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Original Article

Evaluation of Infectious Complications and Their Causative Agents in Pediatric Cancer Patients: A Prospective Single-center Cohort Study

Pediatrik Kanser Hastalarında Enfeksiyonlar ve Etken Ajanların Değerlendirilmesi: Prospektif Tek Merkezli Kohort Çalışması

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ABSTRACT

Objective: This study aimed to evaluate the epidemiological, microbiological, clinical characteristics of the patients followed up with different types of underlying hematologic malignancies and solid tumors.

Method: This cohort study included patients with pediatric malignancy. Eighty-eight patients who were followed up for two years were included. The number of days from the first diagnosis, recurrent infectious episodes, number of days with fever, presence of neutropenia and nonneutropenic episodes, chemotherapy regimens, antimicrobial agents, blood and urinary tract culture samples were recorded.

Results: A total of 149 infectious episodes were observed. The median age was 5.08 years. The mean age was 9.02±5.17 years in patients who had no infectious episodes during the follow-up and 5.70±4.60 years in patients with two and more infectious episodes and was significantly lower (p=0.024). In total, 264 microbial cultures were retrieved from different locations during these infectious episodes. Regarding all the cultures, 27% of blood cultures and 9% of urinary tract cultures were positive. The most commonly isolated microorganism were Gram-positive bacteria (n=23, 57.5%).

Conclusion: Younger children with cancer are at higher risk of infection complications compared to children of older ages. Children with hematologic malignancies are more likely to develop a neutropenic fever during the consolidation and induction periods. Regarding the high rate of FUO in our study, more attempts to increase microbiological diagnosis in this patient population.

Keywords: Febrile neutropenia, cancer, pediatrics

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ÖZ

Amaç: Bu çalışmada, altta yatan farklı tipte hematolojik maligniteler ve solid tümörler ile takip edilen hastaların epidemiyolojik, mikrobiyolojik, klinik özelliklerinin değerlendirilmesi amaçlanmıştır.

Yöntem: Bu kohort çalışmasına pediatrik maligniteli hastalar dahil edilmiştir. İki yıl takip edilen 88 hasta çalışmaya dahil edildi. İlk tanıdan itibaren gün sayısı, tekrarlayan enfeksiyöz ataklar, ateşli gün sayısı, nötropeni ve nötropenik olmayan atak varlığı, kemoterapi rejimleri, antimikrobiyal ajanlar, kan ve idrar yolu kültür örnekleri kaydedildi.

Bulgular: Toplam 149 enfeksiyöz epizod gözlendi. Takipte enfeksiyöz epizodu olmayanlarda yaş ortalaması 9,02±5,17 yıl iken, iki ve daha fazla enfeksiyöz epizodu olanlarda 5,70±4,60 yıldı ve anlamlı olarak daha düşüktü (p=0,024). Bu enfeksiyöz epizodlar sırasında farklı yerlerden toplamda 264 mikrobiyal kültür alındı. Tüm kültürlerde kan kültürlerinin %27'si ve idrar yolu kültürlerinin %9'u pozitifti. En sık izole edilen mikroorganizma Gram-pozitif bakterilerdi (n=23, %57,5).

Sonuç: Pediatrik çağdaki kanserlerde yaş azaldıkça daha yüksek enfeksiyon komplikasyonları riski izlenmiştir. Hematolojik maligniteleri olan çocukların konsolidasyon ve indüksiyon dönemlerinde nötropenik ateş geliştirme olasılığı daha yüksektir. Çalışmamızdaki nedeni bilinmeyen ateş oranlarından da yola çıkarak bu grup hastalıklarda daha iyi mikrobiyolojik tanı için daha fazla çalışma gerekmektedir.

Anahtar kelimeler: Febril nötropeni, kanser, çocuk

INTRODUCTION

Children treated for cancer develop serious complications even death during episodes of infectious complications, most of them being associated with neutropenic fever[1]. Studies have revealed that during the last 50 years survival rates increased from 25% to 80%[2], especially due to intensive chemotherapy and evolving treatment modalities. Improvement in survival rates is achieved with repeated use of multi-agent courses, which resulted in recurrent episodes of severe and prolonged neutropenia. Eight percent of neutropenic episodes due to intensive chemotherapy which persists more than one week are complicated by fever, and about 60% of them have an infectious etiology[3].

