Mortality Risk Factors Among Critically Ill Children With Acute COVID-19 in PICUs: A Multicenter Study From Turkish Pediatric Critical COVID-19 and MIS-C Study Group

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Background: During the coronavirus disease 2019 (COVID-19) pandemic, the world has a large number of reported COVID-19 cases and deaths. Information on characteristics and mortality rate of pediatric intensive care unit (PICU) cases with COVID-19 remains limited. This study aims to identify the risk factors for mortality related to COVID-19 in children admitted to PICU.

Methods: A retrospective multicenter cohort study was conducted between March 2020 and April 2021 at 44 PICUs in Turkey. Children who were 1 month–18-year of age with confirmed COVID-19 admitted to PICU were included in the study. Children with multisystem inflammatory syndrome and asymptomatic for COVID-19 were excluded.

Results: Of 335 patients with COVID-19, the median age was 6.8 years (IQR: 1.2–14) and 180 (53.7 %) were male, 215 (64.2 %) had at least one comorbidity. Age and gender were not related to mortality. Among 335 patients, 166 (49.5%) received mechanical ventilation, 17 (5.1%) received renal replacement therapy and 44 (13.1 %) died. Children with medical complexity, congenital heart disease, immunosuppression and malignancy had significantly higher mortality. On multivariable logistic regression analysis, organ failure index [odds ratio (OR): 2.1, 95 confidence interval (CI): 1.55–2.85], and having congenital heart disease (OR: 2.65, 95 CI: 1.03–6.80), were associated with mortality.

Conclusions: This study presents detailed data on clinical characteristics and outcomes of patients with COVID-19 admitted to PICU in the first pandemic year in Turkey. Our study shows that having congenital heart disease is associated with mortality. In addition, the high organ failure score in follow-up predict mortality.

Key Words: Child, COVID-19, mortality, PICU

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Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was reported first on March 11, 2020, by the Turkish Ministry of Health. There are over 128 million confirmed cases and over 2.8 million deaths worldwide, approximately 3.3 million confirmed cases, and over 31 thousand deaths in Turkey as of April 2021[1–2]. According to the American Academy of Pediatrics, of nearly 25 million cases reported, children constitute 13.4% (3.4 million) of all cases[3]. Children generally have a milder disease course than adults, with typically better prognosis. A small number of children with COVID-19 required pediatric intensive care unit (PICU) admission[4]. Studies including adult patients report that in-hospital mortality is associated with male sex, immunosuppression, renal disease, chronic lung disease, cardiovascular disease, neurologic disorders and diabetes[5,6]. Children were thought to be mildly affected but as the pandemic progressed, severe cases and new studies on mortality have emerged. A study discussing outcomes of children with COVID-19 in US and Canadian intensive care units reveals that prehospital comorbidities play an important role in severe disease[4].

Our aim in this study was to evaluate the independent risk factors associated with the mortality of children with COVID-19 requiring treatment in PICUs in Turkey.

METHODS

Study Population

We performed a retrospective cohort study including pediatric patients with COVID-19 infection who were admitted to PICU between March 1, 2020, and April 1, 2021. This study includes patient data from 44 pediatric intensive care units in 23 cities across Turkey (see list of Study Centers, Supplemental Digital Content 1; http://links.lww.com/INF/E744). All children less than 18 years old who required PICU care and had laboratory-confirmed COVID-19 diagnoses were included in the study. COVID-19 diagnosis was confirmed either by a positive RT-polymerase chain reaction (RT-PCR) on a nasopharyngeal specimen or antibody positivity developed during the disease course when the first RT-PCR and antibody testing were both negative. Only laboratory-confirmed cases were included and analyzed. We identified these cases using the International Classification of Diseases (ICD-9) code for COVID-19. Children who died within 12 h of PICU admission or suspected cases who had radiological or clinical findings that were compatible with COVID-19 but had negative PCR test results or the patients who were hospitalized for non-COVID reasons (such as trauma or surgery) but had incidentally positive COVID-19 PCR results were excluded from the study. The study was approved by the University of Health Sciences Turkey Bakirkoy Dr. Sadi Konuk Research and Training Hospital Ethics Committee (approval number 2021/77) and the Ministry of Health Scientific Research Platform of Turkey (approval number 2021-01-13T14_19_40). Institutional review board approval was obtained from each participating hospital in

accordance with local ethical regulations. The study has been performed in accordance with the ethical standards laid down in the Declaration of Helsinki.

