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Evaluation of the Role of Whole Body Computed Tomography in the Management of Minor Trauma Patients

Minör Travma Hastalarının Yönetiminde Tüm Vücut Bilgisayarlı Tomografinin Rolünün Değerlendirilmesi

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Abstract

Aim: Whole body of computed tomography (WBCT) approach is increasingly being preferred by the clinicians over the traditional selected CT approach worldwide, not only for major trauma patients but even for minor trauma patients. Our aim was to determine the ratio of polytrauma patients in minor trauma patients imaged with WBCT and to determine demographical and clinical predictors of polytrauma.

Material and Method: This retrospective-descriptive-study was conducted at the emergency department with patients older than 16 but had an injury severity scores of less than 16 and those who underwent WBCT trauma patients between January 2015 and December 2018. The presence of polytrauma, which defined presence of injury with an abbreviated injury scale score ≥ 2 according to tomography results in at least two body regions, was considered as the primary outcome of the study.

Results: Total 3924 patients' data were enrolled in the study. Only in 278 of all patients (7.1%) polytrauma was detected. After the multi-logistic regression analysis, fall from height (>3 meters), pedestrian struck, altered mental status (GCS <14), and male sex were found as significant predictor factors for presence of polytrauma. When created a model with these parameters, it was found that it had low diagnostic accuracy value as 0.6 (95%CI: 0.59 to 0.72).

Conclusion: When considered only minor trauma patients with small polytrauma and mortality ratio, routine using of WBCT approach is not rational. The predictors found in our study can be used to develop a clinical decision rule in the future for minor trauma patients.

Keywords: Whole body computed tomography, pan-CT, tomography, X ray computed, multiple traumas, radiation exposure, polytrauma, emergency departments

Öz

Amaç: Tüm vücut bilgisayarlı tomografi (TVBT) yaklaşımı, klinisyenler tarafından sadece majör travma hastaları için değil, hatta minör travma hastaları için de dünya çapında geleneksel seçilmiş BT yaklaşımına göre giderek daha fazla tercih edilmektedir. Amacımız, TVBT ile görüntülenen minör travma hastalarında çoklu travma hastalarının oranını belirlemek ve çoklu travmanın demografik ve klinik belirleyicilerini belirlemekti.

Gereç ve Yöntem: Bu retrospektif-tanımlayıcı-çalışma, acil serviste 16 yaşından büyük ancak injury severty skoru <16 olan ve Ocak 2015 ile Aralık 2018 tarihleri arasında, WBCT çekilmiş olan travma hastalarının verileri incelenerek yapıldı. En az iki vücut bölgesinde tomografi sonuçlarına göre abbreviated injury scale skoru ≥2 olan yaralanma varlığı çalışmanın birincil sonlanımı olarak belirlendi.

Bulgular: Çalışmaya toplam 3924 hastanın verileri dahil edildi. Tüm hastaların sadece 278'inde (%7,1) çoklu travma tespit edildi. Çoklu lojistik regresyon analiz sonuçlarına göre, yüksekten düşme (>3 metre), yayaya araç çarpması, değişen mental durum (GCS <14) ve erkek cinsiyet, çoklu travma varlığı için anlamlı değişkenler olarak bulundu. Bu değişkenlerle bir model oluşturulduğunda, bu modelin 0,6 (%95 Cl: 0,59 ila 0,72) gibi düşük tanısal doğruluk değerine sahip olduğu bulunmuştur.

Sonuç: Çoklu travma ve mortalite oranı küçük olan sadece minör travma hastaları düşünüldüğünde, TVBT yaklaşımının rutin kullanımı akılcı değildir. Çalışmamızda bulunan prediktörler, minör travma hastaları için gelecekte klinik bir karar kuralı geliştirmek için kullanılabilir.

