

















ARTICLE



Risk factors for a severe disease course in children with SARS-COV-2 infection following hematopoietic cell transplantation in the pre-Omicron period: a prospective multinational Infectious Disease Working Party from the European Society for Blood and Marrow Transplantation group (EBMT) and the Spanish Group of Hematopoietic Stem Cell Transplantation (GETH) study

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Risk factors for severe SARS-Cov-2 infection course are poorly described in children following hematopoietic cell transplantation (HCT). In this international study, we analyzed factors associated with a severe course (intensive care unit (ICU) admission and/or mortality) in post-HCT children. Eighty-nine children (58% male; median age 9 years (min-max 1–18)) who received an allogeneic (85; 96%) or an autologous (4; 4%) HCT were reported from 28 centers (18 countries). Median time from HCT to SARS-Cov-2 infection was 7 months (min-max 0–181). The most common clinical manifestations included fever (37; 42%) and cough (26; 29%); 37 (42%) were asymptomatic. Nine (10%) children following allo-HCT required ICU care. Seven children (8%) following allo-HCT, died at a median of 22 days after SARS-Cov-2 diagnosis. In a univariate analysis, the probability of a severe disease course was higher in allo-HCT children with chronic GVHD, non-malignant disease, immune suppressive treatment (specifically, mycophenolate), moderate immunodeficiency score, low Lansky score, fever, cough, coinfection, pulmonary radiological findings, and high C-reactive protein. In conclusion, SARS-Cov-2 infection in children following HCT was frequently asymptomatic. Despite this, 10% needed ICU admission and 8% died in our cohort. Certain HCT, underlying disease, and SARS-Cov-2 related factors were associated with a severe disease course.

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INTRODUCTION

It has been more than 2 years since the World Health Organization announced a global coronavirus disease (COVID-19) pandemic. Within this pandemic, the proportion of children among all COVID-19 cases is increasing [1]. In immunocompetent children, COVID-19 is usually a mild disease with low rates of both intensive care unit (ICU) admissions (0.8%) and of mortality (<0.1%) [2]. However, children with underlying diseases, including those with immune deficiency and cancer, are at higher risk of developing severe COVID-19 than healthy children [3–5].

Data on SARS-Cov-2 infection in hematopoietic cell transplantation (HCT) recipients were prospectively collected by the European Society for Blood and Marrow Transplantation (EBMT) and the Spanish Group of Hematopoietic Stem Cell Transplantation

(GETH). Previous analysis, including cases diagnosed before August 2020, reported an ~30% mortality in HCT recipients following COVID-19 during the first wave [6], with a better outcome in children. Factors associated with a severe clinical course in children with SARS-Cov-2 following HCT are, however, poorly described. In this report, we present clinical and outcome data on SARS-Cov-2 infection in children from this registry.

SUBJECTS AND METHODS

Data concerning patients (both children and adults) who developed SARS-Cov-2 following allogeneic or autologous HCT were prospectively collected by the EBMT [6]. Invitation to participate in the study was distributed among the EBMT centers. All patients give informed consent for their data

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to be included in the EBMT registry. Cases were identified through voluntary reporting. Background HCT-related data routinely reported by all EBMT centers were collected from the EBMT registry, including patient demographics, presence of comorbidities, primary diagnosis, status, HCT type, donor type and conditioning regimen. These data were combined with those relating to the SARS-Cov-2 from specially designed case record forms providing data at diagnosis and 6-weeks follow-up. The forms were updated based on the clinical and management developments reached during the pandemic. A parallel data collection with forms written in Spanish was used to collect data from Spain by GETH [6].

The SARS-Cov-2 information included clinical manifestation, need for hospitalization, need for ICU admission, treatment, and outcome, as well as potential risk factors for a severe disease course at the time of SARS-Cov-2 infection. We defined severe disease as ICU admission during the SARS-Cov-2 infection or death within two months of SARS-Cov-2 diagnosis. Immunodeficiency scoring index was defined as described [6, 7].

We present data on children aged 0–18 years with a SARS-Cov-2 diagnosis reported to the EBMT/GETH survey before December 16, 2021. All children were diagnosed by SARS-CoV-2 positive PCR on respiratory tract samples. Our primary objective was to describe SARS-Cov-2 characteristics and outcomes. The secondary objective was to characterize factors associated with severe disease.

Statistical analysis

The main characteristics of patients were reported by descriptive statistics. Continuous data were presented as median, minimum, and maximum values. Categorical data were presented as numbers and percentage of total. The probability of a severe course was assessed using Kaplan-Meier estimator and compared between groups using log-rank tests and calculating cumulative incidence and hazard ratio. To identify factors associated with severe disease, a univariate Cox regression model was used. The following factors were analyzed: demography, underlying diagnosis, HCT source and conditioning; at the time of SARS-CoV-2 infection: underlying disease status, Lansky score, presence of comorbidities, steroid therapy, neutrophil and lymphocyte counts, presence of acute or chronic graft versus host disease (GVHD), and other immunosuppressive therapy medications within 2 months of SARS-Cov-2 infection onset.