Data Collection

Each center recorded and collected data using preprinted case report forms. The collected variables included age, gender, comorbidities, mode of presentation (ie, asymptomatic, respiratory, gastrointestinal, neurological, hematological or circulatory), Pediatric Risk of Mortality (PRISM) IV[7], organ failure index (OFI)[8–9], pediatric acute respiratory distress syndrome (pARDS) classifications[10], pediatric COVID-19 severity score[4], contact history, presenting symptoms, laboratory parameters on admission, medical treatment, respiratory support, prone positioning, renal replacement therapy (RRT), extracorporeal membrane oxygenation (ECMO), PICU length of stay and outcome. Information on comorbidities was collected from previous medical records, chronic medications and parents. The severity of pARDS was defined as mild, moderate or severe according to the Pediatric Acute Lung Injury Consensus Conference[10]. Mild pARDS is defined as the oxygenation index (OI) of 4–8 [oxygen saturation index (OSI) = 5–7.5], moderate as an OI of 8–16 (OSI = 7.5–12.3) and severe as an OI >16 (OSI >12.3). The respiratory support modalities for which data was available were oxygen support (nasal cannula and oxygen mask), the high-flow nasal cannula (HFNC), noninvasive mechanic ventilation (NIV), invasive mechanical ventilation (IMV), high-frequency oscillatory ventilation (HFOV), prone positioning, surfactant therapy and recruitment maneuvers. Medical treatments such as favipiravir, oseltamivir, lopinavir/ritonavir, remdesivir, hydroxychloroquine, glucocorticoid therapy, intravenous immunoglobulin (IVIG), convalescent plasma transfusion, anakinra, colchicine, tocilizumab, anticoagulation and inotrope treatment and outcome data related COVID-19 were collected.

Statistics

Statistical analyzes in this study were performed using the Number Cruncher Statistical System 2007 Statistical Software (Utah, USA) package program. The Shapiro-Wilk normality test, as well as descriptive statistical methods (mean, standard deviation, median and interquartile range), were used to evaluate the data. Shapiro-Wilk test was used to test for normality. Then Levene's test was conducted to test the homogeneity of variance for the independent *t*-test. The independent *t*-test was used for the comparison of the normally distributed variables in paired groups, and the Mann Whitney U test was used for the comparison of the non-normally distributed variables and pairwise groups. According to Levene's test, the Welch *t*-test was used instead of the independent *t*-test if the equal variance was not assumed. We used univariable logistic regression to analyze the contributing factors for mortality. Then, those statistically significant factors in the univariable logistic regression analysis were enrolled into the binary logistic multivariable regression analysis to identify the independent risk factors for mortality in children with COVID-19. To avoid the interaction effect, we choose OFI rather than PRISM-IV, max vasoactive-inotropic score (VIS) and cardiac involvement. The results were evaluated at the significance level of $P < 0.05$.

RESULTS

There were 20,892 consecutive all-cause admissions at the 44 PICUs and a total of 1506 deaths, for an overall all-cause mortality rate of 7.21% during the study period. Of 20,892 patients, 353 were diagnosed with proven SARS-CoV-2 infection. Two patients >18 years old, a patient who died within 12 hours, and 15 children with a positive PCR test whose primary diagnoses were trauma, poisoning, etc. were excluded from the final analysis of mortality as they were asymptomatic and had no radiologic and laboratory evidence for COVID-19 (see Figure, Supplemental Digital Content 2; http://links.lww.com/INF/E745). In PICUs, the calculated COVID-19 rate was 1.6% (335/20892). Of 335 children, 180 were male (53.7 %); the median age was 6.8 years (IQR: 1.2–14). Table 1 shows baseline characteristics, presenting signs, symptoms and presenting system involvement of all children with COVID-19 admitted to PICUs. Overall, 215 (64.2 %) children had known comorbidity. In all children, 162 (48.4%) were diagnosed with pARDS during the study period; 123 (36.7%) received IMV [median duration of 10.5 days (IQR 5–27)], 43 (12.8%) received NIV, 82 (24.5%) received HFNC oxygen therapy and 49 (12.8%) received only oxygen therapy. Five children (1.5%) who underwent IMV required HFOV. Of 335 children with COVID-19, 44 children died, 37 (11.0%) were discharged with sequelae and 254 (75.8%) were discharged with their baseline status before hospitalization. The calculated COVID-19 PICU mortality rate was 13.1% (44/335). The demographics, comorbidities, treatment and maximum respiratory support were compared between survivors and nonsurvivors and are shown in Table 2. The mean age was 6.78 years (IQR 1.2–13.9) in the survival group and 6.84 years (IQR 1.2–14.9) in the nonsurvival group. Age and gender were not significantly different. Nonsurvivors had more comorbid conditions 39 (88.64 %) compared to survivors 176 (60.48%). Children with medical complexity, congenital heart disease, immunosuppression, and malignancy had significantly higher mortality ($P < 0.05$). The OFI, PRISM scores, the severity of illness and the use of

TABLE 1. Baseline Characteristics of COVID-19 Patients at Admission

Characteristics	n (%) (total n = 335)
Age, month	
≤12	76 (22.69)
13–60	76 (22.69)
61–120	45 (13.43)
≥121	138 (41.19)
Male gender	180 (53.73)
Contact history	220 (65.67)
Household	188 (56.12)
Nonhousehold	32 (9.55)
Comorbidity	215 (64.18)
≥2 Comorbidity	117 (34.93)
Signs and symptoms	
Fever	241 (71.94)
Respiratory distress	225 (67.16)
Cough	212 (63.28)
Fatigue	132 (39.40)
Nausea or vomiting	62 (18.51)
Myalgia	57 (17.01)
Altered consciousness	57 (17.01)
Convulsion	46 (13.73)
Sore throat	45 (13.43)
Diarrhea	38 (11.34)
Abdominal pain	20 (5.97)
Headache	19 (5.67)
Rash	15 (4.48)
Loss of taste	13 (3.89)
Chest pain	12 (3.58)
Loss of smell	9 (2.69)
Presentation	
Respiratory	281 (83.88)
Neurological	79 (23.58)
Gastrointestinal	74 (22.09)
Circulatory	51 (15.22)
Hematological	28 (8.36)
Other	28 (8.36)