The infectious complications are mainly influenced by the type of primary disease. For instance, severe bloodstream infections have been reported in the children with hematologic malignancies compared to cases with solid tumors[4]. The treatment modalities of neutropenic fever include hospitalization, intravenous administration of broad-spectrum empirical antibiotics, and also antifungal and antiviral treatment for some selected patients[5]. Better understanding of the malignancy-specific infectious complications and the time when the risk of infection is increased during the intensive chemotherapy might additionally contribute to the clinical management of these patients.

We have aimed to evaluate the infections and causative microorganisms that emerged during episodes of febrile neutropenia in patients with malignancy.

MATERIALS and METHODS

This prospective cohort study wascarried out between February 2018 and May 2020 in a 28-bed oncology-hematology department of a 400-bed pediatric teaching hospital. The patients aged 1 month to 18 years with the diagnosis of malignancy who were followed up from the time of diagnosis of the primary disease until termination of the study or completion of the primary treatment for malignancy were analyzed retrospectively. The patients who were not followed up for at least three months were not included in the final analysis. Patients were divided into groups of hematologic malignancies including acute lymphoblastic leukemia (ALL), acute myelocytic leukemia (AML) and solid tumors.

The infectious episodes in the patients who were diagnosed with malignancy during their therapy starting from the first day to the end of treatment were included in the study. The data concerning the number of days from the first diagnosis, recurrent infectious episodes, number of days with fever, presence of neutropenia and non-neutropenic episodes, chemotherapy regimens, antimicrobial agents, test results of blood culture samples, and positive cultures of species of pathogenic microorganisms (if any) were also recorded. Blood cultures were considered positive if one or more than one microorganism grew in at least one culture set. Positive cultures were considered contaminated if normal flora of the skin, including coagulase-negative staphylococci (CoNS), viridans group streptococci, *Bacillus* species, *Neisseria* species (other than *Neisseria meningitidis* or *Neisseria gonorrhoeae*), *Micrococcus* species, or aerobic Gram-positive rods grew in only one culture set. If the same skin microorganism were identified in two culture sets, then they were considered true positives, and in the presence of positive signal or positive culture, a second set of blood culture set was prepared within the first 24 hours of the first one[6] In case of identification of only one pathogenic agent in urine culture, isolation of a single pathogen with either 100,000 CFU/mL in the cultures of mid-stream urine or bagged urine specimens or ≥50,000 CFU/mL in catheter tip cultures; and if more than one pathogen was isolated, then growth of one bacteria at 100,000 CFU/mL, and the other one at <50,000 CFU/mL in the cultures of mid-stream and bagged urine specimens, finally growth of 50,000 CFU/mL for one, and <10,000 CFU/mL for the other agent in the catheter tip cultures were considered significant.

Isolation of CoNS was accepted as contamination irrespective of catheter-tip or dual inoculation.

Treatment of ALL and AML was performed according to ALL-IC BFM 2009, AML BFM 2004 protocols and in phases of induction, consolidation, reinduction, and maintenance chemotherapy[6,7]. Neutropenia was described as a total number of granulocytes $<0.5\times10^9$/L or leukocytes $<1.0\times10^9$/L without differential counts available[8]. Febrile neutropenia was defined as either absolute neutrophil counts below 500/mm^3 or expected to decrease below 500/mm^3 within 48 hours in the presence of fever of 38.3 °C with single axillary measurement or above 38 °C persisting for one hour or with two measurements above 38 °C within one hour[9]. Antimicrobial therapy was planned according to Infection Diseases of American Association guideline recommendations[10] .

Microbiologically proven infection was defined as isolation of a pathogen from a sterile body site (blood, urine) in the clinical setting of suspected

infection. Clinically proven infection was defined as clinical or radiological findings of infection where the patient shows a prompt response to antimicrobials without any laboratory evidence of an infectious etiology. Fever of unknown origin (FUO) was defined as fever without any focus or etiology identified by clinical history, physical examination, radiological or microbiologic testing during a minimum hospitalization period of three weeks without an established diagnosis despite an intensive one-week investigation. Central venous blood samples were collected twice for aerobic and anaerobic cultures from patients with fever under aseptic conditions and after disinfection of the central venous access device hub, in addition to a blood culture sample drawn from peripheral veins.

