**TITLE PAGE**

**COVID-19 disease in children and adolescents following hematopoietic stem cell transplantation: A report from the Turkish Pediatric Bone Marrow Transplantation Study Group**

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**Abbreviation list**

|  |  |
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| 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 | Inter quartile range |
| LRTD | Lower respiratory tract disease |
| MIS-C | Multisystem inflammatory syndrome in children |
| OR | Odds ratio |
| OS | Overall survival |
| PCR | Polymerase chain reaction |
| PTCy | Posttransplan cyclophosphamide |
| R | Range |
| SARS-CoV-2 | Severe acute respiratory syndrome coronavirus-2 |
| WHO | World Health Organization |

**ABSTRACT**

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

**Objectives:** We aimed to describe risk factors for a severe course and mortality.

**Method:** In this nationwide study, data were collected retrospectively from 28 transplant centers.

**Results:** One hundred ninety-six children [(63.8% male; median age 8.75 (IQR, 4.86-14.30)] who received allogeneic (n: 184, 93.9%) or autologous (n: 12, 6.1%) HSCT were included. The median time from HSCT to SARS-CoV-2 infection was 207.5 days (IQR, 110.2-207.5). The most common clinical manifestation was fever (58.2%), followed by cough (33.7%); 43 cases (21.9%) were asymptomatic. Lower respiratory tract disease (LRTD) and multisystem inflammatory syndrome in children (MIS-C) developed in 58 (29.6%) and 8 (4.1%) patients, respectively. Twenty-six patients (13.3%) required ICU admission. Nine patients died at a median of 17 days (min-max 1-33) after COVID-19 diagnosis, 6 of whom died due to the disease, with a COVID-19 lethality rate of 3.1%. The 6-week overall survival was 95.4% (95% CI 92.5-98.3). Multivariate analysis found that HSCT with a mismatched donor (OR, 8.98, p: 0.039) and LRTD (OR, 61.55, p: 0.001) were independent risk factors for ICU admission; MIS-C (OR, 9.55, p: 0.044) and lymphopenia (OR, 4.01, p: 0.030) at diagnosis were risk factors for mortality.

**Conclusion:** Overall mortality was lower in children than in adult counterparts, and HSCT with a mismatched donor, lymphopenia, LRTD, MIS-C and ICU admission were important risk factors for adverse outcomes.

**INTRODUCTION**

After severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection, which causes coronavirus disease 2019 (COVID-19), was identified for the first time in December 2019 in Wuhan city, China, reports of the disease in countries such as Northern Italy and Iran rapidly appeared, later becoming worldwide. The World Health Organization (WHO) declared and named this widespread infection the COVID-19 pandemic on March 11, 2020 (1-2). By December 23, 2022, a total of 651,918,402 cases had been diagnosed globally, with 6,656,601 deaths (3). The disease causes a wide spectrum of clinical findings 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 (4-7). Recipients of hematopoietic stem cell transplantation (HSCT) also constitute a group who has a risk because of chemotherapy effects such as myelosuppression and mucositis and 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 (8).

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 (9-11). Despite protective recommendations, transplant recipients retain a risk of infection. In a study of 77 patients who received cellular therapy either auto or allo-HSCT or chimeric antigen receptor T cells), there was a high rate of hospitalization (44%), and 15% of patients with severe disease died (12). In the general population, COVID-19 seems to affect children less severely than adults (13). In a study conducted in HSCT recipients with COVID-19 in Brazil, the mortality rate was 30% in adults and 21% in children (14).

In most studies examining the effects of COVID-19 in patients who underwent HSCT, children were evaluated along with adults, though 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 the pathogenicity and role of SARS-CoV-2 in the setting of pediatric allogeneic HSCT and to identify variables associated with infection severity and overall survival (OS) after COVID-19 in children who underwent HSCT.