TABLE 2. Comparisons of Survivors' vs Nonsurvivors in Children with COVID-19

Parameters	All Patients (n = 335)	Survivors (n = 291)	Nonsurvivors (n = 44)	*P*
Age, month n (%)				
≤12, n (%)	76 (22.69)	66 (22.68)	10 (22.73)	0.96
13–60, n (%)	76 (22.69)	66 (22.68)	10 (22.73)	
61–120, n (%)	45 (13.43)	38 (13.06)	7 (15.91)	
≥121, n (%)	138 (41.19)	121 (41.58)	17 (38.64)	
Male, n (%)	180 (53.73)	155 (53.26)	25 (56.82)	0.66
Comorbidities n (%)	215 (64.18)	176 (60.48)	39 (88.64)	***0.00***
≥2 Comorbidities n (%)	117 (34.93)	92 (31.62)	25 (56.82)	***0.00***
Epilepsy, n (%)	62 (18.51)	54 (18.56)	8 (18.18)	0.95
Developmental delay, n (%)	54 (16.12)	45 (15.46)	9 (20.45)	0.40
Medical complexity[a], n (%)	47 (14.13)	35 (12.03)	12 (27.27)	***0.01***
Congenital heart disease, n (%)	27 (8.06)	20 (6.87)	7 (15.91)	***0.04***
Chronic lung disease, n (%)	25 (7.46)	21 (7.22)	4 (9.09)	0.66
Immune suppression, n (%)	21 (6.27)	14 (4.81)	7 (15.92)	***0.01***
Obesity, n (%)	21 (6.27)	19 (6.53)	2 (4.55)	0.61
Malignancy, n (%)	21 (6.27)	12 (4.12)	9 (20.45)	***0.00***
Diabetes, n (%)	16 (4.78)	14 (4.81)	2 (4.55)	0.94
Asthma, n (%)	14 (4.18)	12 (4.12)	2 (4.55)	0.90
Endocrine disease, n (%)	17 (5.07)	14 (4.81)	3 (6.82)	0.58
Chronic kidney disease, n (%)	11 (3.28)	9 (3.09)	2 (4.55)	0.61
Metabolic disease, n (%)	11 (3.28)	9 (3.09)	2 (4.55)	0.61
Down syndrome, n (%)	9 (2.69)	6 (2.06)	3 (6.82)	0.07
Hematologic disease, n (%)	3 (0.90)	3 (1.03)	0 (0.00)	*1.00*
Psychiatric disease, n (%)	2 (0.60)	1 (0.34)	1 (2.27)	0.12
Post-transplantation, n (%)	2 (0.60)	2 (0.69)	0 (0.00)	0.58
PRISM-IV, median (IQR)	7 (2–16)	6 (2–12)	31.5 (13–63)	***0.00***
OFI n (%)				
1–2 organ failure n (%)	160 (47.76)	148 (50.86)	12 (27.27)	***0.00***
3–4 organ failure n (%)	63 (18.81)	44 (15.12)	19 (43.18)	
5–6 organ failure n (%)	19 (5.67)	6 (2.06)	13 (29.55)	
Severity of illness n (%)				
Mild n (%)	72 (21.49)	72 (24.74)	0 (0.00)	
Moderate n (%)	54 (16.12)	54 (18.56)	0 (0.00)	
Severe n (%)	104 (31.04)	96 (32.99)	8 (18.18)	***0.00***
Critical n (%)	105 (31.34)	69 (23.71)	36 (81.82)	
Vital signs, mean ± SDS				
Heart rate (beats/min), mean ± SD	128.65 ± 30.8	127.28 ± 29.94	137.81 ± 35.04	***0.04***
Respiratory rate (breaths/min) mean ± SD	38.79 ± 14.1	38.49 ± 13.69	41.00 ± 16.85	0.30
SBP mm Hg mean ± SD	98.92 ± 20.47	99.74 ± 19.31	93.57 ± 26.54	0.14
DBP mm Hg mean ± SD	61.21 ± 15.37	61.90 ± 14.77	56.70 ± 18.42	***0.04***