Anahtar Kelimeler: Tüm vücut bilgisayarlı tomografi, pan-CT, çoklu travma, radyasyon maruziyeti, politravma, acil tıp

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INTRODUCTION

The whole-body computed tomography (WBCT) which consists of unenhanced head and cervical, and contrastenhanced chest, abdomen, and pelvis computed tomography (CT), is an important imaging option in the management of multiple trauma patients. Contrary this approach, the traditional selected CT (SCT) approach of the ATLS is primarily to order conventional radiographs and focused abdominal sonography in trauma (FAST), and then to perform CT of the relevant body region within the indication.^[1,2] However, superiority of WBCT to SCT approach is still controversial. The main concerns about WBCT approach can be summarized as unnecessary radiation exposure it may cause and inadequate data on its mortality and morbidity benefit.^[3] Conflicting results regarding the effect of WBCT on mortality rates have been reported in the study results, which were mostly retrospective in the literature.[4-11] Although Sierink et al reported in their randomized controlled study (REACT-2 trial) that there was no significant difference on mortality between two approaches, the effect of WBCT approach on mortality and morbidity is still unclear.[12]

Despite this uncertainty in the literature, WBCT approach is increasingly being preferred by the clinicians over SCT approach worldwide. In fact, this preference is not only for major trauma patients but even for minor trauma patients. Among the possible reasons why WBCT is preferred even in minor trauma patients, some clinicians believe that WBCT may be advantageous in two issues; first, especially those such as crowded emergency departments in the US and Turkey,^[13] as SCT is a time-consuming approach, the WBCT approach decreases the emergency crowd by decreasing the patients' length of stay in the emergency department. Second, again, especially in these crowded emergency departments, it is thought that physicians working under intensive patient burden reduce the risk of misdiagnosis and prevent medicolegal problems when WBCT approach was preferred.

We aimed to analyze the data of minor trauma patients (injury severity score (ISS) <16) underwent WBCT by questioning the necessity of WBCT in these patients. The primary outcome of this study is to identify patients with polytrauma among these minor traumas. We aimed to determine, if detected, what parameters were present in the patient group, in which the WBCT approach was beneficial, the WBCT approach could detect patients with polytrauma.

MATERIAL AND METHOD

Study design and setting

This study was conducted at the emergency department (ED) of a tertiary care teaching hospital having annually 580,000 emergency patient admissions between January 2015 and December 2018. We examined the electronic records of patients admitted to the ED following local ethical committee approval.

Selection of participants

The hospital's electronic patient record management system was used for screening the data of the adult patients admitted to ED with trauma. The patients older than 16 but had an ISS of less than 16 and those who underwent WBCT were included in the study. Pregnant patients, duplicate applications and those with a lack of data were excluded from the study.

Measurements

Trauma patients who underwent unenhanced head and cervical, and contrast-enhanced chest, abdomen, and pelvis CTs were considered to be managed by the WBCT approach. All these CTs were accepted as WBCT protocol only if they were all taken with the same protocol and none were missing.

Five researchers who were emergency physicians with at least 3 years of experience were trained to collect data from the hospital data-registration system and to calculate the ISS of the patients before the study period. They scanned all trauma patients who underwent WBCT during the study period and calculated the ISS according to patients'WBCT results reported by a radiologist and physical examination records. When the agreement of the researchers in the calculation of the ISS is calculated with 100 same patients, the intraclass correlation was found good (intraclass correlation=0.793).

Outcomes

We determined the presence of polytrauma as the primary outcome of the study, as the potential benefit of the WBCT approach is thought to diagnose injuries in other systems outside the body region where the primary injury is. We defined polytrauma as the presence of injury with an Abbreviated Injury Scale (AIS) \geq 2 according to tomography results in at least two body regions.^[14] Accordingly, patients were divided into two groups; those with and without polytrauma. By determining which variables can predict the presence of polytrauma, we aimed to determine which patients could benefit from WBCT.

Analysis

All data were analyzed by IBM SPSS Statistics for Mac, version 25.0 for Mac OS X (IBM Corp., Armonk, N.Y., USA). The normality of the data distribution was determined by the Shapiro-Wilk test, histogram, and Q-Q plots. The categorical values of the patients were expressed as a number and a percentage and were analyzed with a Chi-square test. Continued values were presented as a mean and standard deviation or median values and an inter quartile range of 25%–75%. The non-parametric values were analyzed using the Mann–Whitney U, and the parametric ones with T test. To determine the predictive value of several variables, a multivariate regression model was created using variables whose p value was <0.1 in univariate analyses. To assess the model's goodness of fit, the Hosmer-Lemeshow test was performed. A two-tailed p value <0.05 was considered statistically significant.

