müdahale öncesi dönemde tüm endoürolojik cerrahi girişimler 6 ay süre ile incelendi ve SHİE'yi azaltmaya yönelik hazırlanan önlem paketinin uygulanması ve yapılan eğitimler tamamlandı. Müdahale sonrası dönemde de 2 ay süre ile tüm endoürolojik işlemler incelendi.

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**Bulgular:** Müdahale öncesi dönemde çalışma grubundakilerin %10, SHİE tespit edilirken, müdahale sonrasında ise %4,9 olarak saptandı. Yapılan müdahale programı ile SHİE görülme sıklığının %51,0 oranında azaldığı saptandı (relatif risk: 0,49, %95 güven aralığı: 0,28-0,86). Müdahale öncesi ve sonrası SHİE tespit edilen bireylerin toplam maliyeti SHİE tespit edilmeyen bireylerden daha yüksek idi. Müdahale ile yıllık toplam 146,332,8±139,29 TL ek maliyetin önüne geçildi.

**Sonuç:** SHİE'nin izlenmesi ve sürekli geri bildirimini sağlanması, basit ama son derece etkili kanıta dayalı enfeksiyon kontrol önlemlerinin kullanılması ve yapılan eğitimler ile enfeksiyon sıklıklarının, SHİE'ye bağlı yüksek ek maliyetinin ve uzamış yatış sürelerini azaltmanın mümkün olduğu sonucuna varıldı.

**Anahtar Kelimeler:** Maliyet, Sağlık hizmeti ile ilişkili enfeksiyonlar, Kontrol önlemleri, Türkiye

## Introduction

Although many developments have been observed in the field of medicine, healthcare-associated infections (HAI) have become an important health problem all over the world due to high rates of mortality and morbidity as well as economic losses (1,2). According to the studies carried out in developing countries between 1995 and 2008, while the prevalence of HAIs was 5.7-19.1%, the incidence rate was reported as 1.7-23.6% (3). It has been ascertained that HAIs extend the length of hospital stay for 4 days on average and leads to 60.000 deaths in a year and, the USA spend up to 10 billion dollars more on it (4).

Although all the HAIs cannot be avoided, in a systematic review by Aboelela et al. (5), it has been reported that the interventions containing prevention packages are effective in reducing the HAI frequency. After a training program containing multidimensional infection control approaches, such as bundle of infection control interventions, education, surveillance, and performance feedback, carried out in 15 developing countries, including Türkiye, the incidence rate of HAIs decreased by 37% (6,7).

The prevention attempts against HAIs are cost-effective initiatives (3). In a study examining the cost of HAIs for 4 years after an infection prevention and control program carried out on 82.046 patients in 6 intensive care units in Canada, it has been reported that HAI was prevented in 4.739 patients in total and an additional cost of 9.1 billion dollars was avoided (8). Scarce resources allocated for the offering of health services will be fairly used by reducing the infection frequency through HAI prevention and control efforts by the adaptation of health professionals (9).

The aim of the study was to determine the extra costs brought by HAIs after endourological surgery in the Department of Urology at Eskişehir Osmangazi University Hospital and to evaluate the effects of the infection prevention and control measures on costs.

## Materials and Methods

### Study Design and Study Population

This intervention study was carried out on patients who underwent an endourological surgery in the Department of

Urology at Eskişehir Osmangazi University Hospital between January 2014 and October 2015. In this study, data was gathered by active surveillance based on patient and laboratory records. This study design was approved by the Eskişehir Osmangazi University Ethics Committee (80558721/27). Consent form was filled out by all participants. All endourologic surgeries were examined in the pre-intervention period for six months (1<sup>st</sup> January, 2014 to 30<sup>th</sup> June, 2014) and post-intervention period for two months (1<sup>st</sup> February, 2015 to 31<sup>st</sup> March, 2015). Between July 2014 and January 2015, the seven-month interventional study was carried out.