SPO_2, mean ± SD	91.41 ± 8.83	91.61 ± 9.04	90.14 ± 7.30	0.31
Laboratory finding				
White blood cell count, × 10^9/L, mean ± SD	10887.73 ± 7847.97	10829.42 ± 7774.51	11273.39 ± 8401.63	0.73
Lymphocyte count, × 10^9/L median (IQR)	1680 (950–3300)	1750 (1012–3400)	1200 (656–2300)	***0.00***
Neutrophil count, × 10^9/L, median (IQR)	5240 (2750–9700)	5430 (3000–10287)	3450 (1090–7790)	***0.00***
Platelet count, × 10^9/L, mean ± SD	267.40 ± 147.48	273.55 ± 140.09	226.88 ± 185.99	0.12
Hemoglobin, mean ±SD	11.17 ± 2.25	11.25 ± 2.20	10.64 ± 2.54	0.09
Hematocrit, mean ±SD	33.69 ± 6.76	33.87 ± 6.57	32.50 ± 7.85	0.21
Aspartate aminotransferase, U/L, median (IQR)	36 (25–65)	35 (25–58)	69.5 (35–150)	***0.00***
Alanine aminotransferase, U/L, median (IQR)	25 (15–45)	23.5 (15–41)	33.5 (22–115)	***0.00***
Urea, mg/dl, median (IQR)	21 (15–32)	21 (15–30)	30 (16–47)	***0.01***
Creatinine, mg/dl, median (IQR)	0.47 (0.3–0.68)	0.47 (0.29–0.67)	0.49 (0.37–1.08)	***0.04***
Sodium mEq/L, mean ±SD	137.65 ± 5.41	137.41 ± 5.25	139.27 ± 6.20	***0.03***
Potassium mEq/L, mean ±SD	4.18 ± 0.74	4.20 ± 0.73	4.06 ± 0.82	0.24
Albumin, mg/dl, mean ±SD	3.65 ± 0.62	3.70 ± 0.60	3.31 ± 0.64	***0.00***
Creatine kinase, U/L, median (IQR)	103 (48–221)	101 (50–221)	120 (46–264)	0.79
Lactate dehydrogenase, U/L, median (IQR)	353 (275–526)	337 (272–500)	475 (356–789)	***0.00***
Amylase, U/L, median (IQR)	45 (28–77)	42 (27–72)	61 (31–129)	0.06
Lipase, U/L, median (IQR)	28 (13–48)	24 (11–41)	45 (21–99)	***0.01***
C-reactive protein, mg/dl, median (IQR)	2.1 (0.42–8.19)	1.88 (0.39–7.6)	4.93 (1.1–16.03)	***0.00***
Procalcitonin, ng/mL, median (IQR)	0.32 (0.1–2.3)	0.28 (0.1–1.35)	2.28 (0.31–16.8)	***0.00***
D-dimer, mg/dl, median (IQR)	1 (0.54–2.26)	0.97 (0.5–1.97)	2.08 (1–3.63)	***0.00***
Troponin, median (IQR)	3.3 (0.13–13)	3.9 (0.15–13.3)	1.65 (0.1–11.85)	0.51
Ferritin, mg/dl, median (IQR)	224 (67–555)	194.5 (65.5–487.25)	565 (129.5–1413)	***0.00***
Fibrinogen, mg/dl, median (IQR)	321 (234–447)	329 (241–440)	305.5 (156–466)	0.24
Prothrombin time, s, mean ± SDS	14.69 ± 6.01	14.51 ± 4.73	15.90 ± 11.48	0.47
APTT, s, mean ± SD	30.36 ± 10.43	30.09 ± 9.45	32.10 ± 15.40	0.25
Pro-BNP, median (IQR)	550 (116–2520)	456 (112–1782)	3126 (296–7444)	***0.02***
Creatine kinase–MB, U/L, median (IQR)	3.7 (0.94–20.2)	3.36 (0.95–19)	4.63 (0.87–27)	0.60
IL-6, median (IQR)	34.4 (11.3–72.28)	29.7 (9–66)	55.5 (28.5–1234)	***0.05***

