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COVID-19 disease in children and adolescents following allogeneic hematopoietic stem cell transplantation: A report from the Turkish pediatric bone marrow transplantation study group

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Abstract

Background: Data on the risk factors and outcomes for pediatric patients with SARS-CoV-2 infection (COVID-19) following hematopoietic stem cell transplantation (HSCT) are limited.

Objectives: The study aimed to analyze the clinical signs, risk factors, and outcomes for ICU admission and mortality in a large pediatric cohort who underwent allogeneic HSCT prior to COVID-19 infection.

Method: In this nationwide study, we retrospectively reviewed the data of 184 pediatric HSCT recipients who had COVID-19 between March 2020 and August 2022.

Results: The median time from HSCT to COVID-19 infection was 209.0 days (IQR, 111.7–340.8; range, 0–3845 days). The most common clinical manifestation was fever

Abbreviations: CI, confidence interval; CIBMTR, Center for International Bone Marrow Transplantation registry; COVID-19, coronavirus disease 2019; EBMT, European Group for Blood and Marrow Transplantation; GETH, Spanish Group of Hematopoietic Stem Cell Transplantation; GVHD, graft-versus-host disease; HSCT, hematopoietic stem cell transplantation; ICU, intensive care unit; IQR, interquartile range; LRTD, lower respiratory tract disease; MIS-C, multisystem inflammatory syndrome in children; OR, odds ratio; OS, overall survival; PCR, polymerase chain reaction; PTCy, post-transplant cyclophosphamide; R, range; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; WHO, World Health Organization.

For affiliations refer to page 11.

(58.7%). While most patients (78.8%) had asymptomatic/mild disease, the disease severity was moderate in 9.2% and severe and critical in 4.4% and 7.6%, respectively. The overall mortality was 10.9% (*n*: 20). Deaths were attributable to COVID-19 in nine (4.9%) patients. Multivariate analysis revealed that lower respiratory tract disease (LRTD) (OR, 23.20, *p*: .001) and lymphopenia at diagnosis (OR, 5.21, *p*: .006) were risk factors for ICU admission and that HSCT from a mismatched donor (OR, 54.04, *p*: .028), multisystem inflammatory syndrome in children (MIS-C) (OR, 31.07, *p*: .003), and LRTD (OR, 10.11, *p*: .035) were associated with a higher risk for COVID-19-related mortality.

Conclusion: While COVID-19 is mostly asymptomatic or mild in pediatric transplant recipients, it can cause ICU admission in those with LRTD or lymphopenia at diagnosis and may be more fatal in those who are transplanted from a mismatched donor and those who develop MIS-C or LRTD.

KEYWORDS
adolescents, children, COVID-19, hematopoietic stem cell transplantation

1 | INTRODUCTION

There is a wide spectrum of clinical findings associated with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection that range from asymptomatic-to-severe respiratory tract disease, leading to the need for intensive care. Advanced age in healthy individuals and diseases such as cardiopulmonary disease, obesity, and diabetes pose a great risk.[1–4] Recipients of hematopoietic stem cell transplantation (HSCT) are also at risk of contracting COVID-19 because of chemotherapy effects such as myelosuppression resulting from immunosuppressive therapy for prophylaxis and treatment of graft-versus-host disease. Additionally, respiratory viral infections in allogeneic HSCT recipients are associated with significant morbidity and mortality.[5]

Different groups, such as the European Group for Blood and Marrow Transplantation (EBMT), the American Society of Transplantation and Cellular Therapy Infectious Disease Special Interest Group, and the European Conference on Infections in Leukemia, have published recommendations regarding policies and patient management for COVID-19.[6–8] Despite protective recommendations, transplant recipients are still at risk of infection. In a study of 77 adult patients who received cellular therapy (either auto or allo-HSCT or chimeric antigen receptor T cells), there was a high rate of hospitalization (44%), with a 30-day OS of 78%.[9] In the general population, COVID-19 seems to affect children less severely than adults.[10] In a study conducted on HSCT recipients with COVID-19 in Brazil, the mortality rate was 30% in adults and 21% in children.[11]

In most studies examining the effects of COVID-19 in patients who underwent HSCT, children were evaluated along with adults, although their numbers were much lower than those of adults. Therefore, further studies involving only pediatric patients and evaluating the status of children who underwent HSCT and had COVID-19 are needed. In this national, multicenter, retrospective, collaborative study of the Turkish Pediatric Bone Marrow Transplantation Study Group, we aimed to investigate clinical signs, risk factors for intensive care unit (ICU) admission and mortality in a large pediatric cohort who underwent allogeneic HSCT prior COVID-19 infection.