Statistical Analysis

Collected data were analyzed with SPSS Software version 20 (IBM Corporation, Armonk, NY, USA). Categorical variables were analyzed using relative frequencies, and numerical variables were expressed as median or mean values depending on whether they showed normal distribution or not. Categorical variables were compared using Pearson χ^2 and Fisher's exact tests, and numerical variables with t-test or nonparametric Mann-Whitney U test. For statistical analysis of quantitative data, t-test, Mann-Whitney U, Kruskal-Wallis, and One-Way ANOVA tests were used. The level of significance was taken as $p \leq 0.05$. Dunn's test was used in the post-hoc analysis of Kruskal-Wallis test. Survival analyzes were performed using Kaplan-Meier method, and log-rank test was used for the comparison of factors. Written consent was obtained from all patients.

RESULTS

Demographic Features

Ninety-two newly diagnosed patients including those with solid tumors and hematologic malignancies were enrolled in this study. The patients with hematologic malignancies were followed up for a mean period of 97.80±18.48 days, and those with solid tumors for a mean period of 170.48±32.69 days. Three patients were not followed up for at least three months and one patient was lost to follow-up due to the city change of the family. In the final analysis, 45 (51.1%) female, and 43 (48.9%) male patients were included in the study. Median age of the patient population was 60 months (interquartile range: 30.50-120.00 months). Primary diagnoses were ALL in 44 (50%), AML in 7 (8.0%), and solid tumors in 37 (42%) patients (Table 1).

Development of Infectious Episodes

Among 88 patients, 67 children (76.2%) experienced at least one infectious episode during chemotherapy, and during the study period we observed a total of 149 infectious episodes (Figure 1). The primary diseases of 21 children in whom infectious episodes were not observed, were ALL (n=9), Hodgkin's disease (n=3), neuroblastoma (n=3), rhabdomyosarcoma (n=3), non-Hodgkin's disease (n=1), Ewing's sarcoma (n=1), and pancreas cancer (n=1).

During the follow-up period, 17.6% of patients with hematologic malignancies, and 32.4% of those with solid tumors had not experienced infectious episodes during the follow-up period without any significant difference regarding percentages of infection-free patients between groups ($p>0.05$). Duration of infection-free periods were 60±4.26 days in all patients, while they were 55±10.20, and 60±8.51 days in cases with leukemia and solid tumors, respectively. According to the Kaplan-Meier method, 49±0.070% of leukemia patients, and 48.6±0.082% of those with solid tumors had not experience any infectious episode on the 55th, and 60th days of follow-up, respectively (Figure 2). Duration of infection-free periods were not statistically significantly different between patients with hematologic and solid tumors ($p>0.05$).

Table 1. The distribution of the underlying malignancies of the patients in the study

Cancer types	(n) %
Leukemia	
Acute lymphoblastic leukemia	50 (44)
Acute myelocytic leukemia	8.0 (7)
Lymphoma	
Hodgkin lymphoma	3.4 (3)
Non-hodgin lymphoma	5.6 (5)
Willms tumor	3.4 (3)
Neuroblastoma	10.2 (9)
Rhabdomyosarcoma	8.0 (7)
Bone tumor	
Osteosarcoma	1.1 (1)
Ewing tumor	2.3 (2)
Central nervous system tumor	
Glioma	1.1 (1)
Ependymoma	1.1 (1)
Ovarian epitelial tumor	1.1 (1)
Hepatoblastoma	1.1 (1)
Endodermal sinus tumor	1.1 (1)
Pancreatic tumor	1.1 (1)

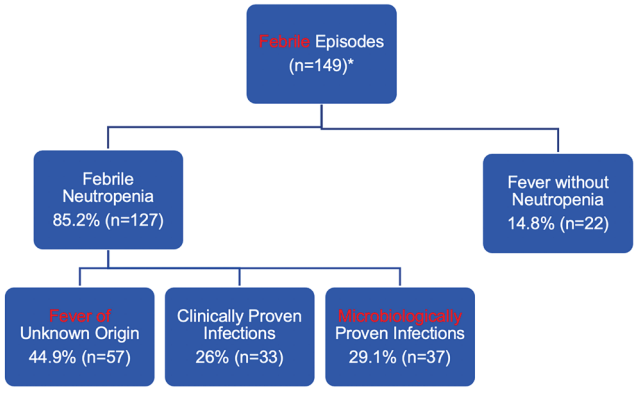

Figure 1. The distribution of the infectious episodes according to the clinical and microbiological features