(*Continued*)

TABLE 2. (*Continued*)

Parameters	All Patients (n = 335)	Survivors (n = 291)	Nonsurvivors (n = 44)	*P*
Baseline blood gases				
pH, mean ±SD	7.33 ± 0.12	7.33 ± 0.12	7.32 ± 0.13	0.34
pCO_2, mm Hg, mean ± SD	44.51 ± 17.1	44.27 ± 16.66	36.12 ± 19.88	0.51
HCO_3, mm Hg, mean ± SD	22.38 ± 6.19	22.36 ± 5.97	22.55 ± 7.60	0.85
Lactate, mmol/L, median (IQR)	1.8 (1.3–2.74)	1.8 (1.3–2.6)	2.55 (1.5–4.1)	***0.00***
pARDS n (%)				***0.00***
Mild, n (%)	67 (20.00)	63 (21.65)	4 (9.09)	
Moderate, n (%)	38 (11.34)	33 (11.34)	5 (11.36)	
Severe, n (%)	57 (17.01)	26 (8.93)	31 (70.45)	
Superinfections				
Gram-positive,n (%)	37 (11.04)	29 (9.97)	8 (18.18)	0.11
Gram-negative,n (%)	37 (11.04)	27 (9.28)	10 (22.73)	**0.01**
Fungi,n (%)	20 (5.97)	15 (5.15)	5 (11.36)	0.11
Treatment				
Favipiravir, n (%)	164 (48.96)	134 (46.05)	30 (68.18)	***0.01***
Oseltamivir, n (%)	44 (13.13)	41 (14.09)	3 (6.82)	0.18
Lopinavir/ritonavir, n (%)	32 (9.55)	28 (9.62)	4 (9.09)	0.91
Remdesivir, n (%)	27 (8.08)	24 (8.28)	3 (6.82)	0.74
Hydroxychloroquine, n (%)	61 (18.21)	54 (18.56)	7 (15.91)	0.67
Glucocorticoid therapy, n (%)	162 (48.36)	134 (46.05)	28 (63.6)	***0.03***
IVIG, n (%)	75 (22.39)	57 (19.59)	18 (40.91)	***0.00***
Convalescent plasma transfusion, n (%)	8 (2.39)	6 (2.06)	2 (4.55)	0.32
Anakinra, n (%)	3 (0.9)	3 (1.03)	0 (0.00)	0.50
Colchicine, n (%)	3 (0.9)	3 (1.03)	0 (0.00)	0.50
Tocilizumab, n (%)	2 (0.6)	2 (0.69)	0 (0.00)	0.58
Anticoagulation, n (%)	177 (52.84)	148 (50.86)	29 (65.91)	0.06
Inotrope treatment, n (%)	84 (25.07)	42 (14.43)	42 (95.45)	***0.00***
Maximum Vasoactive inotrope score, median (IQR)	30 (15–50)	18.75 (10–30)	50 (26.25–205)	***0.00***
Maximum respiratory support				
None, n (%)	38 (11.34)	38 (13.06)	0 (0.00)	***0.00***
Oxygen only, n (%)	49 (14.63)	49 (16.84)	0 (0.00)	
High-flow oxygen, n (%)	82 (24.48)	81 (27.84)	1 (2.27)	
Noninvasive ventilation, n (%)	43 (12.84)	43 (14.78)	0 (0.00)	
Invasive ventilation, n (%)	118 (35.22)	79 (27.15)	39 (88.64)	
HFOV, n (%)	5 (1.49)	1 (0.34)	4 (9.09)	
Other respiratory support				
Prone position, n (%)	80 (23.88)	60 (20.62)	20 (45.45)	***0.00***
Recruitment, n (%)	34 (10.15)	21 (7.22)	13 (29.55)	***0.00***
Surfactant, n (%)	5 (1.49)	2 (0.69)	3 (6.82)	***0.00***
Extracorporeal treatment				
Renal replacement therapy, n (%)	17 (5.07)	3 (1.03)	14 (31.82)	***0.00***
Plasma exchange, n (%)	22 (6.57)	14 (4.81)	8 (18.18)	***0.00***
Hemadsorption, n (%)	2 (0.60)	1 (0.34)	1 (2.27)	0.12
ECMO, n (%)	5 (1.49)	2(0.69)	3 (6.82)	***0.00***
PICU stay, median (IQR)	7 (4–15)	7 (4–14)	11 (6–19)	***0.01***
Hospital stay,median (IQR)	14 (8–24)	14 (8–23)	15 (10–37)	0.31

APTT indicates Activated Partial Thromboplastin Time; BNP, brain natriuretic peptide; DBP, diastolic blood pressure; ECMO, extracorporeal membrane oxygenation; HFOV, High-frequency oscillatory ventilation; IQR, interquartile range; OFI, organ failure Index; IVIG, intravenous immunoglobulin; SBP, systolic blood pressure; SD, standard deviation; pARDS, pediatric acute respiratory distress syndrome; PRISM-IV, Pediatric Risk of Mortality IV.

[a]Medical complexity: Defined as children who had a long-term dependence on technological support (including tracheostomy, etc).

favipiravir, glucocorticoid, IVIG, and inotropes, the severity of pARDS, the utilization of maximum respiratory support, prone positioning, recruitment and surfactant therapy were significantly higher in nonsurvivors ($P < 0.05$). Continuous renal replacement therapy, plasma exchange and ECMO were more performed in nonsurvivors ($P < 0.05$). The laboratory findings on admission comparing survivors to nonsurvivors are also shown in Table 2. Nonsurvivors had significantly higher levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), urea, creatinine, sodium, lactate dehydrogenase (LDH), lipase, C-reactive protein (CRP), procalcitonin, d-dimer, ferritin, pro-brain natriuretic peptide, lactate and lower levels of albumin than survivors ($P < 0.05$). Antiviral treatments were used in 267 patients (80%). The most common of these was favipiravir. Glucocorticoid therapy was used in 162 (48%), IVIG in 75 (22%), convalescent plasma in 8 (2%), anakinra in 3 (0.9%) tocilizumab in 2 (0.6%), anticoagulation in 177 (53%), inotrope in 84 (25%), renal replacement therapy in 17 (5%), plasma exchange in 22 (7%) and hemadsorption therapy in 2 (0.6%) children as a single agent or in combination. Median PICU length of stay for all patients until the study endpoint was 7 days (IQR: 4–15), and significantly higher in nonsurvivors ($P < 0.05$, Table 2).

