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ORIGINAL ARTICLE

Epidemiology of paediatric severe sepsis and septic shock in Turkey: Prevalence, results and treatments study

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Abstract

Aim: This study was aimed at characterising the prevalence, management and outcomes of paediatric severe sepsis and septic shock in tertiary paediatric intensive care units (PICUs) in Turkey.

Methods: A point prevalence study was conducted on 5 days over the course of 1 year in 29 PICUs in Turkey. Outcomes included severe sepsis and septic shock point prevalence, therapies used, duration of PICU stay and mortality at day 28.

Results: Of the 1757 children who were admitted to the PICU during the study period, 141 (8.0%) children met the consensus criteria for severe sepsis and 23 (1.3%) children met the criteria for septic shock. Paediatric severe sepsis and septic shock accounted for 8% and 1.3% of all PICU admissions, respectively. The median age of the patients was 2.6 years (interquartile range [IQR], 0.7–8.6 years). Enteral nutrition (79.3%) was preferred compared to parenteral nutrition (31.1%) for the first 3 days after PICU admission. A total of 39 patients died while in the PICU, for a 23.8% mortality rate, which did not vary by age.

Conclusion: The mortality rate was similar to that in other studies. Hematologic-immunologic comorbidity, parenteral nutrition and the use of vasoactive drugs were independently associated with mortality.

KEYWORDS
intensive care units, mortality, paediatrics, septic shock, severe sepsis

1 | INTRODUCTION

Sepsis, defined as an infection with irregular host response that causes life-threatening organ dysfunction, continues to have a high potential for morbidity and mortality in children.[1] Paediatric sepsis is the most common cause of paediatric death worldwide and results in an estimated 7.5 million deaths per year.[2,3] Severe paediatric sepsis is a life-threatening condition that is widely monitored and treated in paediatric intensive care units (PICUs) worldwide.[2–4] Severe sepsis is defined as infection plus infection-induced organ dysfunction; in children, it is characterised by the presence of sepsis and cardiovascular or respiratory dysfunction or dysfunction in two or more organs (neurological, hepatic, hematologic or renal). The prevalence of severe sepsis in PICUs has been reported to be between 2% and 3% in developed countries[5,6] and between 18% and 46% in developing countries.[7,8] In a study conducted in southwest China, the mortality

The Epidemiology of Pediatric Severe Sepsis and Septic Shock Study Group members presented in Appendix A.

rate due to severe paediatric sepsis in the hospital was found to be 18.8%.[9] In the multicentre prospective SPROUT study, severe paediatric sepsis mortality was found to be 24% in the PICU and 25% in the hospital, and these rates did not change with age.[10]

Septic shock is defined as sepsis accompanied by ongoing cardiovascular dysfunction, despite the administration of ≥40 ml/kg of fluid. The incidence of septic shock in children is reported to be 0.08 cases per 100,000.[11] In a study conducted in Italy, the septic shock mortality rate was reported to be 51%, and the early mortality (<24 h) rate was 30.6%.[12] In this study, the high mortality in septic shock was attributed to inadequate treatment of shock—none of the PICUs used the severe sepsis and septic shock therapy algorithms for children recommended by the American College of Intensive Care Medicine-Paediatric Advanced Life Support. Paediatric consensus guidelines highlight the basic principles of targeted resuscitation, initiation of rapid antimicrobial therapy and supportive care of organ dysfunction in sepsis.[13]

The aim of this observational study was to assess the prevalence, treatments and mortality rates of severe sepsis and septic shock in PICUs in Turkey.

Key Notes

- The study was to assess the prevalence, treatments and mortality rates of severe sepsis and septic shock in PICUs in Turkey.
- Paediatric severe sepsis and septic shock accounted for 8% and 1.3% of all PICU admissions, respectively, and the mortality rate was 23.8%.
- The patient's underlying hematologic-immunologic comorbidity, use of vasoactive drugs and parenteral nutrition were independently associated with mortality.

2 | MATERIALS AND METHODS

The Institutional Ethical Committee of Dokuz Eylul University, Turkey, approved this prospective, point prevalence, multicentre study (approval number: 4720-GOA).