2 | METHODS

Patients who were diagnosed with COVID-19 (≤21 years of age at COVID-19 diagnosis) between March 1, 2020, and August 31, 2022, and had undergone allogeneic HSCT at any time before the diagnosis of COVID-19 were included. The patients needed to have at least 6 weeks of follow-up to analyze the 6-week survival after COVID-19 diagnosis and compare it with other studies in the literature that included survival analysis over this period. Naso-oropharyngeal swabs were tested for SARS-CoV-2 by polymerase chain reaction (PCR) when a patient was suspected of having COVID-19 or had contact history with a confirmed case. Confirmed cases were defined as PCR-positive patients according to the guidelines of the WHO[12] and Ministry of Health of Türkiye.[13] Oxygen support requirements, pulmonary radiology findings, and the presence of clinical signs of the lower respiratory tract, such as shortness of breath, sibilant rales, and cough, were used to define lower respiratory tract disease (LRTD). All patients who had LRTD had thorax X-ray, and LRTD was confirmed by thorax computerized tomography (CT) as much as possible. If only cough was present without other LRTD findings, this complaint was accepted as an upper respiratory tract disease (URTD) finding. The diagnosis of multisystem inflammatory syndrome in children (MIS-C) was based on the CDC criteria.[14] Briefly, 2–6 weeks after COVID-19 PCR positivity or contact with individuals infected with COVID-19, uncontrollable persistent fever and the

presence of at least five of the criteria for inflammation such as high CRP (>30 mg/L), ESR, procalcitonin, IL-6 in the presence of at least two different organs were required for diagnosis in the absence of a more likely alternative diagnosis. In addition to these criteria, thorax CT for lung involvement, echocardiography, and cardiac enzymes such as proPNP, and liver and pancreatic enzymes and radiological evaluation for GI involvement were performed. Patients were classified into four groups regarding the severity of infection as asymptomatic/mild (not requiring oxygen supplementation), moderate (requiring inpatient management for COVID-19-associated symptoms, including oxygen support without the need for ICU-level care), severe (requiring ICU-level care for COVID-19-related symptoms), and critical (requiring mechanical ventilation), as described elsewhere.[15,16] In this study, patients who needed ICU care were considered to have severe/critical course.

Data regarding baseline patient information, underlying diagnosis and transplantation procedure were analyzed. Ethical approval for the study was obtained from Altınbaş University Faculty of Medicine, Ethics Committee, with the number 2022/137.

2.1 | Statistical analyses

We studied the demographic and clinical characteristics of patients undergoing allogeneic HSCT prior to the diagnosis of COVID-19. The primary outcome of this analysis was to investigate variables associated with ICU admission and COVID-19-related mortality in children who underwent allogeneic HSCT by employing a binary regression model. To perform statistical evaluation in more homogeneous groups, we excluded five patients, four of whom received neither a calcineurin inhibitor nor post-transplant cyclophosphamide (PTCy) as graft-versus-host disease (GVHD) prophylaxis and one of whom underwent allogeneic HSCT without any conditioning regimen (primary immune deficiency). Median, range (R), or interquartile range (IQR) values were used for continuous variables; absolute and percentage frequencies were used for categorical variables. For categorical variables, Pearson's Chi-square or Fisher's exact tests were used to establish differences in distributions between subgroups. OS was calculated from the time of diagnosis of COVID-19 to the date of mortality due to any (overall mortality) or COVID-19-related cause (COVID-19-related mortality) or the last follow-up by using the Kaplan–Meier method. Additionally, laboratory data that were missing for more than 40 patients were not included in the multivariate analysis. The results are expressed as odds ratios (ORs) and their corresponding 95% confidence intervals (CIs). In this statistical analysis, only those who were admitted to the ICU for reasons related to COVID-19 were included, and ICU admission was accepted as a "severe/critical course." An OR >1 denotes an unfavorable effect for the occurrence of COVID-19-related mortality or the need for ICU admission (severe/critical disease). A univariable regression model was performed with variables suspected to play a role in the mortality and admission to the ICU of these patients, as follows: age; sex; underlying diagnosis; donor type; HLA match; conditioning regimen; GVHD prophylaxis regimen; presence of grade II-IV acute graft-versus-host disease (aGVHD) and chronic GVHD (cGVHD); corticosteroid usage; hemocytometry markers, such as neutrophils, lymphocytes, and thrombocytes, at COVID-19 diagnosis; comorbidities; LRTD and multisystem inflammatory syndrome in children (MIS-C); and time from HSCT to diagnosis of COVID-19. Because ICU admission itself is an adverse outcome, it was not included in the risk factors to be investigated for mortality. As all patients with MIS-C needed ICU admission, MIS-C was not included in the risk factors for ICU admission analysis. Variables with a p-value <.1 in univariate analysis were included in the multivariate models. A p-value <.05 was considered to indicate statistical significance. All p-values were two-sided. All analyses were performed by using SPSS v22.0 (SPSS, IBM Corp., Chicago, IL, United States).

3 | RESULTS

A total of 184 allogeneic HSCT recipients diagnosed with COVID-19 were included from 30 centers from March 1, 2020, to August 31, 2022. The median age in the entire cohort was 8.66 years (IQR, 4.86–14.11 years), and 64.1% of the patients were male. Acute leukemias (93/184, 50.5%) were the most common indication for allogeneic HSCT. The most common donor source was a matched sibling (n: 75, 40.8%), and calcineurin inhibitors with (n: 110, 59.8%) or without (n: 40, 21.7%) methotrexate were the most common GVHD prophylaxis regimen. 49 patients had aGVHD grade ≥2 and 6.0% cGVHD at the time of COVID-19 diagnosis. Overall, 49 (26.6%) patients had at least one comorbidity, with pulmonary disorders being most frequent (15/49, 30.6%), related to infections requiring antibiotics or GVHD requiring severe immunosuppressive treatment. The baseline clinical characteristics of the study population are shown in Table 1.