RESULTS

In study period, 3924 minor trauma patients (ISS<16) who admitted to our emergency department due to several trauma reasons and underwent WBCT were enrolled in the study. The median age of patients was 33 (IQR25-75%: 24 to 46) and 2979 (75.9%) of them were male. Although there were no significant injuries after evaluation of WBCT in 2618 of all patients (66.7%), several injuries were detected in 1306 patients (33.3%), and only in 278 of all patients (%7.1), injuries of multiple body parts were detected and accepted as polytrauma. Baseline characteristics of all patients were shown on **Table 1**.

When several demographical and clinical characteristics of patients were analyzed according to presence of polytrauma, significantly differences were found terms of several parameters between both groups and they were summarized in **Table 2**. To determine the potential variables for prediction

of polytrauma, a multivariate logistic regression model was created. Fall from height (>3 meters), pedestrian struck, motor vehicle collision, altered mental status (GCS <14), male sex, and age over 65 years were included to initial model. In addition, even though significant difference was found terms of serum lactate level, pH, base excess, and vital signs between both groups in Table 1, these variables were not included to model, because these values were not examined in all patients, only in 574 patients for venous blood gases analysis, in 3085 patients for oxygen saturation, in 1467 patients for respiratory rate, and in 3298 patients for pulse rate. The data of these variables were presented as only univariate analysis in Table 2. Overall, according to final model, fall from height (>3 meters), pedestrian struck, altered mental status (GCS <14), and male sex were found as significant predictor factors for polytrauma (Table 3).

Variables Gender N (%) Male Female Age median (IQR 25-75%)	N:3924 2979 (75.9) 945 (24.1)	Variables Injuries detected by WBCT N (%) Totally normal	N:3924
Male Female Age median (IQR 25-75%)	· · ·		
Female Age median (IQR 25-75%)	· · ·	Totally normal	/
Age median (IQR 25-75%)	945 (24.1)	· · · · · · · · · · · · · · · · · · ·	2618 (66.7)
•		Intraparenchymal hemorrhage	8 (0.2)
	33 (24 to 46)	Subdural hemorrhage	33 (0.8)
Presence of comorbidities N (%)	170 (4.3)	Epidural hemorrhage	23 (0.6)
Chronic hypertension	99 (2.5)	Subarachnoid hemorrhage	57 (1.5)
Diabetes mellitus	65 (1.7)	Cerebral contusion	29 (0.7)
Coronary artery disease	35 (0.9)	Compression fracture	9 (0.2)
Chronic kidney disease	10 (0.3)	Linear fracture	102 (2.6)
Stroke	8 (0.2)	Cervical spine fracture	29 (0.7)
Congestive heart failure	9 (0.2)	Cervical Spondylolisthesis	1 (0.0)
COPD	15 (0.4)	Thoracolumbar spine fracture	297 (7.6)
Mental retardation	5 (0.1)	Thoracolumbar spondylolisthesis	7 (0.2)
Jse of anti-thrombotic agent N (%)		Cot fractures (less than 3)	108 (2.8)
Anticoagulant agent	10 (0.3)	Multiple cot fractures (3 or more)	74 (1.9)
Antiplatelet agent	19 (0.5)	Hemothorax	45 (1.1)
Trauma mechanism N (%)		Pneumothorax	76 (1.9)
Motor vehicle collision	1440 (36.7)	Pulmonary contusion	232 (5.9)
Pedestrian struck	532 (13.6)	Intra-abdominal solid organ injury	41 (1)
Fall from height (≥3 meters)	315 (8)	Gastrointestinal tract injury	2 (0.1)
Fall from height (<3 meters)	416 (10.6)	Renal injury	5 (0.1)
Fall from same level	203 (5.2)	Bladder injury	1 (0.0)
Motorcycle accident	617 (15.7)	Bone fractures of extremities	665 (17)
Bicycle accident	38 (1)	Maxillofacial fractures	97 (2.5)
Violence	238 (6.1)	Patients outcomes N (%)	
Other	125 (3.2)	Exitus in ED	2 (0.1)
/ital signs on admission median (IQR 25-75%)		Admission to ICU	51 (1.3)
Respiratory rate (for 1467 patients)	17 (15 to 18)	Admission to hospital bed	529 (13.5)
Pulse rate (for 3298 patients)	80 (76 to 88)	Transfer to another hospital	25 (0.6)
Oxygen saturation % (for 3085 patients)	98 (97 to 99)	Treatment refusal	188 (4.8)
Systolic blood pressure (for 3394 patients)	123 (119 to 132)	Discharged from ED	3129 (79.7)
Diastolic blood pressure (for 3394 patients)	76 (70 to 80)	Polytrauma N (%)	278 (7.1)
Glasgow coma scale median (min-max)	15 (3 to 15)	Mortality N (%)	270 (7.17)
ISS median (IQR 25-75%)	2 (1 to 5)	Mortality within 30 day	11 (0.3)
aboratory findings on admission median (IQR 25-7		Mortality within first 24 hours	3 (0.1)
pH (for 574 patients)	7.38 (7.35 to 7.42)	Mortality in hospital	8 (0.2)
Base excess (for 574 patients)	0.40 (-1.6 to 2.1)	RBC Transfusion mean/median (min-max)	0.9/ 0 (0-21)
Lactate (for 574 patients)	2.0 (1.5 to 2.9)	Need for intubation N (%)	
Hemoglobin (for 3848 patients)		Need for operation N (%)	33 (0.8) 381 (9.7)
Hematocrit (for 3848 patients)	14.2 (13 to 15.1)		301 (9.7)
INR (for 1427 patients)	42.3 (39 to 44) 1.09 (1.02 to 1.19)		

