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True Bacteremia or Contamination? Predictive Factors for Contamination in Blood Cultures Obtained in the Pediatric Emergency Room

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Abstract

Aim: This study aimed to investigate the factors affecting bacteremia and contamination in patients admitted to the pediatric emergency room.

Materials and Methods: This retrospective study focused on patients 1 month to 18 years of age who underwent blood culture tests at the University of Health Sciences Turkey, İzmir Tepecik Training and Research Hospital from 2013 to 2017. We performed a history and physical examination and noted the presence of fever, pediatric assessment triangle findings on admission, laboratory characteristics, and outcomes associated with true bacteremia and contamination. Patients with no growth in blood culture were excluded from the study. Statistical analysis consisted of the χ^2 test, Mann-Whitney U test, receiver operating characteristic analysis, calculations of sensitivity and specificity, and the multivariable logistic regression model.

Results: Blood culture growth was detected in 514 (12.2%) of 4,200 culture samples assessed during the study period. A total of 449 patients were included in the study. Culture results of 165 patients (36.7%) were defined as indicative of true bacteremia and those of 284 patients (63.2%) as contamination. Patients with true bacteremia were more likely to have fever (81.4% vs. 64.5%, p<0.001), underlying risk factors (61.9% vs. 23.5%, p<0.001), and longer hospital stays (11 days vs. 7 days, p<0.001). Normal pediatric assessment findings on admission were observed between the contamination group and the true bacteremia group (p<0.001). Patients with bacteremia had higher white blood cell counts (13,900 vs. 11,300, p<0.001), C-reactive protein (CRP) (38.5 vs. 6.3, p<0.001), and procalcitonin (1.04 vs. 0.18, p<0.001). The area under the curve was 0.712 for the CRP level. The cut-off value for CRP (mg/L) was 11.75 (sensitivity, 72.6%; specificity, 62.4%). In the multivariable logistic regression analysis, fever on admission [odds ratio (OR), 2.4; 95% confidence interval (CI), 1,037-5,524; p=0.041], male sex (OR, 2.2; 95% CI, 1,066-4,716; p=0.033), and CRP (OR, 1.0; 95% CI, 1,003-1,017; p=0.005) were significantly associated with true bacteremia.

Conclusion: The presence of fever on admission and high CRP levels may be good indicators of which patients require BCs.

Keywords: Bacteremia, blood culture, contaminant, pediatrics

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Introduction

Bacteremia is a severe invasive infection defined by the presence of bacteria in the blood and is associated with high morbidity and mortality rates. Blood culture (BC) is one of the most used microbiological tests in pediatric emergency services as the gold standard method for the diagnosis of bacteremia because the detection of causative microorganisms allows for appropriate antibiotic selection. However, obtaining BCs remains controversial in emergency settings.

Although the risk of bacteremia in children under 3 years of age is less than 1%, BCs are still commonly obtained, resulting in 2-5-fold more false-positive BC results (1,2). False-positive, negative, or contaminated BC results are increasing in pediatric emergency rooms. Previous studies have reported contamination rates of BCs obtained for cellulitis and fever in children between 0.7% and 8% (3-5). This results in wasted resources, financial burden, antibiotic side effects, and a prolonged hospital stay (3). At this time, there are no guidelines for distinguishing between true and false bacteremia in children. Previous studies have explored C-reactive protein (CRP) levels, white blood cell (WBC) counts, and the duration of fever before pneumococcal vaccine (6). Therefore, there is a need to identify predictive factors of contamination that may be used for clinical decision-making upon admission to the pediatric emergency room (7). In this study, we explored the true prevalence of bacteremia in children who underwent BCs in the pediatric emergency room and identified factors affecting true bacteremia and contamination rates.