*Four patients were excluded due to lack of sufficient follow up data

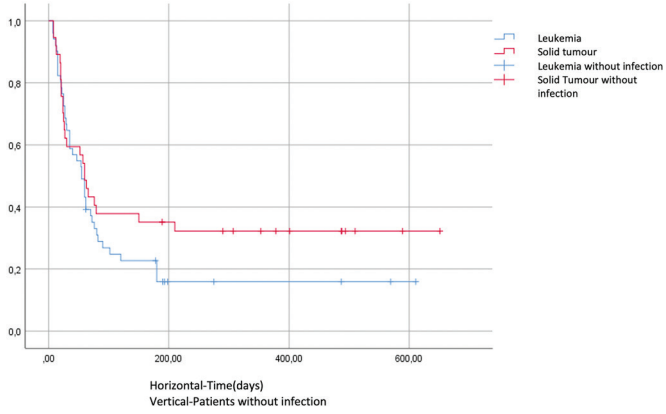

Figure 2. Kaplan-Meier analysis concerning development of infectious episodes, solid tumors and hematologic malignancies

According to the Kaplan-Meier method, 49±0.070% of leukemia patients on the 55th day, and 48.6±0.082% of the patients with solid tumors on the 60th day of the follow-up period had not experienced infectious episodes. A statistically significant difference was not found in terms of time interval passed without infection between patients with hematologic and solid tumors, (p>0.05)

A total of 149 infectious episodes were observed in ALL (n=74; 49.7%), in AML (n=19; 12.8%) patients and in cases with solid tumors (n=56; 37.6%). The number of infectious episodes varied in patients with ALL (0-6), AML (1-5), and solid tumors (0-5) without any significant intergroup difference (p>0.05) (Table 2). The patients who had two or more infectious episodes during follow-up period (mean age: 5.70±4.60; range: 0.75-17.17 years) were statistically significantly younger than those that had not experienced any infectious episodes (mean age: 9.02±5.17 years; range: 2-17.25 years) during that period (p=0.024).

The Characteristics of Infectious Episodes

The patients were neutropenic during 127 (85.2%) and non-neutropenic during 22 (14.8%) episodes. FUO was revealed in 57 (44.9%), clinically confirmed infections in 33 (26%), and microbiologically proven infections in 37 (29.1%) patients during febrile neutropenic episodes (Figure 1).

In our study the number of febrile neutropenic episodes differed between patients with leukemia (n=80; 63%), and the cases with solid tumors (n=47; 37%). Absolute neutrophil counts were ≤100/μL in 69 (54.3%) episodes. In patients with ALL, febrile neutropenic episodes were most frequently observed in the consolidation period (n=38; 29.9%), and in the induction period (n=17; 13.3%). In AML, febrile episodes were detected most frequently during the induction period (n=8; 6.2%). Microbiologically proven infectious episodes lasted significantly longer (14.11±5.55 days) compared to UFO (10.35±3.90 days), and clinically diagnosed infectious episodes (11.12±4.72 days) (p<0.001).

Focus of infection was present in 43 (33.9%), and absent in 84 (66.1%) febrile neutropenic episodes. Patients with febrile neutropenic attacks with identified foci of infection had skin (n=20; 46.6%), lower respiratory tract (n=9; 20.9%), upper respiratory tract (n=6; 13.9%), urinary tract (n=6; 13.9%) and gastrointestinal system (n=2; 4.7%) infections.

Blood cultures were performed either from peripheral vein or catheter tip samples in 97% (n=145), and urine specimens in 79% (n=119) of infectious episodes. A total 264 microbial cultures were performed from different locations during these infectious episodes. Regarding all of the cultures, 27% of blood, and 9% of urine cultures were positive. The most commonly isolated microorganisms were gram-positive bacteria. (n=23, 57.5%) followed by Gram-negative bacteria (n=16, 40%) and fungal agents (n=1, 2.5%). Most commonly isolated bacteria were CoNS (47.5%) followed by *Klebsiella pneumonia* (2.7%), *Staphylococcus aureus* (2.0%), and *Pseudomonas aeruginosa* (2.0%) (Table 3). *Escherichia Coli* was the most common isolated pathogen in urinary tract infections (Table 3).