Variables	Non-Polytrauma (N: 3646)	Polytrauma (N: 278)	P value
Gender N (%)	1011-r orytraulia (14, 5040)	i orytiaulia (14: 270)	0.006
Male	2740 (75 4)	220 (82 7)	0.000
	2749 (75.4)	230 (82.7)	
Female	897 (24.6)	48 (17.3)	0.00
Age median (IQR 25-75%)	33 (24 to 46)	37 (28 to 51)	< 0.00
Age (>65 year) N (%)	243 (6.7)	26 (9.4)	0.08
Presence of Comorbidities N (%)	151 (4.1)	19 (6.8)	0.03
Chronic hypertension	93 (2.6)	6 (2.2)	0.6
Diabetes mellitus	61 (1.7)	4 (1.4)	0.7
Coronary artery disease	32 (0.9)	3 (1.1)	0.7
Chronic kidney disease	9 (0.2)	1 (0.4)	0.7
Prevent stroke	7 (0.2)	1 (0.4)	0.5
Congestive heart failure	5 (0.1)	4 (1.4)	< 0.00
COPD	8 (0.2)	7 (2.3)	< 0.00
Mental retardation	10 (0.2)	0 (0.0)	N/A
Jse of anti-thrombotic agent N (%)			
Anticoagulant agent	8 (0.2)	2 (0.7)	0.1
Antiplatelet agent	16 (0.4)	3 (1)	0.1
rauma mechanism N (%)	10 (0.4)	5(1)	0.1
Motor vehicle collision	1305 (20)	FE (10.9)	-0.00
	1385 (38)	55 (19.8)	< 0.00
Pedestrian struck	483 (13.2)	49 (17.6)	0.04
Fall from height ≥3 meters)	257 (7)	58 (20.9)	<0.00
Fall from height (<3 meters)	385 (10.6)	31 (11.2)	0.7
Fall from same level	192 (5.3)	11 (4)	0.3
Motorcycle accident	581 (15.9)	36 (12.9)	0.2
Bicycle accident	36 (1)	2 (0.7)	0.6
Violence	219 (6)	19 (6.8)	0.5
Other	108 (3)	17 (6.1)	0.04
/ital signs on admission median (IQR25-75%)			
Respiratory rate (for 1467 patients)	17 (15 to 19)	16 (15 to 17)	<0.00
Pulse rate (for 3298 patients)	80 (76 to 88)	82 (76 to 90)	0.01
Oxygen saturation % (for 3085 patients)	98 (97 to 99)	98 (95 to 99)	<0.00
Systolic blood pressure (for 3384 patients)	123 (120 to 132)	124 (115 to 134)	0.5
Diastolic blood pressure (for 3384 patients)	76 (70 to 80)	76 (70 to 82)	0.5
Altered mental status (GCS <14)	41 (1.1)	19 (6.8)	<0.00
SS median (IQR 25-75%)	2 (1 to 4)	9 (8 to 13)	<0.00
	2 (1 (0 4)	9 (8 (0 13)	<0.00
aboratory findings on admission		7 26 (7 22 4 7 44)	0.000
pH (for 574 patients; 489/85)	7.39 (7.36 to 7.42)	7.36 (7.33 to 7.41)	0.002
Base excess (for 574 patients; 489/85)	0.6 (-1.3 to 2.1)	-0.7 (-3.5 to 1.45)	< 0.00
Lactate (for 574 patients; 489/85)	1.9 (1.4 to 2.8)	2.4 (1.9 to 3.6)	<0.00
Hemoglobin (for 3848 patients; 3575/273)	14.2 (13 to 15)	14.1 (13 to 15)	0.6
Hematocrit (for 3848 patients; 3575/273)	42.3 (39 to 44)	42 (39 to 44.6)	0.5
INR (for 1427 patients; 1264/163)	1.09 (1.02 to 1.16)	1.11 (1.05 to 1.1)	0.002
Patients outcomes N (%)			
Exitus in ED	0 (0)	2 (0.7)	N/A
Admission to ICU	26 (0.7)	25 (9)	N/A
Admission to hospital bed	402 (11)	127 (45.7)	N/A
Transfer to another hospital	17 (0.5)	8 (2.9)	N/A
Treatment refusal	178 (4.9)	10 (3.6)	N/A
Discharged from ED	3023 (82.9)	106 (38.1)	N/A
Aortality N (%)	5025 (02.7)	100 (30.1)	N/A
-	E (0 1)	6 (2 2)	-0.00
Mortality within 30 day	5 (0.1)	6 (2.2)	<0.00
Mortality within first 24 hours	0 (0)	3 (1.1)	N/A
Mortality in hospital	3 (0.1)	5 (1.8)	< 0.00
RBC Transfusion mean/median (min-max)	0.6/0(0-21)	0.57/0(0-13)	< 0.001
Need for intubation N (%)	14 (0.4)	19 (6.8)	< 0.001
Need for operation N (%)	298 (8.2)	83 (29.9)	<0.001