Materials and Methods

This study was conducted as a retrospective, cross-sectional study. Files from patients aged between 1 month and 18 years admitted to the Pediatric Emergency Department (ED) of the University of Health Sciences Turkey, İzmir Tepecik Training and Research Hospital between 2013 and 2017 who had BCs drawn for any reason were examined. The patients included in this study were identified from the BC reports requested from the pediatric emergency room by the microbiology laboratory of our hospital. Patients with no growth in BCs were excluded from the study. Patients with positive BCs were divided into two groups-namely, those with "true bacteremia" and those with "contamination". Typical pathogens (*Escherichia coli, Streptococcus pneumonia, Staphylococcus aureus, Salmonella, Klebsiella, Group B Streptococcus, Neisseria*) grown in BCs indicate true bacteremia. Organisms considered contaminants include coagulase-negative staphylococci (*CoNS*), *Corynebacterium* species, *Bacillus* species other than *Bacillus anthracis*, and *Propionibacterium acnes*. If the potential pathogenicity of one of the isolated species was unclear, especially *CoNS,* the pediatric infectious specialist treating disease reviewed the case to determine whether the corresponding BC as should be included in the study as positive for bacteremia. Independent variables (age, sex, nationality, vaccination status, physical examination findings, pediatric assessment triangle (PAT) findings, WBC counts, CRP, procalcitonin, microorganism growth in the BC, other accompanying organ infections, the presence of risk factors, and length of hospital stay) were recorded for both groups. The presence of any abnormalities, including respiratory and pulse rates; any pulmonary or cardiovascular auscultation findings (such as rails, rhonchus, wheezing, murmur, or gallop, cyanosis, respiratory distress findings; prolonged capillary refill time; presence of petechia, purpura, ecchymosis, meningeal irritation findings, or abdominal tenderness; and findings of arthritis, soft tissue infections, lymphadenitis, cellulitis, pharyngeal hyperemia, or otitis were defined as positive physical examination findings. Immunosuppression (chronic renal failure, malignancies, patients undergoing organ transplant, sickle-cell anemia, or hereditary spherocytosis), the presence of intravascular and dialysis catheters or a ventriculoperitoneal shunt, history of invasive diagnostic procedures, hospitalization up to 15 days before admission, and the presence of chronic systemic diseases were identified as risk factors for bacteremia.

PAT is a tool developed by the American Academy of Pediatrics that allows for rapid assessment of children in the field of triage. It consists of evaluating the child based on respiratory status, circulation status, and appearance (state of consciousness) without physically examining the child. If one of these parameters is abnormal, the patient is considered unstable (8). The laboratory values and first BC results of the patients at the time of admission to the pediatric emergency room were recorded and included in the study. We defined "complete" or "incomplete" vaccinations considering whether the vaccine was available in the National Immunization Programme during the children's immunization period.

All blood samples for BCs were taken by nurses in our ED. Blood samples were incubated in a BacT/ALERT 3D (bioMérieux, France) automated BC system. Samples with positive signals in the BC system were examined using the Gram-staining method and simultaneously cultivated on blood agar, eosin methylene blue agar, and chocolate agar media. Identification and antibiotic susceptibility testing of the isolated bacterial strains were performed using the Vitek 2 compact (bioMérieux) and Phoenix (BD, USA) automated systems.

Statistical Analysis

The data were analyzed using IBM Statistical Package for the Social Sciences Statistics (Windows, version 20.0. IBM Corp., USACo).

The χ^2 test was used to compare categorical variables between groups. The Kolmogorov-Smirnov test was used to evaluate the normal distribution assumption for numerical variables. Differences between the two groups were examined using the independent samples t-test for normally distributed variables and the Mann-Whitney U test for non-normally distributed variables. Differences among more than two groups were examined using ANOVA and the Kruskal-Wallis test for normally and non-normally distributed variables, respectively. The discriminatory performance of each variable was determined based on the area under the receiver operating characteristic curve, and the best cut-off values were calculated using the Youden index. A p value of <0.05 was considered indicative of statistical significance.

Ethics

The study was conducted in accordance with the ethical principles stated in the Declaration of Helsinki and approved by the Institutional Ethics Committee of the University of Health Sciences Turkey, İzmir Tepecik Training and Research Hospital (approval number: 2020/13-12, date: 16.11.2020).

Results

The study was conducted at the hospital of the University of Health Sciences Turkey, İzmir Tepecik Training and Research Hospital in the city of İzmir, Turkey. The pediatric ED of this hospital is the only pediatric trauma and emergency center in a public hospital serving the population of the western region of Turkey. It is a busy pediatric ED admitting approximately 165,000 children per year, aged 1 month to 18 years.

During the 4-year study period, we had 675,000 pediatric ED admissions for which 4,200 BCs were taken. BC growth was detected in 514 (12.2%) of the 4,200 culture samples. A total of 449 patients were included in the study after patients with incomplete data and repeated BCs were removed. The culture results of 165 patients (36.7%) were defined as indicative of true bacteremia and those of 284 patients (63.2%) as contamination (Figure 1).