Table 2 depicts the patient characteristics at the time of COVID-19 diagnosis. COVID-19 occurred at a median of 209 days (IQR, 111–341 days) after HSCT. In this cohort, fever (58.7%) was the most common symptom, followed by cough (33.7%). COVID-19 disease severity was mild/asymptomatic in 78.8% of patients, whereas 9.2%, 4.4% and 7.6% had moderate, severe, and critical disease, respectively. Overall, 74/184 patients (40.2%) were hospitalized for COVID-19, with a median overall hospitalization duration of 15 days (IQR 5–26 days). Of 184 patients, 52 developed LRTD (28.3%), 22 (12.0%) needed ICU admission, and 77.3% of those admitted (17/22) required invasive mechanical ventilation. MIS-C occurred in four patients (4/184, 2.2%), with a median age of 12.6 years (IQR, 5.5–15.8 years) and a median of 36 days after PCR positivity (29, 34, 38 and 43 days). All had cardiac involvement with increased BNP, dysrhythmia, shortened ejection fraction with cardiac failure and shock clinical findings, one had Kawasaki-like rash and acute renal failure, and two had subileus with severe abdominal pain mimicking acute appendicitis, as well as pulmonary involvement as acute respiratory distress syndrome. All patients required ICU admission and died.

According to the World Health Organization and the Global Initiative on Sharing Avian Influenza Data, seven peaks occurred, and

TABLE 1 Baseline clinical characteristics of the study population.

	All N: 184 (%)
Age (years, median, IQR)	8.66 (4.86–14.11)
Sex	
Male	118 (64.1)
Female	66 (35.9)
Diagnosis	
Malignant disorders	108 (58.7)
PID	25 (13.6)
Other nonmalignant disorders	51 (27.7)
Donor	
Related	102 (55.4)
Unrelated	82 (44.6)
HLA match	
Well matched (10/10)	112 (60.8)
Partially matched (9/10)	45 (24.5)
Mismatched (≤8/10)	27 (14.7)
Conditioning	
Myeloablative	166 (90.3)
Reduced intensity	17 (9.2)
None	1 (0.5)
GVHD prophylaxis	
Calcineurin inhibitor based (except PTCy)	150 (81.5)
PTCy plus others	30 (16.3)
Others	4 (2.2)
T-cell depletion (in vivo or ex vivo)	53 (28.8)
aGVHD Grade ≥2 at COVID-19 diagnosis	49 (26.6)
cGVHD at COVID-19 diagnosis	11 (6.0)
Corticosteroid at COVID-19 diagnosis	60 (32.6)
Comorbidity[a]	49 (26.6)

Abbreviations: GVHD, graft-versus-host disease; HLA, human leukocyte antigen; PID, primary immunodeficiency; PTCy, post-transplant cyclophosphamide.

[a]Comorbidity; pulmonary disorders (*n*: 15), gastrointestinal disorders (*n*: 9), cardiovascular disorders (*n*: 8), genitourinary system disorders (*n*: 4), others (*n*: 13).

TABLE 2 Characteristics related to the diagnosis and course of COVID-19.

	All, *n*: 184 (%)
Time from HSCT to COVID-19 (median, IQR) days	209.0 (111.7–340.8)
Time after HSCT (%)	
0–100 days	40 (21.7)
101–180 days	43 (23.4)
>180 days	101 (54.9)
Symptoms (%)	
Asymptomatic	39 (21.2)
Symptomatic[a]	145 (78.8)
Fever	108 (58.7)
Cough	62 (33.7)
URTD symptoms (rhinitis, pharyngitis, sore throat)	29 (15.8)
LRTD symptoms (tachypnea, dyspnea, hypoxemia)	56 (30.4)
GI	13 (7.1)
COVID-19 severity score (%)	
Asymptomatic/mild	145 (78.8)
Moderate	17 (9.2)
Severe	8 (4.4)
Critical	14 (7.6)
SARS-CoV-2 variant according to GISAID data (%)	
Alpha	16 (8.7)
Beta	3 (1.6)
Delta	34 (18.5)
Omicron	108 (58.7)
Unclassified	23 (12.5)
Thorax CT findings positivity (*n*: 79)	40 (50.6)
Laboratory findings at COVID-19 diag. (median, IQR) (*n*: 152)	
WBC (μL)	4.5 (2.6–6.8)
Neutrophil (μL)	2.2 (1.2–4.2)
Lymphocyte (μL)	1.2 (0.4–2.0)
Platelet (μL)	101.5 (54.7–205.2)
CRP (mg/L)	11.0 (1.1–38.0)
LDH (U/L)	262.0 (213.2–343.0)
DDimer (ng/mL)	493.0 (310.0–1010.0)
Treatment (%) (*n*: 59)	
Anti-viral[b]	26 (44.1)
Hydroxychloruine with antiviral[c]	6 (10.2)
Anti-inflammatory[d]	27 (45.7)
LRTD	52 (28.3%)
MIS-C (%)	4 (2.2)
ICU admission	22 (12.0)
Mechanical ventilation	14 (7.6)
Nonmechanical ventilation	8 (4.4)

the Omicron variant was the most frequent variant of SARS-CoV-2 in this study period.[17,18] The highest number of hospitalizations occurred during the 5th peak period, which was the week of October 11, 2021, with hospitalization of 35 patients (47.3%, 35/74), followed by 15 hospitalizations (20.3%, 15/74) in the 3rd peak, which was the week of April 2, 2021. With regard to interventions, 33 of the hospitalized patients (44.6%) were given antiviral treatment, most of which was favipiravir, and 36.5% (27/74) received anti-inflammatory treatment (dexamethasone or methyl prednisolone at the doctor's discretion). Data regarding the use of prophylaxis against or treatment of thromboembolic events were not available.