Based on the PRISM score, all patients were divided into 3 categories. While the majority of the cases (211 patients) had a PRISM score lower than 10 points, 58 patients had a PRISM score between 11 and 20 points, and 66 patients had a PRISM score higher than 20 points (Table 3). The need for inotrope was higher in patients with mortality in all PRISM score groups. Renal replacement and plasma exchange therapy were associated with higher mortality in patients with a PRISM score of 11–20. Renal

TABLE 3. Treatment and its Effect on Mortality in Different PRISM Score Categories

	PRISM Score <10 (n = 211)			PRISM Score 11-20 (n = 58)			PRISM Score >20 (n = 66)		
	Survivors (n = 204)	Nonsurvivors (n = 7)	*P* value*	Survivors (n = 49)	Nonsurvivors (n = 9)	*P* value*	Survivors (n = 38)	Nonsurvivors (n = 28)	*P* value*
Favipiravir, n (%)	84 (41.2)	4 (57.1)	0.45	29 (59.2)	7 (77.8)	0.46	21 (55.3)	19 (67.9)	0.30**
Oseltamivir, n (%)	29 (14.2)	0 (0)	0.60	5 (10.2)	1 (11.1)	0.94	7 (18.4)	2 (7.1)	0.28
Lopinavir/ritonavir, n (%)	18 (8.8)	1 (14.3)	0.49	7 (14.3)	0 (0)	0.59	3 (7.9)	3 (10.7)	0.69
Remdesivir, n (%)	16 (7.8)	0 (0)	0.46	6 (12.2)	1 (11.1)	0.92	2 (5.4)	2 (7.1)	0.58
Hydroxychloroquine, n (%)	34 (16.7)	0 (0)	0.60	10 (20.4)	1(11.1)	0.51	10 (26.3)	6 (21.4)	0.65†
Glucocorticoid therapy, n (%)	83 (40.7)	3 (42.9)	0.91	28 (57.1)	7 (77.8)	0.30	23 (60.5)	18 (64.3)	0.76†
IVIG, n (%)	35 (19.5)	1 (14.3)	0.82	13 (26.5)	4 (44.4)	0.43	8 (21.1)	13 (46.4)	***0.03***†
Convalescent plasma transfusion, n (%)	5 (2.5)	1 (14.3)	0.19	1 (2.0)	1 (11.1)	0.29	0 (0)	0 (0)	–
Anakinra, n (%)	2 (1.0)	0 (0)	0.79	0 (0)	0 (0)	–	1 (2.6)	0 (0)	0.58
Colchicine, n (%)	3 (1.5)	0 (0)	0.75	0 (0)	0 (0)	–	0 (0)	0 (0)	–
Tocilizumab, n (%)	1 (0.5)	0 (0)	0.85	0 (0)	0 (0)	–	1 (2.6)	0 (0)	0.58
Anticoagulation, n (%)	96 (47.1)	3 (42.9)	0.83	28 (57.1)	7 (77.8)	0.30	24 (63.2)	19 (67.9)	0.69†
Inotrope treatment, n (%)	14 (6.9)	6 (85.7)	***0.00***	12 (24.5)	9 (100)	***0.00***	16 (42.1)	27 (96.4)	***0,00***†
Renal replacement therapy, n (%)	1 (0.6)	1 (14.3)	0.07	1 (2.0)	6 (66.7)	***0.00***	1 (2.6)	7 (25.0)	***0.01***
Plasma exchange, n (%)	7 (3.9)	0 (0)	0.62	5 (10.2)	4 (44.4)	***0.03***	2 (5.3)	4 (14.3)	0.39
Hemadsorption, n (%)	0 (0)	0 (0)	-	0 (0)	0 (0)	-	1 (2.6)	1 (3.6)	0.67
ECMO, n (%)	0 (0)	0 (0)	-	1 (2.0)	0 (0)	0.67	1 (2.6)	3 (10.7)	0.30

ECMO indicates extracorporeal membrane oxygenation; IVIG, intravenous immunoglobulin.
*Fisher's Exact Test.
†Chi-Square test

replacement and IVIG therapy were associated with higher mortality in patients with a PRISM score higher than 20.

On multivariable logistic regression analysis, OFI score [odds ratio (OR): 2.1; 95%) confidence interval (CI): 1.55–2.85], and congenital heart disease (OR: 2.65; 95% CI: 1.04–6.80) were independently associated with mortality. We observed no independent association of lactate, lymphocyte or CRP with mortality (Table 4).

DISSCUSSION

To our knowledge, this study is one of the largest severe pediatric COVID-19 outcomes to date. In this multicenter retrospective cohort study, we report the characteristics, clinical course and mortality-related risk factors of critically ill children with confirmed COVID-19 at 44 PICUs in Turkey during the first year of the pandemic. The 2 peaks of the COVID-19 disease seen in children were similar to the whole world's disease peaks (Fig. 1)[11].