**METHODS**

Patients who were diagnosed with COVID-19 (≤21 years of age at COVID-19 diagnosis) between 1 March 2020 and 31 August 2022 and had undergone either autologous or allogeneic HSCT at any time before the diagnosis of COVID-19 were included, and the patients needed to have at least 6 weeks of follow-up for analysis. 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 a contact history of a confirmed case while in or out of an inpatient clinic. Confirmed cases were defined as PCR- and/or serology (IgM/G)-positive patients according to the guidelines of the WHO (15) and Ministry of Health of Türkiye (16). 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). Patients were classified into five 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 intensive care unit (ICU)-level care], severe (requiring ICU-level care for COVID-19-related symptoms) and critical (requiring mechanical ventilation), as described elsewhere (17-18).

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

***Statistical Analyses***

We studied the demographic and clinical characteristics of patients undergoing either autologous or allogeneic HSCT at any time before the diagnosis of COVID-19. The primary outcome of this analysis was OS after COVID-19 at the 6th week post-infection. 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 reason or the last follow-up by using the Kaplan‒Meier method. The difference between groups was tested by the log-rank test. A secondary outcome of the study was determining predictors of overall mortality in this cohort by employing a binary regression model in only the allogeneic HSCT cohort, as the number of autologous HSCT recipients was low. To perform statistical evaluation in more homogeneous groups, we excluded 4 patients who received neither a calcineurin inhibitor nor posttransplant cyclophosphamide (PTCy) as graft-versus-host disease (GVHD) prophylaxis (n:3) and who underwent allogeneic HSCT without any conditioning regimen (n:1, primary immune deficiency). Additionally, laboratory data that were missing for more than 40 patients were not included in multivariate analysis. The results are expressed as odds ratios (ORs) and their corresponding 95% confidence intervals (CIs). An OR >1 denotes an unfavorable effect for the occurrence of mortality (or the need for ICU admission in subgroup analysis). A univariable regression model was performed with variables suspected to play a role in the mortality (or admission to the ICU) of these patients, as follows: age; sex; 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. Variables with a *p* value <0.1 in univariate analysis were entered into multivariate models. A *p* value <0.05 was considered statistically significant. All *p* values were 2-sided. All analyses were performed by using SPSS v22.0 (SPSS, IBM Corp., Chicago, IL, United States).

**RESULTS**

A total of 196 patients (184 allogeneic and 12 autologous HSCT) were included from 30 centers from 1 March 2020 to 31 August 2022. The median age in the entire cohort was 8.75 years (IQR, 4.86-14.30), and 63.8% of the patients were male. Acute leukemias (93/184, 50.5%) were the most common indication for allogeneic HSCT; lymphomas (7/12, 58.3%) were the most common indication for autologous HSCT recipients. 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 for allogeneic HSCT. Forty-nine patients had aGVHD grade ≥2 and 5.6% cGVHD at the time of COVID-19 diagnosis. Overall, 51 (26.0%) patients had at least one comorbidity, with pulmonary disorders being most frequent (n: 15, 7.6%), as related to infections requiring antibiotics or GVHD requiring severe immunosuppressive treatment. According to the Global Initiative on Sharing Avian Influenza Data (19), the Omicron variant was the most frequent variant of SARS-CoV-2 in this study period. The baseline clinical characteristics of the study population are shown in Table 1.

According to the Turkish Pediatric Bone Marrow Transplantation Registry, a total of 2215 HSCTs, 1956 of which were allogeneic, were performed in the study period. The crude incidence rate of COVID-19 was 8.8% in all HSCT recipients, 10.6% for allogeneic HSCT and 4.6% for autologous HSCT. Table 2 depicts the patient characteristics at the time of COVID-19 diagnosis. COVID-19 occurred at a median of 207 days (IQR, 110-341) after HSCT. The corresponding median times were 209 days (IQR, 111-341) for allogeneic HSCT and 184 days (IQR, 79-401) for autologous HSCT (*p*: 0.775. In this cohort, fever (58.2%) was the most common symptom, followed by cough (33.7%). COVID-19 disease severity was mild/asymptomatic in 78.5% of patients, whereas 8.2%, 4.1% and 9.2% had moderate, severe and critical disease, respectively. Overall, 74 patients (39.5%) were hospitalized for COVID-19, with a median overall hospitalization duration of 15 days (IQR 5-26). Fifty-eight patients developed LRTD (29.6%), and twenty-six (13.3%) needed ICU admission, 18 (9.2%) of whom required invasive mechanical ventilation. MIS-C occurred in 8 patients, with a median age of 11.0 years (IQR, 8.2-15.5), all of whom required ICU admission and 3 of whom died.