The median age of the bacteremia group (9 months) was significantly higher than that of the contamination group (3 months) (p<0.001). When the patients were examined in four different age groups: 1-3 months (n=44 with bacteremia; n=136 with contamination), 4-12 months (n=47 with bacteremia; n=66 with contamination), 2-5 years (n=47 with bacteremia; n=56 with contamination), and over 5 years (n=27 with bacteremia; n=26 with contamination), a significant difference was found between the bacteremia and contamination groups (p<0.001, Table 1). When comparing subjects with bacteremia or contamination, there were no significant differences according to sex or race. Concerning clinical and medical history, there were no significant differences in vaccination status, the use of antibiotics before admission, and the presence of abnormal physical findings. There was a significant difference in PAT findings (p<0.001, Table 1), with fewer patients with normal PAT findings with

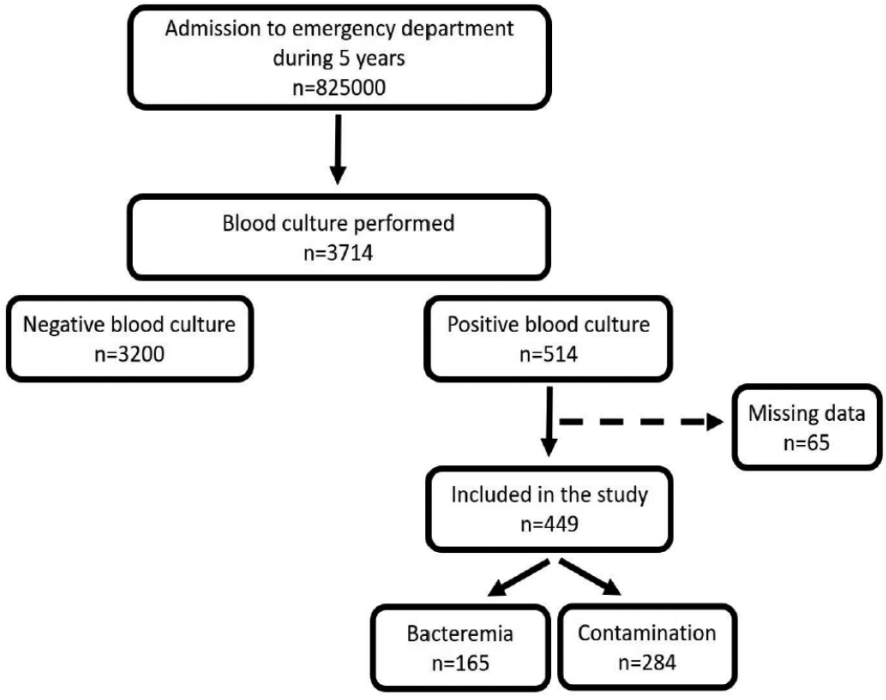

Figure 1. Flow chart of the study population

bacteremia compared with those with contamination. Those with bacteremia were more likely to have fever (81.4% vs. 64.5%, p<0.001), underlying risk factors (61.9% vs. 23.5%, p<0.001), and longer hospital stays (11 days vs. 7 days, p<0.001) (Table 1).

When examining the laboratory results, the bacteremia and contamination groups differed in terms of WBC counts, levels of CRP and procalcitonin, and the number of microorganisms according to Gram staining. Patients with bacteremia had higher WBC counts (13,900 vs. 11,300, p<0.001) and higher levels of CRP (38.5 vs. 6.3, p<0.001) and procalcitonin (1.04 vs. 0.18, p<0.001). The mean WBC, CRP, and procalcitonin levels of the subjects are shown in Table 2.

As shown in Table 3, the most common pathogen in the bacteremia group was *CoNS* (30.9%), followed by *Streptococcus* spp. (20.6%), *E. coli* (13.3%), *Klebsiella* spp. (7.8%), *Staphylococcus aureus* (5.4%), *Streptococcus pneumoniae* (5.4%), *Pseudomonas* spp. (4.2%9, *Acinetobacter* spp. (3.6%), *Stenotrophomonas maltophilia* (2.4%), and others (6.1%).