A bilateral p value <0.05 was considered as statistically significant. All analyses were performed using the statistical software SAS v.9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Study population (Table 1)

Eighty-nine children were reported from 28 centers, in 18 countries. Timing of cases diagnosis is presented in Supplementary Fig. 1. Fifty-two (58%) were male; median age was 9 years (min–max 1–18). Eighty-five (96%) had undergone an allogeneic and 4 (4%) and autologous HCT. The median time from the most recent HCT to SARS-Cov-2 infection was 7 months (min–max 0–181). The most common underlying diseases were acute leukemia (46; 52%), and inherited disorders (15; 17%). Twenty-one (24%) children had comorbidities; among them, seven (8%) had lung pathology; five (6%) had hypertension (one of them with dyslipidemia), three (3%) had cardiovascular comorbidities, and six (7%) children had diabetes, obesity, secondary hemosiderosis, dyslipidemia, and cerebral blood vessels stenosis. At the time of SARS-Cov-2 infection, 19 (22%) and 12 (16%) of children had acute and chronic GVHD, respectively. None was vaccinated.

SARS-CoV-2 infection manifestations and treatment

Clinical and laboratory parameters are presented in Table 2. The median time from symptoms onset to SARS-Cov-2 infection diagnosis in 40 children symptomatic at the time of diagnosis was 2 days (min–max 0–40). Thirty-seven (42%) children were asymptomatic during infection course. The most common clinical manifestations included fever, cough, and upper respiratory tract symptoms, including rhinorrhea, sinusitis, otitis, or pharyngitis. Twenty-four children (27%) had evidence of coinfections, mainly viral (Supplementary Table 1). Forty-nine (55%) children were hospitalized; 21 (43%) due to COVID-19. Nine (10%) children

required oxygen to maintain oxygen saturation above 92%; three (3%) and five (6%) children required non-invasive and invasive ventilation, respectively. Eighteen out of 62 cases (29%) with lung radiology performed had abnormal pulmonary radiological findings. Treatments are summarized in Supplementary Table 2.

Children with a severe course (Tables 1, 2, 3)

Nine (10%) children required ICU care within a median 10.5 days (min–max –5–29) following a SARS-Cov-2 diagnosis. One of these children was in intensive care for five days prior to the diagnosis. Initially hospitalized in the ICU for seizures that improved on treatment, his consciousness decreased two days later, and he developed fever. Brain MRI revealed meningoencephalitis. SARS-Cov-2 PCR, taken for the first time five days after ICU admission, was positive. No other infections were identified, so SARS-Cov-2 infection possibly contributed to this patient's neurological symptoms and ICU admission.

All children hospitalized in the ICU were neutropenic at the time of SARS-Cov-2 diagnosis and were receiving IST as a part of their transplantation management (not for COVID-19 treatment); eight of nine were lymphocytopenic. Three children required non-invasive and five invasive ventilation. Median ICU hospitalization duration was 10.5 days (min–max; 3–38); five of these children died after a median 13 days (min–max, 7–38) from ICU admission.

Seven (8%) children (five males) who developed SARS-Cov-2 infection at a median of 2 months (min–max; 0–147) after HCT died (Tables 1 and 2). All had undergone allo-HCT, all received immune suppression at the time of SARS-Cov-2 diagnosis. The median time from the SARS-Cov-2 diagnosis to death was 22 days (min–max; 5–54). Six had persistent positive SARS-CoV-2 PCR at the time of death. In five children, there was evidence of bacterial, viral, or fungal coinfections that could contribute to death (Supplementary Table 1). In two children, who died one and 22 days after SARS-Cov-2-I diagnosis, the presumed main causes of death were relapse and non-engraftment, respectively. One child died suddenly 54 days after SARS-Cov-2 infection diagnosis. None of children who died received medications listed in Supplementary Table 2.

In the univariate analysis, the probability of a severe disease course was higher in the following children after allo-HCT: non-malignant underlying disease, chronic GVHD, exposure to IST, and specifically to mycophenolic acid (MMF), moderate risk based on immunodeficiency scoring index (vs. low risk), presence of fever, cough, coinfection, and pulmonary radiological findings. C-reactive protein (CRP) levels were significantly higher; and Lansky score was significantly lower at the time of SARS-Cov-2 infection in children with a severe course (Supplementary Figs. 2 and 3). Due to the low number of events, it was not possible to perform the multivariate analysis.

We compared the group of children with malignant and non-malignant diseases, and we found that in the group of children with non-malignant diseases there was a higher proportion of T-cell depletion (26/31; 84% vs. 24/56; 43%, $p = 0.0002$) and comorbidities (9/33; 27% vs. 5/56; 9%; $p = 0.02$). There were no significant differences in the demography, conditioning, immune suppressive treatment, proportion of acute or chronic GVHD, coinfections, neutropenia or lymphocytopenia.