Table 3. Multivariate logistic regression to predict polytrauma in minor trauma patients.						
	Wald	P value	OR (95% CI)			
Fall from height (>3 meters)	62.632	0.001	3.76 (2.7 to 5.2)			
Pedestrian struck	10.323	< 0.001	1.76 (1.2 to 2.4)			
Altered mental status (GCS <14)	38.239	< 0.001	6.07 (3.4 to 10)			
Male sex	7.121	0.008	1.57 (1.18 to 2.1)			
>65-year-old	2.645	0.1	1.44 (0.9 to 2.2)			

When created a model with four parameters (presence of any parameters was accepted as prediction polytrauma and absence of all parameter was accepted as prediction non-polytrauma), it was found that it had low diagnostic accuracy value as 0.6 (95%CI: 0.59 to 0.72), other diagnostic values were as follows; sensitivity was 52% (95%CI: 46 to 58), specificity was 61% (95%CI: 59 to 62), negative likelihood ratio was 0.77 (95%CI: 0.68 to 87) and positive likelihood ratio was 1.37 (95%CI: 1.22 to 1.54).

DISCUSSION

Although indications of WBCT criteria is not well defined and controversies are continued, routine use of WBCT approach is spreading in moderate and severe trauma patients. As a matter of fact, we - as the authors of this study – support this WBCT approaching in management of moderate and severe trauma patients. However, we notice with concern the situation is that this trend is spreading even in minor trauma patients to reduce the likelihood of misdiagnosis and to decrease delay, especially in overcrowded emergency services. Therefore, we decided to focus on minor trauma patients and guery whether there is necessity of WBCT in management of minor trauma patients. Obviously, our study showed that the rate of negative or unnecessary WBCT was high as 66.7%, rate of polytrauma was %7.1, and mortality rate was only 0.3% in minor trauma patients. The unnecessary or negative WBCT rate of the previously studies, which conducted with generally major trauma patients, was reported as lower than our results, ranging from 14 to 30%.[1,8,15,16] Similarly, reported mortality rate in previously studies is too higher than our results, as ranged from 4.7 to 22%.^[1,4,17] When considered these data, it seems that contribution of routine WBCT using is too limited in management of minor trauma patients. Therefore, we believe that routine using of WBCT approach is not rational and when considered unnecessary radiation exposure, it may be harmful.