A prospective, multicentre, point prevalence study in which managements and outcomes were conducted on 5 days between June 2019 to April 2020 to address paediatric patients with severe sepsis and septic shock admitted to PICUs. The PICUs voluntarily participated in an open invitation, and no funding was provided.

2.1 | Inclusion and exclusion criteria

Patients between 29 days and 18 years old who were hospitalised in PICUs at 9:00 A.M. on each study day were included in the study. They were screened for severe sepsis and septic shock using the International Paediatric Sepsis Consensus Conference criteria: (a) two or more systemic inflammatory-response syndrome criteria, (b) confirmed or suspected invasive infection and (c) cardiovascular dysfunction, acute respiratory distress syndrome or dysfunction of two or more organs.[14]

To determine the point prevalence of active severe sepsis, only those patients who met consensus criteria for severe sepsis within the 24-h period from 9:00 A.M., the day before the study day through 9:00 A.M on the study day were included. Patients who were hospitalised in PICUs, previously met the criteria for severe sepsis or septic shock but did not show severe sepsis or septic shock symptoms within 24 h of the study day, were not included in the study, even if they were still being treated in the intensive care unit. Patients with missing data were excluded.

2.2 | Data collection

The demographic characteristics, comorbidities, site of infection and microbiological isolate data of all patients meeting the criteria for severe sepsis and septic shock in PICUs were collected on the study days using the web-based Research Electronic Data Capture (REDCap) application.[15] The laboratory results, antimicrobial administration, vasoactive infusions, mechanical ventilation and treatments were collected for 48 h from 9:00 A.M on the day before the study day until 9:00 A.M on the day after the study day. Data for the Paediatric Index of Mortality (PIM)-3 score[16] and Paediatric Logistic Organ Dysfunction score[17] were collected and calculated on the study day. Demographic data for each patient, accompanied conditions (respiratory, cardiac, metabolic, neurological and oncologic diseases), the units in which they were admitted to intensive care (emergency room, medical ward, operating room and other hospitals), the reason for intensive care admission (medical, surgical, trauma), infection site, source of infection (community and hospital), microbiological results, post-diagnosis treatments (vasoactive infusions, antibiotics, antifungal and adjuvant treatments), intensive care stay and mortality were recorded. Patients with severe sepsis or septic shock were followed for 28 days, except those who died or were discharged earlier.

2.3 | Statistical analyses

Statistical analysis was performed using SPSS software version 22.0 (SPSS) for Windows. Categorical data, expressed as frequencies (%), were analysed using Fisher's exact test. Comparisons were performed using the Mann–Whitney U-test for continuous data and the chi-square for categorical data. Data across, as median interquartile range (IQRs), were analysed using the Kruskal-Wallis test, with patients divided into age groups. Univariate regression analysis was used to evaluate factors associated with mortality in severe sepsis and septic shock. Covariates associated with mortality in the univariate analysis were analysed by multivariate regression analysis. Statistical significance was defined as a p-value <0.05.

3 | RESULTS

A total of 29 tertiary PICUs in Turkey participated in this study. Fifteen of these units were in a university hospital, 11 of these units were in training and research hospitals and three of these units were in state hospitals. Overall, 1757 children were screened and 164 children met the consensus criteria for severe sepsis and septic shock (Figure 1). In our study, the prevalence of severe sepsis and septic shock amongst them was 8% and 1.3%, respectively.

Patient characteristics are shown in Table 1. The median age was 2.6 years (IQR, 0.7–8.6), and 62.8% were male patients. At least one comorbid condition was detected in 133 of the patients (81.1%). The most common comorbid conditions were respiratory diseases (50.7%) and neuromuscular diseases (42.5%). Comorbid conditions were higher in patients who came from the medical ward compared to those who came from the emergency department (31.7% vs. 29.3%, respectively; $p = 0.005$). Medical disease was the most common cause for a patient's admission (86.6%). Most of the patients exhibited respiratory dysfunction (91.5%). The incidence of MODS with dysfunction of two or more organs was 65.2%.