Patients included in the study were those aged 15 years and older and diagnosed with any infection upon questioning about symptoms of the urinary system infection and via physical examination. Neutropenic, pregnant and immunosuppressed patient, and those, who had any infection, urinary catheter inserted for any reason in the last 2 months and stayed in hospital less than 24 hours, were excluded from the study. In the pre-intervention period, of the 1384 endourological surgical procedures, 1095 (79.1%) were examined in accordance with the inclusion criteria. In the post-intervention period, of 595 endourological surgical procedures, 461 (78.5) were examined.

### Baseline Period

Patient age, gender, diagnosis, chronic diseases, hospital admission and discharge dates, the order in the queue for the operative room and presence of HAI were recorded. Following the collection of the data, the patient's billing information was taken from the hospital information system and recorded with the permission of the hospital management.

The cost of the treatment was included in the study. The billing information was examined in detail and the treatment costs were calculated. Costs were analyzed in four groups as service cost, drug cost, medical equipment cost and total cost.

Following the completion of the pre- and post-intervention periods, patients having HAI and those without HAI were matched. Age, gender and primary diagnosis of patients were used as matching variables.

Patients who met the matching criteria with no HAI were matched with each patient with HAI. With a simple random number generating algorithm, a patient with no HAI was

selected for each patient with HAI. Thus, it was aimed to reduce the confounding effect of other causes that increases cost. With this new dataset, the additional cost of HAI was determined.

### Intervention Period

#### Determination of Possible Causes that Increase Infection Incidence

At this stage of the study, a questionnaire consisting of 6 open-ended questions was prepared based on the the aim of determining the HAI prevention packages (10,11). This questionnaire was administered to the urology department lecturers, research assistants, operating room team and inpatient care nurses.

After analysing the questionnaire, it was realised that inadequate number of staff, improper sterilization, inadequate medical supplies, inadequate education and inadequate physical environment of the healthcare workplace lead to nosocomial infections.

#### Developing the Prevention Package

A prevention package was developed to reduce HAIs by evaluating the results of the feedbacks. Implementation of the prepared prevention packages and trainings were completed in January 2015.

The prevention package consisted of the following items;

- Assigning a specialised nurse for the urology operating room by the chief physician,
- Use of ethylene oxide for the sterilization of the device and sterilization system renewed by the chief physician,
- Training of nurses, research assistants and operating room personnel to prevent HAIs; while the objective of the training was to prevent and control HAIs, the goal of the education was to provide patient and employee safety and to promote and protect the awareness of health. The trainings included the definition of HAIs, the frequency of HAIs in the world and our country, the standard measures (hand washing, barrier precautions, medical waste management, isolation, sterilization and disinfection, etc.) to be taken to prevent HAI, the purpose of the infection control program and the effectiveness of package measures (face-to-face by using visuals, 4 sessions, 80 minutes in total, by the main author),
- Distribution of informative brochures prepared to prevent HAIs; the brochure emphasizes that all individuals could play a role in the prevention of infections and indicate what can be done to keep patients and their relatives healthy while receiving health care (face-to-face, 1 sessions, 10 minutes, by the main author). In addition, the brochure included the correct hand washing steps with visual supports suggested

by the World Health Organization (WHO), five-stepped, and objective tasks to teach the right hand washing behavior. These steps were one of the most important steps in preventing HAIs (12).

#### Definition of Healthcare-associated Infections

In terms of urinary system infection; at least one of the following sign or symptoms should be present: fever ( $>38^{\circ}\text{C}$ ), urgent need for urination, frequent urination, dysuria, suprapubic tenderness, pain or tenderness at the costovertebral angle, and positive urine cultures ( $>105$  cfu/mL) which are the main criterion for HAIs with the presence of at least one of the laboratory findings such as positive dipstick test for leukocyte esterase and/or nitrite, pyuria, and microorganisms in gram examination (13). Relative risk (RR) was also calculated in groups with and without HAIs. The incidence density was used to determine the HAIs dimension.