With regard to interventions, 33 patients (16.8%) were given antiviral treatment, and 27 (13.8%) received anti-inflammatory treatment. Data regarding use of prophylaxis against or treatment of thromboembolic events were not available.

The mortality rate of this cohort was 4.6%, with a total of 9 deaths; all of these patients were allogeneic recipients. Six patients died due to COVID-19, with an overall COVID-19 lethality rate of 3.1%. For the remaining 3 patients, causes of death were GVHD (n: 2) and thrombotic microangiopathy and multiorgan failure (n: 1). All patients died during follow-up in the ICU. Furthermore, among patients admitted to the ICU, a significantly higher mortality rate was observed in those with invasive mechanical ventilation vs. those without (9/18, 50.0% vs. 0/8, 0%, *p*: 0.023). Although the median time from HSCT to COVID-19 diagnosis in patients who died seemed to be much shorter than that in surviving patients [144 days (IQR, 24-263) vs. 210 (IQR, 114-350)], the difference did not reach statistical significance (*p*: 0.076). At the 6-week follow-up period, OS was 95.4% (95% CI 92.5-98.3) for all patients, with no significant difference between allo- and autoHSCT [95.1% (95% CI 92.0-98.2) vs. 100%, *p*=0.438] (Figure 1).

In univariable binary logistic regression analysis (Table 3), risk factors influencing mortality in allogeneic HSCT recipients were HLA match in previous transplantation (*p*: 0.049), lymphopenia less than 0.5.103/µL and thrombocytopenia less than 75.103/µL at the time of COVID-19 diagnosis (*p*: 0.012 and *p*: 0.037, respectively), and LRTD and MIS-C development during the follow-up period for COVID-19 (*p*: 0.007 and 0.001, respectively). Regarding HLA match, the mortality risk of patients with transplant involving a partially matched or mismatched donor [OR, 13.87 (95% CI 1.57-122.40), *p*: 0.018 and OR, 13.87 (95% CI 1.38-139.19), *p*: 0.025, respectively] was statistically higher than for those with transplant involving a well matched donor. The need for admission to the ICU had a very strong impact on mortality (*p*<0.001). Notably, age group, sex, primary diagnosis, donor type, conditioning intensity, GVHD prophylaxis, T-cell depletion, cGVHD, corticosteroid usage, comorbidity at the time of diagnosis of COVID-19, and time from HSCT to COVID-19 were not associated with increased mortality. There was a tendency toward higher mortality rate in patients who had aGVHD and neutropenia at the time of COVID-19 diagnosis, but the difference did not reach statistical significance (p=0.063 and *p=0*.065, respectively). In multivariate analysis, MIS-C and lymphopenia less than 0.2.103/µL were associated with an increased risk of a fatal outcome (Table 3) if the ICU was not included in the model.

In subgroup analysis, factors significant in univariate analysis for the requirement of ICU admission were primary immunodeficiency (*p*: 0.018), HSCT from a donor other than a well-matched donor (0.025), presence of aGVHD grade ≥2 (*p*: 0.030), COVID-19 developing in the posttransplant 100 days (*p*: 0.005), LRTD (*p*<0.001), neutropenia (≤0.5.103/µL, *p*: 0.001), lymphopenia (*p*<0.001) and thrombocytopenia (*p*<0.001) at the time of COVID-19 diagnosis (Table 4). Although the patients who received posttransplant cyclophosphamide (PTCy) as GVHD prophylaxis or corticosteroids for GVHD treatment and had any comorbidities had a higher need for ICU admission, these differences did not reach statistical significance (*p*=0.065, *p*=0.082 and *p*=0.099, respectively). In multivariable analysis, HSCT involving a mismatched donor [OR: 8.98 (95% CI 1.16-238.40), *p*: 0.039] and LRTD [OR: 61.55 (95% CI 5.46-693.37), *p*: 0.001) were independent risk factors associated with a higher requirement of ICU admission (Table 4) if MIS-C was not included in the model.