The site of infection and microbiologic aetiology of severe sepsis and septic shock are listed in Table 2. The most common primary infection sites were respiratory (76, 46.3%) and bloodstream (34, 20.7%). Microbiological tests were performed on 161 patients, 100 (61.0%) of them were positive for infectious organisms; microbiologic tests were not performed on the three patients. Blood culture was identified positively in 53 patients (32.9%); amongst them, resistant microorganisms were isolated in the blood cultures of 23 patients (43.4%), with methicillin resistance being found most frequently ($n = 10$, 43.5%). *Klebsiella pneumonia* (15, 9.1%) was isolated as the most common gram-negative bacteria in the blood cultures. The most common gram-positive agents isolated were *Staphylococcus epidermidis* (9, 5.5%) and *S. aureus* (8, 4.9%).

Therapies used within the 48-h data collection window are listed in Table 3. The most commonly used vasoactive agents in patients were epinephrine (44.5%) and norepinephrine (32.3%). In all, 40.2% of patients were treated with corticosteroids, steroid-treated 29 days–12 months (27, 40.9%), 1–5 years (24, 36.4%), 6–13 years (8, 12.1%) and 13–18 years (7, 10.6%), and accordingly, a statistically significant difference was found in terms of steroid use in treatment ($p < 0.05$). The rate of steroid use was higher in the under 6 years age group when compared to that in the over 6 years age group ($p = 0.03$). Insertion of a central venous catheter was higher and statistically significant in patients using vasoactive agents ($p < 0.05$). Most of the patients used invasive mechanical ventilation, with the rates of non-invasive ventilation use and high-flow nasal cannula therapy being

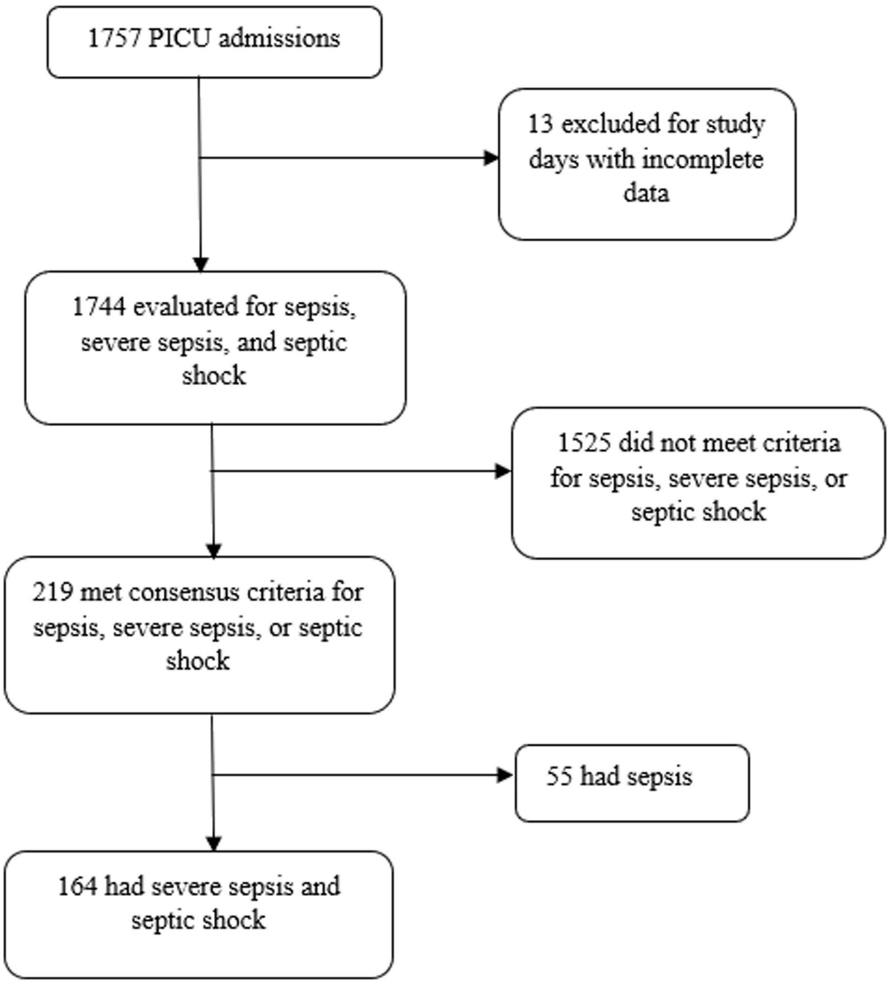

FIGURE 1 Diagram showing the distribution and characteristics of the patients included in the study