TABLE 2 (Continued)

	All, *n*: 184 (%)
Outcome at 6th week of diagnosis	
Alive	174 (94.6)
Death[e]	10 (5.4)

Abbreviations: GI, gastrointestinal (including diarrhea, nausea, vomiting); GISAID, Global Initiative on Sharing Avian Influenza Data; HSCT, hematopoietic stem cell transplantation; ICU, intensive care unit; LRTD, lower respiratory tract disease; LRTD, lower respiratory tract disease; MIS-C, multisystem inflammatory syndrome in children; URTD, upper respiratory tract disease; WBC, white blood cell count.

[a]Symptomatic, some symptomatic patients showed more than one symptom.

[b]Antiviral treatment, favipiravir: 10, remdesivir: 8, lopinavir/ritonavir: 4.

[c]Hydroxychloroquine + antiviral, hydroxychloroquine+favipravir: 3, hydroxychlorouine+remdesivir: 3.

[d]Antiinflamatory treatment, dexamethasone or methyl prednisolone at doctor's discretion.

[e]Deaths, 7 were attributable to COVID-19 infection, 3 were due to relapsed/progressive disease, TMA, and aGVHD, each.

Overall, 20 (10.9%) patients died after a median of 42.5 days (IQR, 17–116 days) after the diagnosis of COVID-19. Of these, 9 (4.9%) died from COVID-19-related causes. For the remaining 11 patients, the causes of death were relapse/progressive disease/sepsis in 5, aGVHD in 2, cGVHD (sepsis and bronchiolitis obliterans organizing pneumonia, each) 2, and relapse/progressive disease/thrombotic microangiopathy in 1. One patient died of sepsis 197 days after the diagnosis of COVID-19 while being monitored on a ventilator for lung sequelae. With a median follow-up time for the surviving patients of 278 days (r, 52–880 days), overall mortality was 10.9% (20/184), while COVID-19-related mortality was 4.9% (9/184) in this cohort. At the 6-week follow-up period, OS considering only COVID-19-related deaths was 96.2% (95% CI 93.4–98.9).

In univariable binary logistic regression analysis (Table 3), risk factors influencing COVID-19-related mortality in pediatric allogeneic HSCT recipients were HLA matching (*p*: .034), lymphopenia (ALC $<0.5\times10^3/\mu L$) (*p*: .010), and thrombocytopenia ($\leq75\times10^3/\mu L$) (*p*: .042) at the time of COVID-19 diagnosis and LRTD and MIS-C (*p*: .005 and <.001, respectively). Regarding HLA matching, the mortality risk of patients with transplants involving a partially matched or mismatched donor [OR, 10.83 (95% CI 1.18–99.75), *p*: .035 and OR, 19.30 (95% CI 2.06–180.76), *p*: .009, respectively] was significantly higher than that of patients with transplants involving a well-matched donor. Notably, age group, sex, primary diagnosis, donor type, conditioning intensity, GVHD prophylaxis, T-cell depletion, acute and chronic GVHD, corticosteroid usage, comorbidity at the time of diagnosis of COVID-19, and time from HSCT to COVID-19 were not associated with increased mortality. In multivariate analysis, transplantation from a mismatched donor [OR, 54.04 (95% CI 1.54–1889.78), *p*: .028], LRTD [OR, 10.11 (95% CI 2.03–50.46), *p*: .035], and MIS-C [OR, 31.07 (95% CI 3.25–297.40), *p*: .003] were associated with an increased risk of COVID-19-related mortality (Table 3).

The factors significant in univariate analysis for the requirement of ICU admission (severe/critical disease) were primary immunodeficiency (*p*: .005), HSCT from a mismatched donor (*p*: .041), COVID-19 developing in the first 100 days post-transplant (*p*: .011), LRTD ($p<.001$), neutropenia ($\leq0.5\times10^3/\mu L$) ($p<.001$), lymphopenia ($<0.5\times10^3/\mu L$) ($p<.001$), and thrombocytopenia ($\leq75\times10^3/\mu L$) (*p*: .002) at the time of COVID-19 diagnosis (Table 4). In multivariable analysis, LRTD [OR: 23.20 (95% CI 3.64–147.96), *p*: .001], and lymphopenia $0.201–0.499\times10^3/\mu L$ [OR: 5.21 (95% CI 0.69–39.34), *p*: .006] were independent risk factors associated with a higher requirement of ICU admission (Table 4).

4 | DISCUSSION

SARS-CoV-2 has infected both immunocompetent and immunocompromised people with a high mortality rate since 2019. Although the prevalence of COVID-19 has decreased worldwide, it remains an important cause of morbidity and mortality for immunocompromised post-transplant patients.[19] Data on risk factors and outcomes of COVID-19 among pediatric HSCT recipients are scarce, with most studies including a very small number of pediatric patients.[16,20–22] Here, we report, to the best of our knowledge, the largest pediatric series in HSCT patients, summarizing the clinical course and factors related to severe/critical disease and COVID-19-related mortality.