DISCUSSION

In this cohort study with 2 years of the follow-up period, a total of 88 patients with pediatric hematologic malignancies and solid tumors were monitored for the development of infections. A total of 149 infectious

Table 2. Clinical characteristics associated with infections in children diagnosed with malignancy during the study period

Number of infectious episodes	0	1	>2	p-value
Age (median)	9.01*	6.45	5.70*	0.024*
Gender - n (%)				
Girl	11 (12.5)	7 (8.0)	27 (30.7)	>0.05
Boy	10 (11.4)	14 (15.9)	19 (21.6)	
Diagnosis - n (%)				
ALL	9 (20.5)	12 (27.3)	23 (52.3)	
AML	-	1 (14.3)	6 (85.7)	>0.05
Solid tumors	12 (32.4)	8 (21.6)	17 (45.9)	
Total - n (%)	21 (23.9)	21 (23.9)	46 (52.3)	>0.05

ALL: Acute lymphoblastic leukemia, AML: Acute myelocytic leukemia, *Kruskal-Wallis H 7,419

Table 3. The distribution of microorganisms identified during the microbiologically proven infection episodes

Identified microorganisms	Bloodstream culture (peripheral) n (%)	Urinary tract culture n (%)
Staphylococcus epidermidis	12 (8.1)	
Streptococcus acidominimus	1 (0.7)	
Staphylococcus hominis	6 (4.0)	
Staphylococcus hemoliticus	1 (0.7)	
Staphylococcus aerus(mssa)	3 (2.0)	
Pantoea agglomerans	1 (0.7)	
Acinetobacter baumanii	1 (0.7)	
Serratia marcescens	1 (0.7)	
Stenotrophomonas maltophilia	1 (0.7)	
Klebsiella oxytoca	1 (0.7)	1 (0.7)
Klebsiella pneumonia	4 (2.7)	
Salmonella	1 (0.7)	
Pseudomonas aeruginosa	3 (2.0)	1 (0.7)
Escherichia coli		8 (5.4)
Citrobacter werkmanii		1 (0.7)
Enterobacter cloacae	3 (2.0)	
Candida parapsilosis	1 (0.7)	

episodes including febrile neutropenic (85.2%), and febrile non-neutropenic (14.8%) episodes were observed. According to the classification of febrile neutropenia; these episodes were categorized as FUO (44.9%), clinically defined (26%), and microbiologically proven (29.1%) infections.

Despite lack of statistically significant intergroup differences, during the follow-up period, patients with solid tumors had more frequently experienced infection-free periods when compared to those with hematologic malignancies This is not a surprising finding because infectious complications are among the major causes of morbidity and mortality in patients undergoing cancer therapy. Hematologic malignancies, in particular AML, have been more frequently associated with infectious complications compared to solid tumors[4,11-14]. Al-Tawfiq et al.[16] also detected febrile neutropenic episodes due to chemotherapy at indicated rates in cases with leukemia (80%) and solid tumors (10-50%)[15].

During our study, 76.2% of the patients had at least one febrile infectious episode. A cohort study of 101 pediatric patients aged 7-16 years, reported that 79% of the patients had infectious episodes at least once[16]. Among childhood cancers, the highest risk in terms of invasive infection was found in patients diagnosed with acute myeloid leukemia and relapsed ALL[5,17,18].

In our study, the median infectious episode rate was 3 at the AML patients. In support of our findings, a recent study has reported greater number of infectious episodes and prolonged antibiotherapy in AML patients compared to patients with other diagnoses[16].

Children with AML are particularly susceptible to the development of severe infections, due to the intense treatment and prolonged and profound neutropenia.

In our study, the longer hospitalization periods of AML patients compared to ALL patients also supported the findings of previous reports. Basu et al.,[19] investigated 12,446 children with cancer and detected comparatively longer hospitalization periods in patients with AML[20].