TABLE 1 Characteristics of patients with severe sepsis and septic shock

Characteristics	Value
Age, year, *n* (%)	2.6 (0.7–8.6)
29 day-12 months	51 (31.1)
1–5 years	60 (36.6)
6–12 years	35 (21.3)
13–18 years	18 (11.0)
Sex, *n* (%)	*n* (%)
Female	61 (37.2)
Male	103 (62.8)
Comorbid condition	*n* (%)
Respiratory	68 (50.7)
Neuromuscular	57 (42.5)
Genetic/Metabolic	43 (32.1)
Cardiovascular	37 (27.6)
Gastrointestinal	31 (23.1)
Hematologic/immunologic	19 (14.2)
Renal	17 (12.7)
Oncologic	15 (11.2)
Type of PICU admission	*n* (%)
Medical	142 (86.6)
Surgical	18 (11)
Trauma	4 (2.4)
Source of admission	*n* (%)
Emergency department	48 (29.3)
Medical ward	52 (31.7)
Operating room	10 (6.1)
Other hospital	54 (32.9)
Organ dysfunction present at screening	*n* (%)
Respiratory	150 (91.5)
Cardiovascular	119 (72.6)
Neurologic	101 (61.6)
Hematologic	74 (45.1)
Hepatic	52 (31.7)
Renal	45 (27.4)
Number of organ dysfunction	*n* (%)
<2	57 (34.8)
≥2	107 (65.2)
PELOD-2 score, median (IQR), *n* (%)	9 (6–13)
PIM-3 score, median (IQR), *n* (%)	10 (1.2–27)

Note: Data are presented as median (interquartile range). PIM-3 was measured at time of PICU admission. PELOD-2 score was calculated from data within a 48-hour time window around the study day. (09:00 on the day before to 09:00 the day after the study day).

Abbreviations: PELOD-2, paediatric logistic organ dysfunction-2; PICU, paediatric intensive care unit; PIM-3, paediatric index of mortality-3.

similar (20.7% vs. 20.2%). Other adjuvant therapies, such as renal replacement therapy (17.5%) and plasma exchange (14%), were used, and two out of four patients who were treated with ECMO died.

TABLE 2 Site of infection and microbiologic aetiology of severe sepsis and septic shock

Characteristic	*n* (%)
Primary site of infection	
Respiratory	76 (46.3)
Primary bloodstream	34 (20.7)
Central nervous system	9 (5.5)
Genitourinary	9 (5.5)
Abdominal	7 (4.3)
Skin	5 (3)
Other	2 (1.2)
Unknown	22 (13.4)
Microbiological	
Total patients with a positive isolate	100 (61.0)
Gram-negative bacteria	46 (28)
Klebsiella pneumoniae	15 (9.1)
Pseudomonas aeruginosa	14 (8.5)
Escherichia coli	7 (4.3)
Acinetobacter baumannii	2 (1.2)
Stenotrophomonas maltophilia	2 (1.2)
Other	6 (3.7)
Gram-positive bacteria	30 (18.3)
Staphylococcus epidermidis	9 (5.5)
S. aureus	8 (4.9)
Streptococcus pneumoniae	3 (1.8)
Enterococcus species	3 (1.8)
Other	7 (4.3)
Viruses	23 (14)
Influenza A	12 (7.3)
Respiratory syncytial virus	3 (1.8)
Adenovirus	2 (1.2)
Cytomegalovirus	2 (1.2)
Other	4 (2.4)
Fungi	29 (17.7)
Candida species	26 (15.9)
Aspergillus species	2 (1.2)
Other	1 (0.6)

Note: Categories do not add up to 100%, as some infections were polymicrobial. Sources of positive isolates include blood, urine, cerebrospinal fluid and respiratory system (nasopharynx, tracheal and bronchoalveolar lavage).

The mechanical ventilator days, PICU length of stay and mortality rates provided in Table 4. Although the number of mechanical ventilator days increased with the patient's age, there was no statistically significant difference ($p = 0.07$). The PICU length of stay did not differ by age ($p = 0.61$). A total of 39 patients died while in the PICU, with a 23.8% mortality rate. Although the mortality rate was higher in the 1–5 age group, no significant difference was found between the groups ($p = 0.94$).