In our study, 64.2% of patients had comorbidities and among them, the most common comorbidities were epilepsy, developmental delay and medical complexity. Furthermore, malignancy, immune suppression, medical complexity and congenital heart disease were significantly higher in nonsurvivors compared to survivors. According to studies in the early days of the pandemic, adults with COVID-19 indicated that comorbidities, such as diabetes, hypertension, malignancies, chronic respiratory disease and obesity are significant risk factors for severe infection[12–16]. Shekerdemian et al[4] reported that in children with COVID-19 admitted to PICU, common comorbidities were medical complexity, immune suppression/malignancy and obesity. A recent meta-analysis including 275,661 children without comorbidities and 9353 children with comorbidities showed that children with comorbidities had a higher risk of severe COVID-19 and associated mortality than children without comorbidity. In addition, the study notes that childhood obesity probably leads to a worse COVID-19 prognosis[12]. In our study, obesity was not associated with mortality, which may be due to the fact that there was the small number of obese patients in the nonsurvivor group. A study from India reported that 94 children with any form of heart disease had a higher risk of mortality when they acquired COVID-19 infection[17]. The majority of deaths occurred in unoperated patients. Similar to this report, in multivariable logistic regression analysis, having congenital heart disease is independently associated with mortality in our study. These findings suggest that preventive measures are needed for improving the outcomes in children with congenital heart disease.

Scoring measurements such as PRISM-IV, OFI and VIS were used for mortality prediction and disease severity in our study. As expected, all these scores were statistically higher in nonsurvivors. In multivariable logistic regression analysis, the OFI score was significantly associated with higher mortality.

In this report, we also compared the treatment modalities between survivors and nonsurvivors. The respiratory support modalities, prone positioning, recruitment and surfactant therapy were significantly more used in nonsurvivors. Likewise, continuous RRT, plasma exchange and ECMO were significantly more performed in nonsurvivors. Not surprisingly, more ill children required more treatments, and many of those who died got maximum treatment. We analyzed treatments and their effect on mortality in different PRISM Score categories to describe the effect of giving or

TABLE 4. Variables Predictive of COVID-19 Mortality According to Logistic Regression

	Univariable Analysis		Multivariable Analysis	
	OR	95% CI	OR	95% CI
PRISM-IV score	1.05	1.04–1.07		
Organ failure Index	2.65	2.05–3.44	2.1	1.55–2.85
Congenital heart disease	2.56	1.02–6.47	2.65	1.04–6.80
Cardiac involvement	9.03	4.46–18.2		
Maximum VIS	1.02	1.01–1.04		
Lactate	1.19	1.07–1.33	1.19	0.94–1.5
Lymphocyte (x10^3/mm^3)	0.57	0.39–0.85	0.77	0.47–1.27
C-reactive protein	1.05	1.02–1.08	1.01	0.96–1.06
D-dimer	1.08	1.03–1.14	1.05	1.00–1.10

CI indicates confidence interval; OD, odds ratio; PRISM-IV, pediatric risk of mortality IV; VIS, vasoactive-inotropic score.

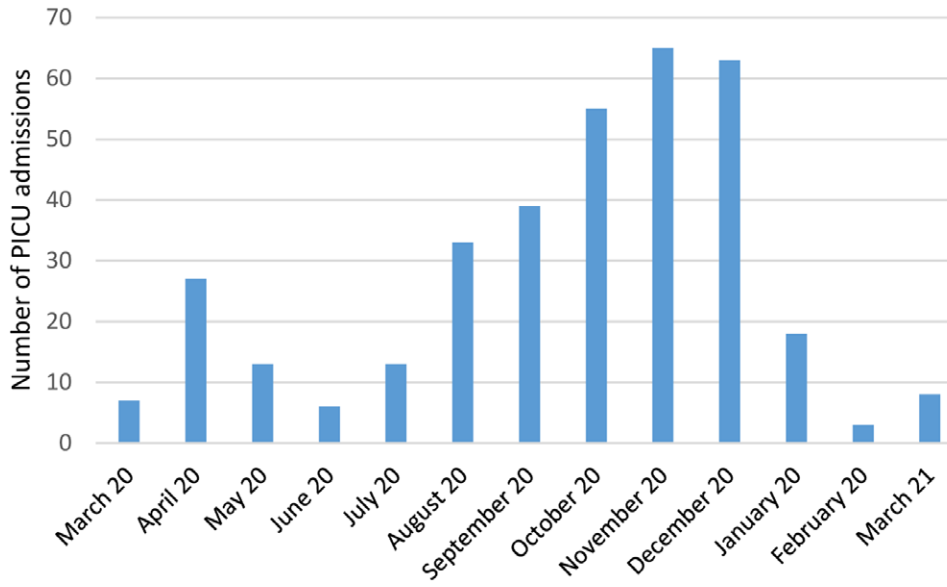

FIGURE 1. Monthly number of new PICU admissions with COVID-19. full color online

not giving specific treatment within each group on mortality. We think that larger patient series are needed in each severity group for a more accurate conclusion.