**DISCUSSION**

Community-acquired respiratory viruses include a variety of RNA viruses, such as the coronavirus family, and DNA viruses and can affect up to 50% of transplant patients; outcomes vary, ranging from asymptomatic replication to significant disease that typically affects very young and very old populations, patients with chronic medical conditions, and those with inherited, acquired, or drug-induced immune dysfunction. Contrary to most members of the coronavirus family, SARS-CoV-2 has infected both immunocomponent and immunocompromised people with a mortality rate higher than expected since 2019. Although the prevalence of COVID-19 has decreased worldwide, it remains an important cause of morbidity and mortality for immunocompromised posttransplant patients. Here, we report to our knowledge the largest pediatric series, summarizing the incidence, clinical course and factors related to disease severity and mortality. The most common clinical manifestation of COVID-19 was fever (58.2%), and 21.9% of the patients were asymptomatic. During the follow-up period for COVID-19, 29.6% developed LRTD, and 13.3% of patients required ICU care. The mortality rate was 4.6%, with a total of 9 deaths, 6 of which were due to COVID-19. The probability of a severe disease course was higher in patients who underwent transplant involving a mismatched donor and had LRTD. Lymphopenia at diagnosis, MIS-C and ICU requirement were associated with an increased risk of mortality.

Our study findings show some consistency with previous studies involving cohorts of COVID-19 patients, including adults and a small number of pediatric patients undergoing HSCT, showing better OS than in adults. 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 (20-23). Four large international cohort studies describing outcomes of HSCT recipients with COVID-19, 2 of which included only pediatric HSCT recipients have been published (24-27).The 6-week OS of the EBMT and Spanish Group of Hematopoietic Stem Cell Transplantation (GETH) study was 78% and 72% for allogeneic and autologous HSCT recipients, respectively, in a cohort of 382 patients who underwent HSCT, which included 32 pediatric HSCT recipients (allogeneic 29 and autologous 3) diagnosed with COVID-19. In comparison, the OS of pediatric patients was 93%, which is consistent with our data (6-week OS 94.1%). In the first Center for International Bone Marrow Transplantation Registry (CIBMTR) data, 30-day OS was 68% and 67% for allogeneic and autologous recipients, respectively. Only 1 patient among the 29 pediatric patients reported in that cohort had died (24). The second report from CIBMTR focusing on only pediatric HSCT recipients with COVID-19 included those who had been included in the first published study, and the 45-day OS was 95% and 90% for allogeneic and autologous HSCT recipients, respectively (26). In this population in which the median time from HSCT to COVID-19 was 15 months for allogeneic HSCT recipients and 16 months for autologous HSCT recipients, the cumulative incidence of COVID-19 was 1.9% at 6 months after HSCT and continued to increase 4.5% and 13% at 1 and 2 years after HSCT, respectively. It is speculated that this low mortality rate in this pediatric population may be in part due to the median duration between HSCT and COVID-19 diagnosis being more than one year, which was found to be a risk factor in the first CIBMTR study (24). Our OS and COVID-19 incidence rates were very similar to those in the CIBMTR study, but the median time from HSCT to COVID-19 of approximately 6 months in our study was much shorter. Zimmermann and Curtis (28) pointed out that the underlying causes of differences in survival rate between children and adults might be age-related differences in immune function, expression and distribution of angiotensin-converting enzyme 2 receptor, which is a receptor used by the virus to gain entry into cells, endothelial and clotting function and comorbidities. Furthermore, recent exposure to other viruses and routine vaccines in children might be associated with protective cross-reactive antibodies and T cells against SARS-CoV-2. Although mortality rates in pediatric patients with COVID-19 followed by HSCT were lower than those in the adult population, they were higher than the previously reported general pediatric mortality rates after COVID-19 (29). Bhatt et al. (26) emphasized that this difference in mortality rates between pediatric HSCT recipients and the general pediatric population might be explained by the nascent immune system and overall organ impairment caused by treatment-related toxicities among HSCT recipients.