Mortality, discharge or the 28-day study period was the study endpoint. A total of 39 patients died while in the hospital, with a mortality rate of 23.8%. Hematologic-immunological comorbidity was associated with mortality. Mortality was associated with the use of vasoactive agents ($p < 0.001$), enteral nutrition ($p < 0.001$) and parenteral nutrition ($p < 0.001$). Higher rates of diuretic treatment ($p = 0.032$) and blood products replacements ($p = 0.001$) were detected in non-survivors compared to survivors. Renal replacement therapy ($p = 0.002$) and plasma exchange ($p = 0.001$) were more prevalent in patients who were non-survivors. PIM-3 and PELOD-2 scores were also statistically significantly higher in patients who were non-survivors. Gender, age and PICU length of stay (in days) did not have a significant effect on mortality (Table 5). Multivariate regression analysis of variables in patients demonstrated that hematologic-immunologic comorbidity, parenteral nutrition and the use of vasoactive inotropic drugs increased mortality independently. Although the rate of parenteral nutrition was higher in patients who died in the multivariate regression analysis, the rate of enteral nutrition initiated in the 48-hour data collection window was higher in patients who survived (Table 6). Parenteral nutrition and vasoactive drug use were associated with higher mortality (OR 3.9; $p = 0.002$: OR 4.3; $p = 0.013$, respectively).

TABLE 3 Therapies used within the 48-Hour data collection window

Characteristic	*n* (%)
Vasoactive infusion[a]	99 (60.4)
Epinephrine	73 (44.5)
Norepinephrine	53 (32.3)
Dopamine	45 (27.4)
Milrinone	33 (20.1)
Dobutamine	17 (10.4)
Other	2 (1.2)
Use of antibiotics	162 (98.8)
Use of antifungals	77 (47)
Use of antivirals	37 (22.6)
Corticosteroids	66 (40.2)
Diuretics	107 (65.2)
Blood products[b]	111 (67.7)
IVIG	22 (13.4)
GCSF	8 (4.9)
Nutrition, enteral	130 (79.3)
Nutrition, parenteral	51 (31.1)
Invasive mechanical ventilation	140 (85.4)
Non-invasive mechanical ventilation	34 (20.7)
High-flow nasal cannulation	33 (20.2)
Continuous renal replacement therapy	29 (17.5)
Plasma exchange	23 (14)
ECMO	4 (2.4)

Note: Data are presented as *n* (%).

Abbreviations: ECMO, extracorporeal membrane oxygenation; GCSF, granulocyte colony-stimulating factor; IVIG, intravenous immunoglobulin.

[a]Includes dopamine 0.5 mcg/kg/min; dobutamine 0.5 mcg/kg/min; or any dose of epinephrine, norepinephrine, milrinone or a vasodilator.

[b]Includes packed red blood cells, platelets, fresh frozen plasma and cryoprecipitate.

4 | DISCUSSION

This study is the first multicentre, point prevalence prospective study conducted in PICUs in Turkey. In this study, paediatric severe sepsis and septic shock prevalence, treatments and outcomes are demonstrated. In our study, the prevalence of severe sepsis and prevalence of septic shock were found to be 8% and 1.3%, respectively, in 1757 inpatients in the PICUs. The prevalence of paediatric severe sepsis has been reported to be 7.7%[2] in developed countries, and the prevalence of septic shock has been reported to be 18%–46% in developing countries and 2%–3% in developed countries.[18] According to the results of this study, the prevalence of paediatric severe sepsis in our country was similar to that of Western countries, while the prevalence of septic shock was found to be higher than in developed countries.