#### Statistical Analysis

The data was analysed using IBM-SPSS (version 22.0) statistical package program. For descriptive statistics, the frequencies, percentage, mean  $\pm$  standard deviation, median, minimum (min), maximum (max) and interquartile range (25-75) values were used. A chi-square test and the Kolmogorov-Smirnov test were used to compare the frequency between the groups. For the analysis of the costs, the Shapiro-Wilk test was performed and the Mann-Whitney U test was used for the comparison of the groups because the normality test did not fit the normal distribution. EPI Info V7 (CDC, Atlanta, Georgia, USA) package program was used to calculate the risk ratio. For statistical significance,  $p \leq 0.05$  was accepted.

#### Results

At the pre-intervention period, a total of 1.095 (79.1%) endourological surgeries were performed in 673 patients with a total of 2.428 bed-days. The average age of the patients was  $57.2 \pm 15.1$  (min: 15.0, max: 91.0) years. 26.6% ( $n=179$ ) of the patients were female and 73.4% ( $n=494$ ) were male. At the post-intervention period, a total of 461 (78.5%) endourological surgeries were performed in 306 patients with a total of 1.089 bed-days. The average age of the patients was  $55.5 \pm 15.3$  (min: 15.0, max: 91.0) years. 77.5% ( $n=237$ ) were male. There was no difference between the pre- and post-intervention groups in terms of gender ( $p=0.177$ ) and age ( $p=0.583$ ).

At the pre-intervention period, 10.1% of patients had nosocomial infection. At the post-intervention period, the nosocomial infection rate decreased to 4.9%. The incidence density of nosocomial infection was 28.0%<sup>0</sup> at the pre-intervention group, however, this value was measured as 13.7%<sup>0</sup> after the intervention. There was no difference between the pre- and post-intervention groups in terms of nosocomial infection with regard to gender, age group, physician-diagnosed diabetes, and

the presence of multiple chronic diseases ( $p>0.05$  for each) (Tables 1, 2).

The risk of nosocomial infections was increased in patients with a later order in the operation queue, and the number of bed-days in patients having nosocomial infection was higher in both pre- and post-intervention period ( $p<0.001$  for each) (Table 3).

**Table 1. The distribution of healthcare-associated infections presence in terms of study stages**

HAIs	Pre-intervention period		Post-intervention period		Total	
	n	%	n	%	n	%
No	605	89.9	291	95.1	896	91.5
Yes	68	10.1	15	4.9	83	8.5
Total	673	100.0	306	100.0	989	100.0

HAIs: Healthcare-associated infections  
 $\chi^2: 7.336; p=0.007$

After matching the data set, the costs of patients with nosocomial infection were higher than those of without nosocomial infection for both pre- and post-intervention period ( $p<0.001$  for each). Although the total cost of the patients without nosocomial infection at the post-intervention period was higher than the costs at the pre-intervention period, this value did not change for the patients with nosocomial infection ( $p=0.012$  and  $p=0.287$ , respectively) (Table 4).

The study groups were designed following matching; cost difference was calculated by subtracting the cost of patients with nosocomial infection from that of patients without nosocomial infection at the pre- and post-intervention period. While the difference in the median cost between patients with and without nosocomial infection before intervention was 1.002.9 TL, this value increased to 1.288.3 TL after intervention. After the matching, the difference in cost between patients with nosocomial infection and those without nosocomial

**Table 2. The distribution of healthcare-associated infections presence in terms of study stages with regard to some characteristics**