Overall survival was 96.2% at 6 week after COVID-19 diagnosis in this pediatric only cohort. This finding is in parallel to the 45 day OS of 95% reported by CIBMTR for postHSCT patients <21 year of age.[23] In the most recently published, retrospective, multicenter, multinational study, including only adult patients, the OS was 21%,[19] meaning that the OS in our pediatric cohort is higher in comparison with the adultHSCT recipients ith COVID-19 infection. This OS is higher in comparison to the adult HSCT recipients with COVID-19 infection. In an EBMT-GETH study including both adult and pediatric population, the 6-week overall survival of the entire cohort was 78% for allogeneic HSCT recipients but the overall survival of the pediatric population was 93% which was significantly better than the adult counterparts ($p=.03$).[24] Additionally, in a CIBMTR study including both adult and pediatric patients, 40/184 (22%) allogeneic HSCT recipients died, of whom the majority (37 [93%] of 40) died due to complications of COVID-19 but only one patient died among 29 pediatric patients.[25] The causes of this higher OS in pediatric HSCT recipients compared to adults are not well understood. The longer median time to COVID-19 infection (median 15 months) after HSCT in CIBMTR study including pediatric and young adult HSCT patients was suggested as one of the factors of the high survival in their cohort,[26] but we also found similar high survival rates in our cohort despite a shorter median time from HSCT to COVID infection (median 7 months). Age-related differences in immune function, expression and distribution of angiotensin-converting enzyme 2 receptor in pediatric population, which is a receptor used by the virus to gain entry into cells, endothelial and clotting function were suggested as other cause of better survival rates in children.[27] However, the 12%

TABLE 3 Binary regression model for risk factors influencing COVID-19-related mortality in pediatric allogeneic HSCT recipients (*n*: 184)[a].

		Univariate		Multivariate	
Variable	**Events**	**OR (95% CI)**	***p*-Value**	**OR (95% CI)**	***p*-Value**
Age (years)			.284		
0.0–5.0	2/46	1.00		–	
5.1–10.0	1/65	0.34 (0.03–3.91)	.389		
10.1–15.0	2/37	1.26 (0.17–9.38)	.823		
>15.0	4/36	2.75 (0.47–15.94)	.259		
Sex			.584		
Male	5/118	1.00		–	
Female	4/66	1.46 (0.38–5.63)			
Diagnosis			.204		
Malignant	5/108	1.00		–	
PID	3/25	2.81 (0.62–12.63)	.478		
Other nonmalignant	1/51	0.41 (0.05–3.62)	.424		
Donor			.491		
Related	6/102	1.00		–	
Unrelated	3/82	0.61 (0.15–2.51)			
HLA match			.034		.087
Well (10/10)	1/112	1.00		1.00	
Partially (9/10)	4/45	10.83 (1.18–99.75)	.035	20.89 (0.58–752.22)	.097
Mismatched (≤8)	4/27	19.30 (2.06–180.76)	.009	54.04 (1.54–1889.78)	.028
Conditioning			.607		
Myeloablative	9/166	1.00		–	
Reduced	0/17	0.04 (0.00–735.45)			
GVHD prophylaxis			.184		
Calcineurin inhibitors based	6/150	1.00		–	
PTCy	3/30	2.67 (0.53–7.98)			
T-cell depletion (in vivo/ex vivo)			.297		
No	5/131	1.00		–	
Yes	4/53	2.06 (0.14–3.46)			
At COVID-19 diagnosis					
aGVHD grade ≥2			.642		
No	6/135	1.00		–	
Yes	3/49	1.40 (0.34–5.84)			
cGVHD			.614		
No	9/173	1.00		–	
Yes	0/11	0.04 (0.00–751.80)			
Corticosteroid usage			.962		
No	6/124	1.00		–	
Yes	3/60	1.03 (0.25–4.29)			
Comorbidity			.642		
No	6/135	1.00		–	
Yes	3/49	1.40 (0.34–5.84)			
Time after HSCT to COVID-19 diag.			.555		

TABLE 3 (Continued)

Variable	Events	Univariate OR (95% CI)	Univariate *p*-Value	Multivariate OR (95% CI)	Multivariate *p*-Value
-3–100 days	4/40	2.13 (0.54–8.39)	.278		
101–180 days	0/43	0.04 (0.00–856.98)	.970		
>180 days	5/101	1.00		–	
LRTD			.005		.035
No	2/132	1.00		1.00	
Yes	7/52	10.11 (2.03–50.46)		10.11 (2.03–50.46)	
MIS-C			<.001		.003
No	5/180	1.00		1.00	
Yes	4/4	76.57 (18.24–321.45)		31.07 (3.25–297.40)	
ANC (μL)			.169		
$\leq 0.5 \times 10^3$	4/24	2.75 (0.88–8.59)	.104		
$0.501–0.999 \times 10^3$	1/11	2.32 (0.45–11.92)	.312		
$\geq 1 \times 10^3$	4/149	1.00		-	
ALC (μL)			.010		.279
$\leq 0.2 \times 10^3$	3/25	9.14 (1.44–57.82)	.019	5.65 (0.18—166.66)	.327
$0.201–0.499 \times 10^3$	4/23	14.10 (2.42–82.32)	.003	3.45 (0.30–39.37)	.319
$\geq 0.5 \times 10^3$	2/136	1.00		1.00	
Platelet (μL)			.060		.644
$\leq 75 \times 10^3$	7/65	9.05 (1.08–76.65)	.042	1.66 (0.15–18.53)	.128
$76–149 \times 10^3$	1/43	1.79 (0.31–27.07)	.685	0.52 (0.02–14.53)	.448
$\geq 150 \times 10^3$	1/76	1.00		1.00	