In our study, the mortality rate in the PICUs was found to be 23.8%. In the studies conducted in the United States on paediatric severe sepsis mortality, the mortality rate in PICUs was reported to be 25%.[3,4] In another study performed in PICUs, the mortality rate was reported to be 21%–32% for North America, Europe, Australia

TABLE 4 Outcomes for total cohort and by age category

Outcomes	29 d–12 m (*n* = 51)	1–5 years (*n* = 60)	6–12 years (*n* = 35)	13–18 years (*n* = 18)	Total	*p* Value
Ventilator free days[a]	6 (0–14)	5 (0–20.7)	7 (0–17.2)	6.5 (0–13)	11.9 (8.8–15.0)	0.96
Days on mechanical ventilator[a]	9 (3–21)	8 (4–21.7)	14 (5–28)	14.5 (4–23.5)	15.6 (11.7–19.5)	0.07
PICU length of stay[a]	24 (10–28)	23.5 (10–28)	28 (16–28)	19.5 (11.7–28)	27.7 (23.1–32.3)	0.61
PICU mortality[b]	11 (28.2)	14 (35.9)	9 (23.1)	5 (12.8)	39 (23.8)	0.94

Note: Kruskal-Wallis test.

[a]Data are presented as median (interquartile range).

[b]Data are presented as *n* (%).

TABLE 5 Comparisons between severe sepsis and septic shock survivors and non-survivors

Variables	Total $n = 164$	Non-survivors $n = 39$	Survivors $n = 125$	p Value
Age, m, median	32.2	32.1	32.3	0.700
Female gender, *n* (%)	61/164 (37.2)	15/39 (38.5)	46/125 (36.8)	0.852
PIM-3, median, IQR	10.1 (1.2–27.1)	28.8 (9.3–67.4)	5.6 (1–23.2)	<0.001
PELOD-2, median, IQR	9 (6–13)	16 (11–18)	7 (5–11)	<0.001
Presence of comorbid condition, *n* (%)				
Respiratory	68 (41.5)	16 (42.0)	52 (41.6)	0.949
Neuromuscular	57 (34.8)	9 (23.1)	48 (38.4)	0.079
Genetic/metabolic	43 (26.2)	10 (25.6)	33 (26.4)	0.925
Cardiovascular	37 (22.6)	12 (30.8)	25 (20.0)	0.160
Gastrointestinal	31 (18.9)	8 (20.5)	23 (18.4)	0.760
Hematologic/immunologic	19 (11.6)	10 (25.6)	9 (7.2)	0.020
Renal	17 (10.4)	5 (12.8)	12 (9.6)	0.565
Oncologic	15 (9.1)	6 (15.4)	9 (7.2)	0.122
PICU length of stay in days, median, IQR	25 (12–28)	23 (10–46)	28 (13–28)	0.868
Nutrition				
Enteral nutrition	130 (79.3)	22 (56.4)	108 (86.4)	<0.001
Parenteral nutrition	51 (31.1)	22 (56.4)	29 (23.2)	<0.001
Use of vasoactive inotropic	99 (60.4)	34 (87.2)	65 (52)	<0.001
Adjuvant treatment, *n* (%)				
Corticosteroids	66 (40.2)	16 (41)	50 (40)	0.909
Diuretics	107 (65.2)	31 (79.5)	76 (60.8)	0.032
Blood products	111 (67.7)	35 (89.7)	76 (60.8)	0.001
IVIG	22 (13.4)	4 (10.3)	18 (14.4)	0.507
GCSF	8 (4.9)	4 (10.3)	4 (3.2)	0.074
Extracorporeal therapy, *n* (%)				
RRT	28 (17.1)	13 (33.3)	15 (12)	0.002
Plasma exchange	23 (14)	12 (30.8)	11 (8.8)	0.001
ECMO	4 (2.4)	2 (5.1)	2 (1.6)	0.212

Abbreviations: ECMO, extracorporeal membrane oxygenation; GCSF, granulocyte colony-stimulating factor; IVIG, intravenous immunoglobulin; PELOD-2, paediatric logistic organ dysfunction-2; PIM-3, paediatric index of mortality-3; RRT, renal replacement therapy.

TABLE 6 Association between variables and mortality in multivariate regression analyses

	Multivariate Model		
Variable	OR	95% CI	p Value
Hematologic/immunologic comorbidity	5.490	1.968–15.318	0.001
Enteral nutrition	0.187	0.070–0.484	0.001
Parenteral nutrition	3.901	1.610–8.972	0.002
Use of vasoactive inotropic	4.350	1.371–13.804	0.013

Abbreviation: OR, Odds ratio.

and New Zealand; 11%–40% for South America; and 40% for South Africa. In our study, the mortality rates of severe sepsis and septic shock were found to be similar to those of developed countries. The most important factors here are the development of paediatric intensive care in our country in the last 15 years, the fact that the physicians who took part in the initial establishment phase were trained in developed countries with well-established PICUs, and the use of up-to-date guidelines in sepsis treatment in paediatric intensive care units in country, in addition to widespread use of technological opportunities.