Some characteristics	HAIs (Pre-intervention period)						HAIs (Post-intervention period)						
	No		Yes		Total		No		Yes		Total		
	n	%	n	%	n	%	n	%	n	%	n	%	
Gender	Male	445	90.1	49	9.9	494	73.4	227	95.8	10	4.2	237	77.5
	Female	160	89.4	19	10.6	179	26.6	64	92.8	5	7.2	69	22.5
Test (p)	0.791						0.305						
Age (years)	15-39	78	87.6	11	12.4	89	13.2	49	94.2	3	5.8	52	17.0
	40-49	85	86.7	13	13.3	98	14.6	45	97.8	1	2.2	46	15.0
	50-59	146	93.0	11	7.0	157	23.3	65	92.9	5	7.1	70	22.9
	60-69	159	90.3	17	9.7	176	26.2	75	98.7	1	1.3	76	24.8
	$\geq 70$	137	89.5	16	10.5	153	22.7	57	91.9	5	8.1	62	20.3
Test (p)	0.510						0.287						
Physician-diagnosed diabetes*	No	382	89.3	46	10.7	428	87.2	115	92.7	9	7.3	124	75.2
	Yes	59	93.7	4	6.3	63	12.8	40	97.6	1	2.4	41	24.8
Test (p)	0.281						0.262						
Presence of multiple chronic disease*	No	338	90.9	34	9.1	372	75.8	114	92.7	9	7.3	123	74.5
	Yes	103	86.6	16	13.4	119	24.2	41	97.6	1	2.4	42	25.5
Test (p)	0.176						0.247						

HAIs: Healthcare-associated infections

\*Data from patients whose information was confirmed were evaluated

**Table 3. The distribution of the queue number for the surgery and the number of bed-days in terms of the presence of healthcare-associated infections according to study stages**

	HAIs (Pre-intervention period) Mean ± SD (Minimum-maximum)		HAIs (Post-intervention period) Mean ± SD (Minimum-maximum)	
	No	Yes	No	Yes
	Queue number for the surgery	4.2±3.2 (1.0-21.0)	5.2±3.5 (1.0-19.0)	4.9±3.1 (1.0-16.0)
Test (z; p)	8.824; <0.001		4.712; <0.001	
Number of bed-days	3.2±2.8 (1.0-29.0)	7.2±5.3 (2.0-33.0)	3.3±2.7 (1.0-25.0)	8.7±5.0 (1.0-21.0)
Test (z; p)	8.824; <0.001		4.712; <0.001	

SD: Standard deviation, HAIs: Healthcare-associated infections

**Table 4. The distribution of total costs of new study group after matching with and without healthcare-associated infections**

		Without HAIs infection		With HAIs infection		Test z; p	
		Pre-intervention period	Post-intervention period	Pre-intervention period	Post-intervention period	Pre-intervention period	Post-intervention period
Service cost (TL)	Median	424.9	555.1	1.216.9	1.605.2		
	IQR 25-75	308.8-687.1	432.9-1.085.4	873.0-1.767.2	876.3-2.134.5	8.230; <0.001	3.629; <0.001
	Test (z; p)	2.225; 0.026		1.018; 0.309			
Drug cost (TL)	Median	54.3	70.4	183.8	275.9		
	IQR 25-75	36.2-80.3	23.1-87.9	113.8-481.1	157.1-496.7	7.956; <0.001	3.754; <0.001
	Test (z; p)	0.438; 0.661		0.864; 0.388			
Medical equipment cost (TL)	Median	17.2	103.7	102.1	180.8		
	IQR 25-75	7.5-67.2	65.2-201.9	76.7-125.5	22.1-379.9	6.942; <0.001	1.182; 0.237
	Test (z; p)	4.343; <0.001		0.604; 0.546			
Total cost (TL)	Median	532.0	779.54	1.651.2	2.180.1		
	IQR 25-75	375.1-836.7	589.18-1.201.05	1.124.9-2.595.7	1.408.1-2.796.0	8.426; <0.001	4.003; <0.001
	Test (z; p)	2.521; 0.012		1.065; 0.287			

HAIs: Healthcare-associated infections, IQR: Interquartile range

infection was not changed with intervention at all the fields of intervention ( $p>0.05$  for each) (Table 5).