Abbreviations: ALC, absolute lymphocyte count; ANC, absolute neutrophil count; GVHD, graft-versus-host disease; HLA, human leukocyte antigen; LRTD, lower respiratory tract disease; MIS-C, multisystem inflammatory syndrome in children; PID, primary immunodeficiency; PTCy, post-transplant cyclophosphamide.

[a]We excluded five patients, four of whom received neither a calcineurin inhibitor nor post-transplant cyclophosphamide (PTCy) as graft-versus-host disease (GVHD) prophylaxis and 1 of whom underwent allogeneic HSCT without any conditioning regimen (primary immune deficiency).

ICU admission and 4.9% COVID-19-related death rate in our cohort is still higher than the general pediatric population with COVID-19 infection.[28] The Centers for Disease Control and Prevention 2021 Morbidity and Mortality Weekly Report data reported an ICU requirement rate of 0.8%, with COVID-19-related mortality less than 0.1% in the 0- to 17-year-old pediatric population.[29] Overall organ impairment caused by treatment-related toxicities as well as comorbidities among HSCT recipients could be the causes for the survival difference between the healthy pediatric population versus pediatric HSCT recipients.[26,28]

The clinical features of the patients with COVID were similar to other studies, fever being the most common clinical presentation followed by cough. Characteristics of the patients in our cohort in comparison to other pediatric studies are summarized in Table 5.[23,26,30,31] In univariate analysis transplantation involving donors other than an HLA well-matched donor, lymphopenia $<0.5 \times 10^3/\mu L$ and thrombocytopenia $\leq 75 \times 10^3/\mu L$ at COVID-19 diagnosis, LRTD and MIS-C were found to be adverse risk factors for COVID-19-related mortality. The multivariate analysis indicated that mismatched donor, MIS-C and LRTD were independent risk factors for mortality. In general, transplantation involving a non-HLA well-matched donor might require more intensive or long-term immunosuppressive treatment for GVHD prophylaxis or treatment, negatively impacting T-cell responses that lead to adverse effects on the time to resolution of infection and increase the risk of LRTD and ICU admission requirements in allogeneic HSCT recipients.[32,33] The main changes in hemocytometry markers are characterized by neutrophilia, lymphopenia, and thrombocytopenia in COVID-19.[34–36] Thrombocytopenia has been proven to be associated with hospital mortality in patients with severe COVID-19.[37,38] Lymphopenia and its severity levels may serve as reliable predictive factors for COVID-19 clinical outcomes, including mortality, need for intensive care, and oxygen requirements. Delshad et al[39] suggest that lymphopenia at the initial presentation of COVID-19 is associated with poor prognosis. MIS-C is a rare postinfectious hyperinflammatory disorder associated with SARS-CoV-2. It is characterized by overwhelming systemic inflammation, fever, hypotension, and cardiac dysfunction.[40] In our cohort, MIS-C developed in 4 (2.2%) patients, all of whom required ICU admission and died. In all patients, in addition to severe pulmonary involvement, there was severe cardiac involvement leading to cardiac failure and shock, which was emphasized as a poor prognostic

TABLE 4 Binary regression model for risk factors influencing admission to the ICU (severe/critical course of disease) after COVID-19 diagnosis in pediatric allogeneic HSCT recipients (*n*: 184)[a].

		Univariate		Multivariate	
Variable	**Event**	**OR (95% CI)**	***p* Value**	**OR (95% CI)**	***p* Value**
Age at COVID-19 diag. (yrs)			.879		
0.0–5.0	4/46	1.00		–	
5.1–10.0	8/65	1.47 (0.42–5.22)	.548		
10.1–15.0	5/37	1.64 (0.41–6.61)	.486		
>15.0	5/36	1.69 (0.42–6.83)	.459		
Sex			.673		
Male	15/118	1.00		–	
Female	7/66	0.81 (0.31–2.11)			
Diagnosis			.008		.365
Malignant disorders	10/108	1.00		1.00	
PID	8/25	4.61 (1.59–13.35)	.005	3.03 (0.49–18.59)	.230
Other nonmalignant disorders	4/51	0.77 (0.25–2.80)	.769	0.65 (0.08–5.36)	.687
Donor			.205		
Related	15/102	1.00		–	
Unrelated	7/82	0.54 (0.21–1.40)			
HLA match			.100		.129
Well matched (10/10)	9/112	1.00		1.00	
Partially matched (9/10)	7/45	2.11 (0.73–6.06)	.166	2.46 (0.83–5.76)	.248
Mismatched (≤8/10)	6/27	3.27 (1.05–10.17)	.041	3.01 (0.93–7.08)	.097
Conditioning			.427		
Myeloablative	21/116	1.00		–	
Reduced	1/17	0.43 (0.05–3.42)			
GVHD prophylaxis			.098		.226
Calcineurin inhibitor based	14/150	1.00		1.00	
PTCy plus others	6/30	2.43 (0.85–6.94)		2.74 (0.54–14.05)	
T-cell depletion			.504		
No	17/131	1.00		–	
Yes	5/53	0.70 (0.24–2.00)			
aGVHD at COVID-19 diagnosis			.112		
No	13/135	1.00		–	
Yes	9/49	2.11 (0.84–5.31)			
cGVHD at COVID-19 diagnosis			.764		
No	21/173	1.00		–	
Yes	1/11	0.72 (0.09–5.94)			
CS at COVID-19 diagnosis			.176		
No	12/124	1.00		–	
Yes	10/60	1.87 (0.76–4.60)			
Comorbidity			.112		
No	13/135	1.00		–	
Yes	9/49	2.11 (0.84–5.31)			
Time after HSCT (days)			.005		.300
0–100	11/40	3.45 (1.33–8.95)	.011	2.14 (0.39–11.69)	.381
101–180	1/43	0.22 (0.03–1.75)	.151	0.21 (0.01–3.61)	.280