As shown in Figure 2, the area under the curve (AUC) was 0.712 for the CRP level. The cut-off value for CRP level (mg/L) based on the AUC was 11.75 (sensitivity, 72.6%; specificity, 62.4%). We performed logistic regression analysis after controlling for potential confounding factors and found that male sex [odds ratio (OR), 2,242, p=0.033], high fever (OR, 2,392, p=0.041),

Table 1. Demographical and clinical characteristics of patients with bacteremia and contamination

Characteristics	Bacteremia (n=165)	Contamination (n=284)	p value
Age, months[a]	9 (2-34.5)	3 (1-16)	<0.001
Age groups[b]			<0.001
1-3 months	44 (26.6)	136 (47.8)	
3-12 months	47 (28.4)	66 (23.2)	
1-5 years	47 (28.4)	56 (19.7)	
>5 years	27 (16.3)	26 (9.1)	
Gender (male)[b]	98 (59.4)	151 (53.1)	0.201
Race (Turkish)[b]	141 (85.4)	242 (85.2)	0.944
Use of antibiotics prior to admission[b] (n=327)	30/127 (23.6)	34/200 (17)	0.141
Incomplete/no vaccination[b] (n=333)	15/126 (11.9)	10/207 (4.8)	0.018
Underlying risk factors[b]	61 (36.9)	67 (23.5)	0.002
Normal pediatric assessment triangle[b] (n=445)	67/165 (40.6)	183/280 (65.3)	<0.001
Abnormal physical examination[b] (n=443)	94/164 (57.3)	148/279 (53)	0.383
Presence of fever[b] (n=433)	132/162 (81.4)	175/271 (64.5)	<0.001
Outcome[b] (n=442)			<0.001
Discharged from the emergency	21/161 (13)	88/281 (31.3)	
Admission to pediatric services	105/161 (65.2)	167/281 (59.4)	
Admission to pediatric intensive care unit	29/161 (18)	20/281 (7.1)	
Day of hospitalization[a] (n=321)	11 (6-16)	7 (5-11)	<0.001

[a]Values are given median and IQR (25-75%), [b]Values are given as percentage.
IQR: Interquartile range

Table 2. Laboratory characteristics of patients with bacteremia and contamination

	Bacteremia (n=165)	Contamination (n=284)	p value
White blood cell count, /μL[a] (n=443)	13900 (9000-19800)	11300 (8500-14800)	<0.001
C-reactive protein, mg/L[a] (n=448)	38.5 (6.5-133.3)	6.3 (1.7-21.0)	<0.001
Procalcitonin, ng/mL[a] (n=280)	1.04 (0.18-10.48)	0.18 (0.11-0.29)	<0.001
Microorganism according to gram staining[b]			<0.001
Positive	107 (64.8)	284 (100)	
Negative	58 (35.1)	-	

[a]Values are given median and IQR (25-75%), [b]Values are given as percentage.
IQR: Interquartile range

and high CRP levels (OR, 1,010, p=0.005) were risk factors for bacteremia (Table 4).

Discussion

In this study, we found that the rate of true bacteremia was 4.4% and the overall contamination rate was 7.6% in the 1-month- to 18-year-old pediatric patients. These results conflict with those of previous studies conducted in emergency services, which reported a bacteremia rate of 0.25% to 2.1% (9-11). However, most previous reports included children under 3 years of age febrile illness or occult bacteremia. The reasons for the high rate of true bacteremia in our study may be that we included not only infants with occult bacteremia or febrile infants, but children in all age groups with focal or systemic infections and bacteremia risk factors (such as children with an indwelling catheter, etc.). We also included isolated growth of *CoNS*, which were identified as true pathogens by pediatric infectious specialists that contribute to bacteremia. Although previous reports (12,13) showed that contamination rates vary significantly among institutions, from 6% to 11%, acceptable rates were reported as lower than 2-3% (14). The reason for our high contamination rate is that we have a broad population with a younger age who typically have a higher rate of contamination (2 of 3 BCs of 180 infants aged 1-3 months were contaminated) because obtaining BCs from very uncooperative infants significantly increases the risk for contamination (14). As expected, we found that the median age of the contamination group was significantly lower than that of the bacteremia group in our study. Additionally, variation in taking and collecting BC samples (e.g., blood collected during night shifts, nursing skills, busy ED, etc.) in our ED might have resulted in a higher contamination rate. Furthermore, the significant differences among age groups in terms of bacteremia (highest rate in children younger than 1 year) were consistent with the study by Chiu et al. (15). They found that both bacteremia and contamination rates increased with a younger age (the highest true bacteremia rate was found in the group younger than 1 year) and reported an overall contamination rate of 3%. Similar to a previous report (15-17), although there was no significant difference between the groups in terms of sex, there were more males than females in both groups. However, we showed that the risk of true bacteremia was 2.2-fold higher in males based on regression analysis.