The infection frequency was decreased from 10.1% to 4.9% after the intervention carried out in the study. It was determined that with this intervention programme, a 51.0% decrease was observed in the incidence rate of nosocomial infection [RR: 0.49; 95% confidence interval (CI): 0.28-0.86;  $p<0.001$ ]. Two months after the intervention, nosocomial infection was seen

in 15 patients out of 306. If the intervention was not carried out, 31 patients would have had nosocomial infection by taking infection incidence rate before the intervention into consideration.

As a result, nosocomial infection was prevented by our intervention in 16 patients. When the post-intervention costs were considered, 146.332.8±139.29 TL were saved by preventing the development of the infection.

**Table 5. The distribution of cost differences of the patients with nosocomial infection with regard to that of the patients without healthcare-associated infections**

Cost differences		Median	IQR 25-75	Test (z; p)
Total cost (TL)	Pre-intervention period	1.002.9	745.7-1.774.1	-0.284; 0.776
	Post-intervention period*	1.288.3	294.8-1.889.8	
Service cost (TL)	Pre-intervention period	754.8	497.7-1.114.3	-0.651; 0.515
	Post-intervention period*	519.2	248.2-1.737.6	
Drug cost (TL)	Pre-intervention period	135.8	57.8-360.9	0.710; 0.478
	Post-intervention period*	189.8	71.4-427.1	
Medical equipment cost (TL)	Pre-intervention period	78.6	25.0-163.1	-0.635; 0.523
	Post-intervention period*	61.5	-56.4-297.9	

IQR: Interquartile range

\*A 5% discount was applied for the post-intervention period

## Discussion

Today, HAIs are the most common complications affecting hospitalized patients in the world (1,2). Besides posing a big threat to patient safety, HAIs are important cause of mortality. The incidence rate varies from 5.7% to 19.1% in low and middle income countries (3). In their one-day prevalence study performed in a university hospital, Metintaş et al. (14) found a hospital infection prevalence of 13.4%.

It has been put forward that HAIs cause serious extra costs in both developed countries and in Türkiye. Due to HAIs, the annual financial losses in the USA and Europe are approximately 6.5 billion US dollars and 7 billion euros, respectively (15). Extra cost for an infected patients has been reported to be 1.963 US dollars by Erbay et al. (16), and 2.026 US dollars by Esatoğlu et al. (17). In our study, the total cost of patients with nosocomial infection at the pre- and post-intervention period was higher than that of patients without nosocomial infection ( $p < 0.001$  for each). It has been reported that the costs increase owing to extended length of bed-days for patients with HAI, additional diagnostic tests and in particular, high-cost of antibacterial medicines used for treatment (5).

Reducing health-care costs and control of expenditures are the priority of many developing countries. While the share of health expenditures of the gross domestic product in the USA was 8.8% in 1980s, it increased to 15.2% in 2003 (18). Likewise, the share of health spending of the gross domestic product in France, Switzerland, Germany, Belgium, Austria, and Canada is above 10%, while the Organisation for Economic Co-operation and Development average is 9.3% (19). Although the share of health expenditures in general budget is increasing every year, it was 5.4% in Türkiye in 2013 (20). Many countries work on strategies for controlling and minimizing medical errors like HAIs. The USA has not been paying the additional costs of HAIs

since 2008 (21,22). It is being discussed whether hospitals with high levels of HAI should receive their reimbursement with 5% deduction on the basis of the Health Practices Statement (20).

Aboelela et al. (5) reported that interventions containing prevention strategies were effective in decreasing HAI frequency. It is possible to obtain such potential gains as reducing HAI loads, mortality rates and health expenditures through changing health-care workers behaviors, adoption of infection control practices and ensuring the continuation of prevention measures (23). It has been demonstrated that use of prevention measures in adult intensive care units of International Nosocomial Infection Control Consortium member hospitals have decreased the incidence rates of HAI by 37-58% and HAI mortality by 58% (23,24,25).