In this study, 81.1% of the patients had one or more comorbidities, with the most common comorbidity being respiratory. In a similar study, one or more underlying accompanied problems were found in 74% of the patients, with the most common comorbidity being cardiovascular.[2] In our study, mortality was found to be high in patients with immunologic/hematologic comorbidities, just as in other studies.[1,19] In a retrospective, multicentre study conducted in PICUs in Australia and New Zealand between 2002 and 2013, the presence of a major comorbidity was an independent predictor of mortality, and more than two-thirds of all patients who died from sepsis and septic shock had a comorbidity.[10] In our study, hematologic-immunologic comorbidity was found to be an independent predictor of mortality in patients with severe sepsis and septic shock. However, it could not be determined whether the death was due to sepsis or an underlying comorbidity. Similar to the results of the study conducted in southwest China,[9] comorbidity in patients transferred to the PICUs from wards was higher compared to the patients transferred from the emergency department. This suggests that, when treating patients with comorbidities, more attention should be paid to the prevention of severe sepsis and septic shock, rather than focusing only on the causative agent-oriented treatment.

Mortality increases as sepsis-related organ damage increases. In our study, although the length of stay in the PICU was longer in patients with dysfunction in two or more organs, no statistically significant difference was detected when compared with patients with dysfunction of one organ. Organ dysfunction during hospitalisation in the PICU was associated with prolonged hospitalisation, and it was found that the length of hospitalisation was prolonged for each additional organ system affected[20] Use of extracorporeal treatment was found to be high in paediatric patients with severe sepsis and MODS with dysfunction in two or more organs,[21] and the rates were similar to our study (79.8%).

In our study, similar to another research, the most common focus of infection was found to be respiratory and bloodstream infections.[3] The causative agent was produced in the cultured samples of 61% of patients (n = 161), and these microorganisms were isolated from PCR, blood, urine, mini-bronchoalveolar lavage and endotracheal aspiration cultures. In our study, the most isolated agents were *S. epidermidis* (5.5%), a gram-positive agent; *K. pneumonia* (9.1%), a gram-negative agent; and *Candida* spp. (26%), fungal infections. Similarly, the most commonly isolated agent in PICUs was reported to be coagulase negative staphylococci (25.5%), followed by *Candida* spp. (13.5%) and *K. pneumonia* (10.8%).[22] In our study, treatment with antibiotics were initiated in 98.8% of patients with septic shock and severe sepsis. In another study reported that antibiotics were initiated in 68.6% of patients with severe sepsis and septic shock.[23] The mortality rate was found to be lower in patients who started antibiotics early compared to those who started late (septic shock: 22% vs. 34%, severe sepsis: 10% vs. 15%).[24] The high rate of initiation of antibiotics indicates that the treatment was done in accordance with the treatment guidelines.

Adjuvant treatments other than corticosteroids, diuretics and blood products were rarely used in our study, but it is unknown whether this is due to underlying diseases or lack of data. In our study, although corticosteroids were started more frequently in patients younger than 1 year of age, no significant correlation was detected between mortality and corticosteroid use. In the study, corticosteroid use was found to be independently correlated with mortality.[25] In our study, renal replacement therapy was the most frequently used treatment amongst extracorporeal treatments, and renal replacement therapy and plasma exchange were applied more frequently in surviving patients than in patients who died, which was found to be statistically significant. In a study on the use of extracorporeal therapy in paediatric patients with severe sepsis, the most commonly used treatment modalities were found to be renal replacement therapy (7%) and ECMO (3.4%) ECMO was used rarely (2.4%), and mortality was approximately 50%, which similar to a study on the use of extracorporeal therapy in severe sepsis.[21]