On the other hand, some authors in their well written review pointed out that diagnosing occult injuries with routine WBCT allows of safe and fast disposition from ED and obviates requiring of subsequent imaging and medical evaluation when patients present for follow-up with nonspecific pain or other complaints.^[18] And, rightly again, they concluded that even some minor injuries, that may be misdiagnosed when WBCT wasn't used, can be fatal in the special population. Similarly, in our study, though number is few, there were also polytrauma subjects (7.1%) in minor trauma patients. Through our regression analysis, we have found four parameters (fall from height (>3 meters), pedestrian struck, altered mental status (GCS <14), and male sex) that can predict which WBCT scanning have polytrauma. To our knowledge, there is no study focused only minor traumas investigating the effectiveness of WBCT. Previously studies aimed to develop a criterion for WBCT have generally focused on all trauma patients. In a prospective study, conducted by J. Babaud et al., the Vittel criteria, which consist of several preadmission physiological variables, trauma mechanism, anatomic location of injuries, and comorbidities, was evaluated to whether could be used to determine the need for WBCT.^[19] Finally, Glasgow Coma Scale (GCS) score less than 13, penetrating trauma, and resuscitation with greater than 1000 mL of colloids were found as independent predictor for needing WBCT. Another retrospective study was conducted by Davies et al., a model created and evaluated to detect significant injuries as a decision rule for WBCT in major trauma patients.^[14] After final regression model, five independent predictors of polytrauma clinical signs in more than one body region, GCS score < 14, presence of hemodynamic abnormality (SBP <100 mmHg, or heart rate >100 bpm), presence of respiratory abnormality (respiratory rate >24 breaths/min, or pSO₂ <93%), and mechanism of the injury. However, when evaluated diagnostic accuracy of this model, the accuracy or the area under the curve (AUC) of the receiver operating characteristic (ROC) was reported as 0.82, with the sensitivity and specificity values of 79% and 71%, respectively. Finally, in another retrospective study which was conducted by Hsiao et al. with 660 trauma patients, it was aimed to identify the independent predictors and create a diagnostic decision rule to detect needing WBCT.[11] After regression analysis, independent predictors were defined as; male sex, GCS score < 9, mechanism of the injury (fall > 5 m and being a cyclist). The accuracy of this model was reported as 0.74 (95% CI: 0.67–0.80). In addition, the authors reported the accuracy of only clinical decision trauma leader without any formal protocol as 0.70 (95% CI 0.63-0.76) and they concluded that there was not any clinically significant contribution of their decision rule. Similarly, in our study, though we found four significant independent predictors, the accuracy of the model that created with them is found so low as 0.6.

Due to retrospective nature of this present study, several potential predictor factors could not be considered such as; detail of trauma mechanism (vehicle estimated speed, presence helmet/seat belt), detail of resuscitation in prehospital period, etc. When considered our predictors inadequate to explain variance on outcome variable (polytrauma) in our model, these potential predictors might have been explained to important part of variance on outcome variable. Similarly, though vital signs and several laboratory results on admission were evaluated in this study, these potential predictors could not be included to model since there is no record for every patient. Finally, another potential limitation is that ISS values were calculated retrospectively based on CT findings and medical records.

CONCLUSION

As a conclusion, when considered the results of previous and present studies, though it seems that several predictors including trauma mechanism, clinical findings on admission, laboratory examining in the early period of resuscitation are related to needing WBCT, models created with these predictors seem to be far from being sufficient for determine indication WBCT. When considered only minor trauma patients with small polytrauma and mortality ratio, routine using of WBCT approach is not rational and when considered unnecessary radiation exposure, it may be harmful. Though our data is not enough to suggest a decision model to determine needing of WBCT, we believe that predictors found in our study (fall from height (>3 meters), pedestrian struck, altered mental status (GCS score <14), and male sex), along with other possible predictors, can be used to develop a clinical decision rule in the future for minor trauma patients..

ETHICAL DECLARATIONS

Ethics Committee Approval: University of Health Sciences, Umraniye Training and Research Hospital, Clinical Research Ethics Committee, Approval date: 23.01.2019, Decision No: B.10.1.THK.4.34.H.GP.0.001/12.

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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