We also explored vaccine history, physical exam findings, underlying risk factors, the presence of fever (≥38 °C axillar) upon admission, and PAT evaluation findings in the triage room that could be used to differentiate bacteremia from contamination. In our analysis, the use of antibiotics before admission, incomplete vaccinations, and any abnormal physical examination findings

Table 3. List of microorganisms causing bacteremia in patients

Microorganisms	Bacteremia (n=165)
CoNS	51 (30.9)
Streptococcus spp. (including *Streptococcus pyogenes*)	34 (20.6)
Escherichia coli	22 (13.3)
Klebsiella spp.	13 (7.8)
Staphylococcus aureus	9 (5.4)
Streptococcus pneumoniae	9 (5.4)
Pseudomonas spp.	7 (4.2)
Acinetobacter spp.	6 (3.6)
Stenotrophomonas maltophilia	4 (2.4)
Others	10 (6.1)

CoNS: Coagulase negative staphylococci

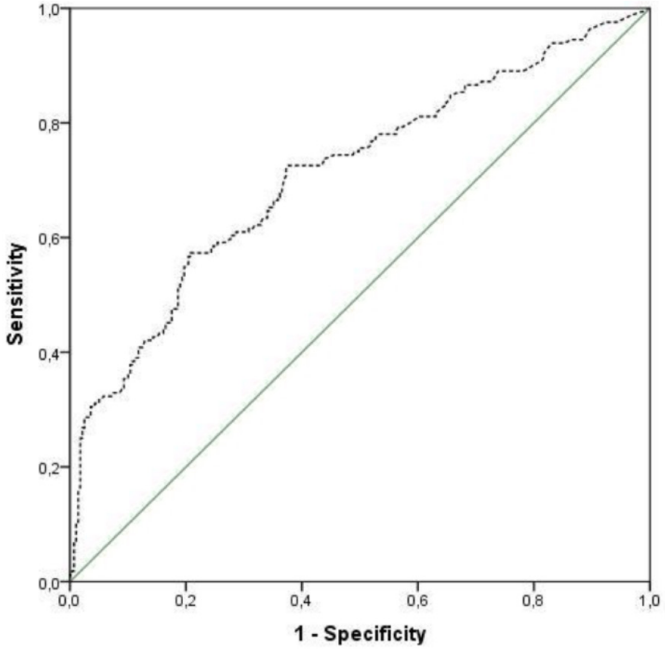

Figure 2. Reciever operating curve for C-reactive protein

Table 4. Multivariate analysis for effect on bacteremia

Variables	Odds ratio (95% CI)	p value
Age	0.998 (0.989-1.008)	0.754
Gender (male)	**2.242 (1.066-4.716)**	**0.033**
Incomplete/no vaccination	1.794 (0.513-6.278)	0.360
Abnormal PAT	0.493 (0.237-1.04)	0.058
Fever	**2.392 (1.037-5.524)**	**0.041**
Underlying risk factors	0.941 (0.411-2.154)	0.086
White blood cell count	1.01 (1-1)	0.802
C-reactive protein, mg/L	**1.010 (1.003-1.017)**	**0.005**
Procalcitonin, ng/mL	1.046 (0.906-1.099)	0.073

CI: Confidence interval, PAT: Pediatric assessment triangle

were not differentiating factors between bacteremia and contamination. We found that true bacteremia was only significantly associated with the presence of fever at admission, underlying risk factors, and abnormal PAT findings in the triage room. In our country, a pneumococcal conjugate vaccine was introduced in 2007. Therefore, the study population included older children who had missed the vaccination schedule during the study period. Although we did not find statistical significance, children with incomplete vaccination were more likely to be in the bacteremia group. We found significant differences between the bacteremia and contamination groups in terms of the presence of fever and underlying risk factors, which agrees with the pattern of septicemia and previous adult studies including immunosuppressed patients (18).