TABLE 4 (Continued)

Variable	Event	Univariate OR (95% CI)	Univariate *p* Value	Multivariate OR (95% CI)	Multivariate *p* Value
>180	10/101	1.00		1.00	
LRTD			<.001	1.00	.001
No	2/132	1.00		23.20 (3.64–147.96)	
Yes	20/52	40.62 (9.03–182.82)			
ANC (μL)			.001	5.92 (0.85–41.45)	.200
$\leq 0.5 \times 10^3$	9/24	6.85 (2.48–18.91)	<.001	1.34 (0.07–26.35)	.073
$0.501–0.999 \times 10^3$	1/11	0.90 (0.13–9.69)	.903	1.00	.847
$\geq 1 \times 10^3$	12/149	1.00			
ALC (μL)			<.001	0.55 (0.03–9.87)	.019
$\leq 0.2 \times 10^3$	6/25	5.82 (1.77–19.17)	.004	5.21 (0.69–39.34)	.632
$0.201–0.499 \times 10^3$	9/23	11.85 (3.82–36.72)	<.001	1.00	.006
$\geq 0.5 \times 10^3$	7/136	1.00			
Platelet (μL)			.005	1.96 (0.27–14.47)	.699
$\leq 75 \times 10^3$	15/65	11.10 (2.43–50.67)	.002	1.01 (0.10–9.75)	.508
$76–149 \times 10^3$	5/43	4.87 (0.90–26.27)	.066	1.00	.991
$\geq 150 \times 10^3$	2/76	1.00			

Abbreviations: ALC, absolute lymphocyte count; ANC, absolute neutrophil count; CS, corticosteroid; GVHD, graft-versus-host disease; HLA, human leukocyte antigen; LRTD, lower respiratory tract disease; PID, primary immunodeficiency; PTCy, post-transplant cyclophosphamide.

[a]We excluded 5 patients, 4 of whom received neither a calcineurin inhibitor nor post-transplant cyclophosphamide (PTCy) as graft-versus-host disease (GVHD) prophylaxis and 1 of whom underwent allogeneic HSCT without any conditioning regimen (primary immune deficiency).

criterion in an international survey.[41] Among them, 2 had comorbidities (deep neutropenia and neurological disorder, each). To our knowledge, this study is the first to report the incidence and outcome of MIS-C in a large group of pediatric patients who had COVID-19 after HSCT. Therefore, our MIS-C data can make an important contribution to the literature for the pediatric HSCT community. In a study of 2035 children with cancer, 24 patients (1.2%) of which 4 had a previous HSCT, developed MIS-C. Among children with MIS-C, 100% were admitted to the hospital, 54.2% to the ICU, while COVID-19 contributed to the death of 20.1%.[42] As we do not have more detailed information about our patients who developed MIS-C, we cannot explain why the fatality rate was so high in this group. Univariate analysis showed that patients with primary immunodeficiency, transplantation from a mismatched donor, COVID-19 diagnosis within 100 days post-transplant, LRTD, neutropenia $\leq 0.5 \times 10^3/\mu L$, lymphopenia $<0.5 \times 10^3/\mu L$, and thrombocytopenia $\leq 75 \times 10^3/\mu L$ at COVID-19 diagnosis, LTRD and MIS-C needed more ICU admission during COVID-19. Lymphopenia was a strong indicator for severe/critical disease requiring ICU admission in the multivariable analysis. As discussed above, it is valid as a marker of disease severity and mortality. It has been recognized as a potential predictive factor for COVID-19 outcomes. The severity levels of lymphopenia can offer valuable insights into the prognosis of patients with COVID-19.[43] Our study indicated that LRTD where cough is the most common accompanying complaint is another indicator for severe/critical disease. In a Japanese study evaluating the impact of respiratory symptoms on COVID-19 outcomes, cough was the most frequent respiratory symptom, and lower respiratory tract symptoms were associated with a poorer prognosis.[44] In a German study, the frequency of LRTD was 56.2% of all hospitalized COVID-19 cases in the first three waves, and the ICU requirement in this cohort was 63.7%.[45]