In our study, the average age of those who had no infectious episodes during follow-up was found to be significantly higher than those who had 2 and/or more infectious episodes. Inaba et al.,[21] conducted a research study on 409 pediatric patients, and found that older patients had suffered from lesser number of infectious episodes, as well[19].

Auletta et al.[15] investigated the infections developed in 155 pediatric cancer patients , and found that cases under 3 years of age had suffered more frequently from infectious episodes[14]. However, connection of infections with age in children receiving chemotherapy has not been fully confirmed[21,22]. One of the reasons for failure to prove the connection between development of infections and age of the children is that statistical significance of age in univariate analyzes could not be demonstrated in multivariate analyzes due to the presence of other confounding factors[23].

Some studies in the literature have indicated an increase in the frequency of mucositis in younger patients, possibly related to the increasing mitotic index[24,25]. Different chemotherapy protocols exert effects of varying intensity on bone marrow. In their study, Lyman et al.,[26] stated that some regimens were more myelotoxic[27]. Febrile neutropenic episodes were detected mostly during the consolidation (n=38; 29.9%), and induction (n=17; 13.3%) phases of chemotherapy in indicated number of ALL patients. In AML, febrile neutropenic episodes were most frequently observed during induction phase of chemotherapy (n=8; 6.2%). Yilmaz et al.,[28] examined 239 febrile neutropenic episodes in 82 pediatric patients with leukemia, and found that the most frequently, febrile neutropenic episodes occurred during the consolidation period[26].

Considering the classification of febrile neutropenia; in our study group, FUO was the most commonly seen clinical entity. Among febrile infectious episodes predominantly skin and respiratory tract infections were observed. Febrile neutropenic patients are susceptible to infections due to decreased neutrophil count and dysfunction and increased permeability as a result of altered skin barrier balance[28]. In support of our findings, lower respiratory tract, upper respiratory tract, soft tissue, and gastrointestinal tract infections can often be seen in febrile neutropenia[26].

The impact and rate of positive cultures in the diagnosis of neutropenic fever especially in the children were reported to be at a lower level[29]. According to the studies in the literature, growth of pathogenic microorganisms is detected in only 15% of the cultures taken and the culture positivity rate in our study was found to be higher than that cited in the literature. Daef et al.[30] found bacteremia in 25 (29.4%) of 85 febrile neutropenic attacks in 68 patients, and gram-positive growth was found in 15 (53.6%) attacks in the same study[31]. The rate of positive cultures might change depending on the sample collection methods, capacities of microbiology laboratories, and characteristics of the hospital's working conditions. In our study, the most common isolated microorganism was CoNS which is responsible for nearly half of the bloodstream infections. Recent studies have reported that CoNS and *Staphylococcus aureus* were isolated in nearly 50% of positive cultures[30,32]. The higher rate of Gram-positive bacteria identified during febrile neutropenic episodes was mainly due to presence of indwelling vascular catheters and multiple interventions performed[6].

This study was approved by the University of Health Sciences Turkey, Dr. Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital Ethics Committee (decision number: 2019/06-04; date: 11.04.2019).

Study Limitation

This study has several limitations. First, the malignancies in the study group were heterogenous especially regarding diagnoses, and includes both hematologic malignancies and solid tumors which might change the development of the infectious complications. Secondly, the treatment modalities change depending on the stage and the grade of the primary disease which also affects the nature of the infectious complications.

CONCLUSION

In conclusion, younger children with cancer are at higher risk of infectious complications compared to children of older ages. Children with hematologic malignancies are more likely to develop a neutropenic fever during the consolidation and induction periods. Regarding the high rate of FUO in our study, more attempts should be made to increase the rates of microbiological diagnosis in this patient population.

Ethics

Ethics Committee Approval: This study was approved by the University of Health Sciences Turkey, Dr. Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital Ethics Committee (decision number: 2019/06-04; date: 11.04.2019).

Informed Consent: Written consent was obtained from all patients.

Author Contributions

Surgical and Medical Practices: D.B., Concept: D.B., İ.Ç., E.B., Design: D.B., E.K., Data Collection or Processing: D.B., S.O.A., Analysis or Interpretation: D.B., N.T., Literature Search: D.B., T.H.K., Writing: D.B., Ö.Ö.Ş., B.D., İ.D.

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

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