Interestingly, the type of transplant did not impact OS in the present cohort, similar to EBMT and CIBMTR data (25, 26). Although it was shown that allogeneic HSCT recipients were more likely to develop more serious complications against respiratory viruses such as RSV and parainfluenza (30), no difference was found in terms of fatal outcome risk in autologous and allogeneic HSCT recipients with influenza during the H1N1 “swine flu” pandemic (31-32).

Regarding clinical symptoms, the most common clinical manifestation was fever, followed by cough, in our study, similar to other published pediatric studies (26, 27, 33, 34) (Table 5). Compared to the Centers for Disease Control and Prevention 2021 Morbidity and Mortality Weekly Report data reporting 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 (35), we found a higher proportion of children with LRTD confirmed by clinical and/or radiological findings and the need for ICU admission, as in other pediatric studies (26, 27, 33, 34). The mortality in this cohort was lower than that in published studies involving the adult population (14, 24, 25); when compared with general pediatric mortality rates after COVID-19, it was still higher (35, 36). This difference may result from organ toxicities due to transplantation in HSCT recipients.

In our study, transplantation involving donors other than an HLA well-matched donor, lymphopenia and thrombocytopenia at COVID-19 diagnosis, LTRD and MIS-C development during COVID-19 follow-up and ICU admission requirement were found to be adverse risk factors for outcome in univariate analysis. 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 time to resolution of infection and increase risk of LRTD and ICU admission requirement in allogeneic HSCT recipients (37-38). The main changes in hemocytometry markers are characterized by neutrophilia, lymphopenia and thrombocytopenia in COVID-19 (39-41). Thrombocytopenia has been proven to be associated with hospital mortality in patients with severe COVID-19 (42, 43). 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. The current study suggests that lymphopenia at initial presentation of COVID-19 is associated with poor prognosis (44). In multivariate analysis without ICU admission, as all deceased patients were admitted to the ICU, we found that the presence of lymphopenia at the time of diagnosis increased mortality by approximately 11 times and development of MIS-C mortality by 10 times in pediatric allogeneic HSCT recipients. 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 (45). Younger children may present with features of Kawasaki-like disease, and older children are often admitted to the ICU with cardiogenic shock (46). Patients admitted with shock were more likely to require ventilator and inotropic support, and up to 55% of patients required ICU admission. Although the clinical picture of MIS-C is highly concerning, the mortality rate is as low as approximately 2% (46-48). In our cohort, MIS-C developed in 8 (3.6%) patients, with a median age of 11.0 years (IQR, 8.2-15.5), all of whom required ICU admission, with a fatality rate of 62.5% (5/8), which was much higher than reported in the literature (44-46). Among them, only 2 patients had comorbidities (one had deep neutropenia and one neurological disorder). As we do not have more detailed information about the patients who developed MIS-C, we cannot explain why the fatality rate was so high in this group.

Univariate analysis showed that patients who underwent HSCT involving a nonwell-matched donor and those who had a diagnosis of primary immunodeficiency, aGVHD, neutropenia, lymphopenia and thrombocytopenia and were diagnosed with COVID-19 within 100 days posttransplantation needed ICU care during the course of COVID-19. LRTD and transplantation involving a mismatched donor were very strong indicators for ICU requirement in multivariable analysis. Organ toxicities associated with aGVHD and immunosuppressive agents used in its treatment may have aggravated the course of the disease, causing LRTD and increasing the ICU requirement in patients. Risk factors for mortality and severe disease in studies involving pediatric cases in the literature in comparison with our study are shown in Table 5.

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. 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 asymptomatic; nonetheless, 13% 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 the overall pediatric patient population.

**CONFLICT OF INTEREST**

The authors declare no competing financial interest.

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**LEGEND**

**Figure 1.** Cumulative survival after COVID-19 according to HSCT type.