In this study the infection frequency has decreased from 10.1% to 4.9% through the intervention which equals to 51.0% decrease in rates (RR: 0.49; 95% CI: 0.28-0.86;  $p < 0.001$ ). In a prospective study carried out in Argentina through an intervention executed (phase 1: surveillance without an education and performance feedback; phase 2: addition of the education; phase 3: addition of performance feedback) HAI rates were decreased by 75% (RR: 0.25; 95% CI: 0.17-0.36;  $p < 0.0001$ ) (26). In analogy to our work, it has been shown in this article that education and training of healthcare workers can result in significant reduction in the rates of HAI. Similarly, in another study carried out in Mexico, an intervention (phase 1: active surveillance; phase 2: control of surveillance period and performance feedback) have made it possible to reduce the HAIs rate by 58% and the mortality rate from 48.5% to 32.8% (RR: 0.68; 95% CI: 0.50-0.31;  $p < 0.01$ ) (27).

Health systems, both private and publicly funded, face with the problem of providing cost effective and quality care. In Türkiye, the cost of many infection control measures is directly financed by the own budget of hospitals, while the extra costs caused by HAIs are paid by social security institutions (20).

Due to limited resources, it is important to make economically rational decisions in determining the measures to be taken for infection control. In this way, the limited resources are not only wasted and can be used more effectively. Measures for controlling infections and savings will enable individuals to reach health services more fairly (9).

In the study conducted by Esatoğlu et al. (17), the extra cost of HAI was reported to be 202.670 US dollars and it was stated that 30.754 US dollars could be saved in 4 months for 57 patients. Similarly, a study carried out on 82.046 patients in 6 intensive care units in Canada which examined the HAI costs after infection prevention and control programs, 4.739 cases of HAI were avoided and a total of 9.1 million Canadian dollars was saved (8).

After the matching, the difference in cost between patients with and without nosocomial infection did not change with the intervention in all the fields of intervention ( $p>0.05$  for each). The reason for this issue could be that the purpose of the intervention was decreasing HAI frequency rather than reducing the costs of offered services. As a result, 16 cases of nosocomial infection were prevented through the intervention carried out within the study period. When the post-intervention costs were considered, it was observed that  $146.332.8 \pm 139.29$  TL were saved through preventing the development of the infection.

In a systematic review by Bell et al. (28) investigating the cost-efficiency analyses published between 1976 and 2001, it was reported that only 9% (130 out of 1433) of the studies saved money and improved health simultaneously. According to the report by WHO, any intervention which provides saving three times more than gross national product per capita in a country could be counted as a cost-effective intervention (29). When gross national product per capita in Türkiye in 2014 (22.753 TL) is taken into consideration, the intervention carried out within the study could be counted as a cost-effective intervention on annual-basis.

### Study Limitations

In this study, only direct cost was calculated, but indirect cost was not included.

### Conclusion

While it is not possible to prevent all the cases of HAIs, it is possible to decrease the frequency of HAIs, high extra costs, high levels of mortality and lengthy bed-days through continuous monitoring and feedback of HAIs, use of simple but extremely effective evidence-based infection control systems and education and trainings. In order to realize all these developments, it is necessary to spend vigorous efforts; however, these efforts will contribute not only to decreasing HAI rates but also to eliminating economic losses.

### Ethics

**Ethics Committee Approval:** This study was approved by Ethics Committee of Eskişehir Osmangazi University Faculty of Medicine (approval number: 80558721/27).

**Informed Consent:** Consent form was filled out by all participants.

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

### Authorship Contributions

Concept: M.E.G., B.I., B.B., Design: M.E.G., B.I., B.B., Data Collection or Processing: M.E.G., B.I., Analysis or Interpretation: M.E.G., B.I., Literature Search: M.E.G., Writing: M.E.G.

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

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