In this study, prehospital oral antibiotic use had no significant effect on bacteremia. This finding is interesting and similar to that of Nannan Panday et al. (19), who performed their study in adults. This may be because most patients in our study had used narrow spectrum oral antibiotics at insufficient doses. Our study showed that more than half of the children (almost 60%) in the bacteremia group were classified as having abnormal PAT findings at the triage. Moreover, up to 65% of the children in the contamination group were stable and appeared "well" in the initial PAT assessment. However, upon multivariable regression analysis, we did not find any association between abnormal PAT findings and bacteremia. Our findings in terms of abnormal PAT outcomes in the bacteremia group conflicts with that of the multicenter prospective study of Gomez et al. (20) involving 15 EDs. They reported that 65.7% of patients with positive BCs had normal PAT findings upon arrival to the ED. As a result, although PAT is an empirical tool for predicting the severity of the clinical condition of the patients, it may not be predictive of true bacteremia. When we compared the length of hospital stay between the two groups, the bacteremia group had longer hospitalizations due to their antibiotic use, as expected.

Our study showed that although considered a contaminant, *CoNS* (which were considered true pathogens after review by pediatric infectious doctors and clinical evaluation) was the dominant isolated pathogens among those contributing to bacteremia. Although they exhibit low virulence, *CoNS* can cause bacteremia (especially in malignancy, immunocompromised patients, and patients with catheters) (21,22). In a study evaluating 76,331 BCs from 13,519 pediatric patients over an 11-year period, *CoNS* was the most common cause of bacteremia, and the true pathogen rate was reported to be 23.8% (23). Because our study focused on identifying the predictive factors of true bacteremia, we did not examine the variables and outcomes associated with pathogens or contaminants.

For laboratory markers, this study also showed that CRP has a better predictive ability than WBCs, which is similar to a previous study by Chiu et al. (15). Despite numerous studies that demonstrate the superiority of procalcitonin over CRP in diagnosing bacteremia (24-28), we found that among the biomarkers, CRP had a one-fold effect on bacteremia based on multivariable regression analysis. Moreover, in this study, the CRP AUC value was 0.712 for differentiating true bacteremia from contamination. When a cut-off value of 11.75 mg/dL was used for CRP, the sensitivity and specificity were 72.6% and 62.4%, respectively. If the CRP cut-off value (≥11.75 mg/dL) is used, approximately 28% of true bacteremia patients would be missed.

Study Limitations

A limitation of this study is that we could not include patients with no growth in BCs. Another limitation of this study is that it is a retrospective design with chart review for clinical and history data from a single center. The third limitation is that due to the lack of clear guidelines for indications for obtaining BCs in pediatric EDs, patients with true bacteremia might not have had samples taken for BCs and therefore were excluded from the study. Additionally, we could not evaluate the reason BCs were drawn or the disease diagnosis (such as urinary tract infections, pneumonia, occult bacteremia, and/or any other specific local infections). Despite these limitations, our study highlights the need for future investigation into factors of BC contamination to generate guidelines and prevent unnecessary BCs.

Conclusion

Based on the results of this study, to reduce the BC samples in pediatric EDs, it is important to evaluate the vaccination status, underlying risk factors (especially for *CoNS* as a true pathogen), fever, and PAT findings at admission. Additionally, among the wide variety of clinical features, the presence of fever and elevated CRP values may support and improve the efficiency of BC in EDs.

Acknowledgment

The English in this document has been checked by at least two professional editors, both native speakers of English. For a certificate, please see: http://www.textcheck.com/certificate/GOdF7U

Ethics

Ethics Committee Approval: The study was conducted in accordance with the ethical principles stated in the Declaration of Helsinki and approved by the Institutional Ethics Committee of the University of Health Sciences Turkey, İzmir Tepecik

Training and Research Hospital (approval number: 2020/13-12, date: 16.11.2020).

Informed Consent: This study was conducted as a retrospective, cross-sectional study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: E.B., S.B.Y., G.G., M.A., Design: E.B., E.K.Ö., S.B.Y., M.A., D.Y.Ç., Data Collection and Processing: E.B., Ş.B., Ş.D., G.D., A.Ç., Analysis and Interpretation: E.B., E.K.Ö., A.Ç., N.Y., Literature Search: E.B., S.B.Y., Writing: E.B., E.K.Ö., N.Y., M.A., D.Y.Ç.

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