The prognostic significance of laboratory tests was also evaluated between survivors and nonsurvivors. Nonsurvivors had significantly higher levels of AST, ALT, urea, creatinine, sodium, LDH, lipase, CRP, procalcitonin, d-dimer, ferritin, pro-brain natriuretic peptide, lactate and lower levels of albumin, lymphocyte and neutrophil count than survivors at admission (Table 2). Yang et al[18] reported that lymphopenia was detected in 80% of critically ill adults with COVID-19. However, there is an inconsistency between existing studies regarding the correlation of hematological findings with disease severity in children. The association between lymphopenia and COVID-19 severity in children was documented in a few studies[19–20]. Although lymphocyte count is significantly lower in nonsurvivors, no relationship was found between lymphopenia and mortality in multivariable analysis in our study.

In adults, hospitalization status and increased oxygen support requirements with elevated d-dimer levels are associated with worse outcomes, including thrombosis[13]. Additionally, an elevated d-dimer level at admission was an independent risk factor of mortality in adults[21]. In children with COVID-19, elevated d-dimer levels also have been reported, but much less is known about the relationship with mortality. Similar to adults, Mitchell et al[22] reported that coagulopathy, elevated D-dimer, and increased thrombotic events were observed in 27 children with severe respiratory complications related to COVID-19. In our cohort, d-dimer levels were significantly higher in nonsurvivors. Our study suggests that; severe pediatric patients particularly those with respiratory failure, d-dimer levels should be closely monitored and early initiation of antithrombotic therapy should be considered.

In our study, of 335 children with critical COVID-19, 49.5% of them were mechanically ventilated, 25% of them needed inotrope treatment, 48% of them had 1–2 organ failures, and 24.5% of them had 3 or more organ failures (Table 2). In a study from North America, of the 48 children with COVID-19 admitted to 14 PICUs in a 20-day study period, 46% of them were mechanically ventilated, 25% of them needed inotrope support, 8% of them had 3 or more organ failure and the mortality rate was 4.2% up to the time of the report. Twenty percent of patients were still being treated with the severe condition at the study endpoint. Compared with this report, the higher mortality rate may be due to the fact that disease severity and the number of organ failure was higher in our study, and also the early termination of the North American study without providing all critical patients outcome[4]. In a study from Indonesia that included 50 critically ill children with confirmed COVID-19, the observed mortality rate was 40% which is higher than our study[23]. In an Egyptian study, 103 severe COVID-19 patients were admitted to PICU, 41.7% of patients were mechanically ventilated with a mortality rate of 20%[24]. In a Spanish study conducted in 76 hospitals including 666 hospitalized children, 123 of them required PICU admission. Seventy-six of 123 patients (62%) diagnosed with Multisystem Inflammatory Syndrome in Children (MIS-C), 26% of patients were mechanically ventilated with a mortality rate of 7%. In this study, the lower percentage of the patients who underwent mechanical ventilation indicates less disease severity that may explain the lower rate of mortality[25]. In our study, we did not include MIS-C patients in our cohort because it has a different clinical course and prognosis from the severe acute COVID-19 illness in children. The difference in mortality rates in different countries might be explained by different disease severity of the patients who were admitted to the PICUs and also differences in accessibility to PICU level of care.

There is a wide variety of publications on the relationship between age and mortality. In some studies, it was reported that children under 1 year were at risk, whereas in others, only neonates had a greater probability of developing the severe disease[26–28] An adult study showed that a 10-year increase in age and male sex were significantly associated with mortality[6]. In our cohort, although boys were more admitted to PICU, mortality was not related to age groups or gender.

A recent meta-analysis showed that the most common clinical manifestations were fever 51%, cough 41%, sore throat 16%, nasal congestion 17% and rhinorrhea 14% in children[29]. In our study, although fever was the most common symptom in children at admission, it was followed by respiratory distress and cough. The most common system presentation was respiratory (84%) followed by neurological (23.6%), gastrointestinal (22%), circulatory (15.2%), and hematological (8.4%).

This study has limitations. First, the fact that the study is retrospective thus, the data may be subject to incomplete reporting. Second, we could not obtain the total number of outpatient and hospitalized cases with COVID-19 from the 44 participating centers, so we could not calculate the case fatality rate, hospitalization rate and PICU admission rate in children. We could only calculate the mortality rate of critically ill COVID-19 patients admitted to the PICU. Third, the unequal sample size between survivors and nonsurvivors which may have impacted the results. Therefore, the nonassociation between age and mortality may be due to the small sample size of the mortality group.

In conclusion, a high organ failure index, and having congenital heart disease are associated with higher mortality in pediatric severe COVID-19. Our study suggests that strategies to improve outcomes are needed in children with congenital heart disease such as priority of vaccination, prioritization of surgery, etc. and d-dimer levels should be closely monitored in critically ill children with COVID-19. Another study comparing PICU data in between the 1st year and 2nd years of the pandemic is at the data collection stage. While the 2nd year pandemic mortality data are presented, a mortality analysis will also be performed for the variants.

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