Our large study has some limitations. Because of the inherent limitations of a retrospective study, certain COVID-19-specific details were not available, especially regarding patients with MIS-C, details of SARS-CoV-2 variants and treatment details. Furthermore, a significant proportion of data about laboratory characteristics were missing, and our study did not include long-term consequences of COVID-19. In addition, our cohort covers a period that Omicron variant was the most frequent variant of SARS-CoV-2 but it has to be kept in mind that like other RNA viruses, coronaviruses evolve rapidly, and continues mutations in strains could result in different clinical pictures both in healthy population as well as in HSCT recipients. Despite these limitations, this multicenter study provides valuable information about a homogeneous pediatric population to the HSCT community. COVID-19 in children following HSCT is frequently mild/asymptomatic; nonetheless, 12% of patients have such severe disease that they need intensive care. Although mortality in pediatric HSCT recipients is lower than that in their adult counterparts, it is still higher than that in the overall pediatric patient population. This information could play a crucial role in clinical decision-making and patient management.

TABLE 5 Comparison of the present study to other multicenter studies including more than 50 patients who reported data focusing on children who underwent HSCT at any time before the diagnosis of COVID-19.

	Present study	Averbuch[26]	Bhatt[22]	Zama[31]	Mukkada[30]
Region	Multicenter Turkish Study	Multinational EBMT Study	North & South America CIBMTR study	Multicenter Italian Study	Multinational Global Registry Study
Study period	March 2020–August 2022	March 2020–December 2021	March 2020–May 2021	March 2020–August 2021	April 2020–February 2021
Patient population	Children postHSCT	Children postHSCT	Children postHSCT	Children with cancer and postHSCT	Children with cancer and postHSCT
Malign disease	108/184 (58.7%)	56/89 (62.9%)	85/135 alloHSCT (63.0%)	15/23 (65.2%)	69/81 (85.2%)
Number of patients	184	89	167	153	81
Median age (min-max) years	8.66 (0.84–20.04)	9 (1–18)	Allo 15 (<1–21) Auto 7 (1–21)	7 (0–17) in total population[a]	8 (IQR, 4–13), in total population
Males	118 (64.1%)	52 (58%)	106 (64%)	86 (56.2%) in total population	891 (59.4%) in total population
HSCT type	184 allo	85 allo (96%) 4 auto (4%)	135 allo (80.8%) 32 auto (19.2%)	19 allo (83%) 4 auto (17%)	Allo/auto, numbers N/A
Time since HSCT to COVID, median, min-max	209 (IQR, 111–341) days	7 (0–181) months	Allo: 15 (IQR, 7–45) Auto 16 (IQR, 6–59) months	219 (50–3910) days	6/81 (<30 days) 13/81 (31–99 days) 20/81 (100–300 days) 31/81 (>300 days) 11/81 (unknown)
Asymptomatic	39 (21.2%)	35 (41%)	146 (87%) mild/asymptomatic	9 (47%) allo 3 (75%) auto	642 (43%) in total population
Fever	108 (58.7%)	36 (43%)	N/A	40 (75%) in total population	619 (41%) in total population
Respiratory symptom	62 (33.7%) Cough 29 (15.8%) URTD 56 (30.4%) LRTD	26 (31%) cough	N/A	10 (19%) in total population	356 (24%) cough 310 (21%) URTD 231 (15%) LRTD in total population
GI symptom	14 (6.2%) Diarrhea	9 (11%)	N/A	11 (21%) in total population	152 (10%) in total population
Hospitalization	74 (40.2%)	49 (55%)	N/A	62 (40.5%) in total population	889 (67.4%) in total population
Severe/critical disease	22 (12.0%) ICU 14 (7.6%) MV	9 (10%) ICU	6 (4%) MV	2 (9%) ICU	122 (9%) ICU in total population
Death	20 (10.9%) overall 9 (4.9%) COVID-19-related	7 (8%) for allo 0 (0%) for auto	8 (6%) for allo 2 (6%) for auto	0%	83 (6%) in total population
Risk for ICU and mortality	ICU: LRTD, lymphopenia at diagnosis Mortality: HSCT from a mismatched donor, MIS-C, LRTD	ICU/mortality in alloHSCT: GVHD, nonmalignant disease, IST (specifically MMF), ISI Fever, cough, coinfection, pulmonary radiologic findings, low Lansky score, high CRP levels	COVID-19 diagnosis: HSCT-CI score 1–2 Mortality: HSCT outside the US those transplanted in 2014–2020	Moderate, severe and critical disease: Infections occurring earlier than 60 days after underlying disease or HSCT	Severe disease: low-income, lower-middle income or upper-middle income country, age 15–18 years, lymphopenia, neutropenia, intensive IST

Abbreviations: CIBMTR, Center for International Blood and Marrow Transplant Research; CRP, C-reactive protein; EBMT, European Blood and Marrow Transplantation Society; GVHD, graft-versus-host disease; HSCT, hematopoietic stem cell transplantation; HSCT-CI, hematopoietic stem cell transplantation comorbidity index; ICU, intensive care unit; IQR, interquartile range; ISI, immunodeficiency scoring index; IST, immunosuppressive treatment; LRTD, lower respiratory tract disease; MMF, mycophenolate mofetil; MV, mechanical ventilation; N/A, not available; URTD, upper respiratory tract disease.

[a]Percentages are presented in HSCT recipients if available and if not in the total population.

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