Our data support the use of additional treatment options in paediatric patients with severe sepsis. In our study, enteral nutrition was preferred (79.3%) compared to parenteral nutrition (31.1%) for the first 3 days after hospitalisation in the PICU. In a study found a significant relationship between parenteral nutrition and mortality; however, they did not detect a significant relationship between the length of hospitalisation in the PICU and the duration of mechanical ventilation. Mortality was found to be lower in enterally fed patients, and the length of stay in the PICU was found to be shorter for enterally fed patients compared to parenterally fed patients. According to our study results, enteral nutrition should be preferred in patients followed in the PICU, and it should be started as soon as possible. It is suggested that parenteral nutrition increases the risk of infection and protein-induced over nutrition and inhibits autophagy.[26] In addition, as specified in the PEPaNIC study, early enteral nutrition is effective in reducing both the development of sepsis and healthcare costs.[27]

In our study, while no statistically significant difference was found regarding the duration of mechanical ventilation according to age groups, the duration of mechanical ventilation was longer inpatient groups older than 6 years of age. In the literature, the duration of mechanical ventilation was found to be longer in the PICU in patients younger than 12 months.[28] In our study, a respiratory comorbidity was higher in children older than 6 years of age. However, in another study found prolonged mechanical ventilation in patients under 2 years of age with severe chronic comorbidities.[29] It was thought that high airway pressure in the mechanical ventilator and sedation given according to the respiratory disease were factors in prolongation of mechanical ventilation time. While there was no statistically significant correlation between age groups and mortality, in the first 5 years of life, mortality was higher. In our study, comorbidity, PIM-3 score at the time of hospitalisation, use of inotropes and a higher number of involved organs were found to be associated with mortality in patients under 5 years of age. In a study conducted in the United States, mortality was found to be higher in patients with severe sepsis under 4 years of age when compared to other age groups, and comorbidities were found to be higher in these patients.[2] In the multivariate regression analysis performed after the

univariate regression analysis, parenteral nutrition and multiple vasoactive inotropic agents need was found to be associated with increased mortality.[30] This result is associated with the fact that the more severe patients, with a higher mortality rate, required multiple inotropic agents and did not receive enteral nutrition.

There were some limitations in our study. Firstly, although the participating hospitals had level III intensive care units, the availability of some treatment modalities in these units were different, which limited the use of both adjuvant and extracorporeal treatments. Secondly, mortality in the first 28 days of the hospitalisation in the PICU was calculated. Therefore, hospital mortality and morbidity could not be calculated. Despite these limitations, the reported results are important, encouraging following the guidelines and the implementation of the protocols for the management of diagnosis and treatment of complex diseases with high mortality, such as severe sepsis and septic shock.

5 | CONCLUSION

This report is the first to present the prevalence, treatments and outcomes of paediatric severe sepsis in the main PICU centres in Turkey. Paediatric severe sepsis and septic shock incidence and mortality rates were similar to that of Europe. The patient's underlying hematologic-immunologic comorbidity, use of vasoactive drugs and parenteral nutrition were independently associated with mortality. The mortality rate remains high; therefore, improved clinical management and implementation of large-scale clinical trials are necessary to improve early diagnosis and treatment.

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APPENDIX A

Epidemiology of Paediatric Severe Sepsis and Septic Shock Study Group: Agop Citak, Mutlu U. Yazici, Merve Havan, Edin Botan, Nazik Yener, Resul Yilmaz, Alaaddin Yorulmaz, Ferhat Sari, Muhterem Duyu, Feyza G. Incekoy, Nilufer Y. Ozturk, Ilknur Tolunay, Bulent Karapinar, Pinar O. Yazici, Serdar H. Kihtir, Zeynep Kihtir, Ali E. Arslankoylu, Mehmet Alakaya, Ayşe B. Anil, Pinar Kulluoglu, Gazi Arslan, Oguz Dursun, Erdem Cebisli, Serhat Emeksiz, Oktay Perk, Nihal Akcay, Esra Sevketoglu, Faruk Ekinci, Arda M. Kilinc, Alper Koker, Yasemin Coban, Murat Kangin, Mehmet N. Talay, Arzu Oto, Nevin Kilic, Çağlar Odek, Hasan Agin, Ekin Soydan, Özlem T. Koksoy, Mey T. Petmezci, Umit Saritas, Gokhan Kalkan, Emine Akkuzu.