DISCUSSION

In this quite large series of pediatric HCT recipients with SARS-Cov-2 infection, we present the clinical picture and report the factors related to the underlying disease and HCT course (chronic GVHD, non-malignant disease, exposure to IST, and specifically to MMF, moderate risk based on immunodeficiency scoring index (vs. low risk), lower Lansky score) and to SARS-Cov-2-I course (fever, cough, radiological pulmonary findings, co-infections, high CRP) that were associated with severe disease. Our finding that chronic GVHD and

Table 1. Patients' characteristics.

	Total	Auto	Allo-HCT				P value
			Allo total	ICU admission ^a	Died ^a	Severe course ^a	
Numbers	89	4	85	9 (10)	7 (8)	11 (12)	
Demography							
Gender							0.4
Male	52 (58)	2 (50)	50 (59)	7 (14)	5 (10)	8 (16)	
Female	37 (42)	2 (50)	35 (41)	2 (6)	2 (6)	3 (9)	
Age (in years) median (min–max) at diagnosis COVID	9 (1–18)	12 (7–18)	9 (1–18)	8 (1–13)	12 (4–14)	11 (1–14)	0.9
Median time from most recent HCT to COVID-19 (months) (min–max)	7 (0–181)	8 (1–31)	7 (0–181)	2 (0–17)	2 (0–147)	6 (0–147)	0.8
Time from the most recent HCT to COVID-19 (number of children)							
≤100 days	29 (33)	1 (25)	28 (33)	5 (18)	4 (14)	5 (18)	0.4
>100 days	60 (67)	3 (75)	57 (67)	4 (7)	3 (5)	6 (11)	
Underlying disease data							
Diagnosis							0.02^b
Malignant disease	56 (63)	4 (100)	52 (61)	2 (4)	3 (6)	3 (6)	
Acute lymphoblastic leukemia	31 (35)	0 (0)	31 (36)	2 (6)	3 (10)	3 (10)	
Acute myelogenous leukemia/ myelodysplastic syndrome	15 (17)	0 (0)	15 (18)			0 (0)	
Solid tumors	5 (6)	3 (75)	2 (2)			0 (0)	
Other malignancy ^c	5 (6)	1 (25)	4 (5)			0 (0)	
Non-malignant disease	33 (37)	0 (0)	33 (39)	7 (21)	4 (12)	8 (24)	
Inherited disorders ^d	15 (17)	0 (0)	15 (18)	3 (20)	2 (13)	4 (27)	
Hemoglobinopathies	8 (9)	0 (0)	8 (9)			0 (0)	
Bone marrow failure	6 (7)	0 (0)	6 (7)	4 (67)	2 (33)	4 (67)	
Other non-malignant diseases ^e	4 (4)	0 (0)	4 (5)			0 (0)	
Disease status before COVID-19 (on 55 patients with malignant disease and data available)							
Complete remission	45/55 (82)	1/3 (33)	44/52 (85)	2 (5)	2 (5)	2 (5)	
Not complete remission	10/55 (18)	2/3 (67)	8/52 (15)	0 (0)	1 (13)	1 (13)	
Lansky median (min–max) ^f	90 (50–100)	90 (80–100)	90 (50–100)	90 (70–100)	80 (50–100)	90 (50–100)	0.01
Stem cell source (allo-HCT)							
Bone marrow			55/83 (66)	4 (7)	2 (4)	5 (9)	
Peripheral blood			25/83 (30)	5 (20)	5 (20)	6 (24)	
Cord blood			3/83 (4)	0 (0)	0 (0)	0 (0)	
HLA match (allo-HCT)							
Identical sibling			19/83 (23)	3 (16)	1 (5)	3 (16)	
Unrelated			34/83 (41)	1 (3)	2 (6)	2 (6)	
Mismatched relative			27/83 (33)	4 (15)	3 (11)	5 (19)	
Matched other relative			3/83 (4)	1 (33)	1 (33)	1 (33)	
Conditioning							
Myeloablative	65/87 (75)	4 (100)	61/83 (73)	6 (10)	5 (8)	8 (13)	1
Reduced intensity	22/87 (25)	0 (0)	22/83 (27)	3 (14)	2 (9)	3 (14)	
In-vivo T cell depletion (allo-HCT)							
Yes			50/83 (60)	5 (10)	3 (6)	6 (12)	
No			33/83 (40)	4 (12)	4 (12)	5 (15)	
Acute GvHD (allo-HCT)							
Yes			19 (22)	4 (21)	3 (16)	4 (21)	
No			66 (78)	5 (8)	4 (6)	7 (11)	

Table 1. continued

	Total	Auto	Allo-HCT				P value
			Allo total	ICU admission ^a	Died ^a	Severe course ^a	
Chronic GVHD (number of allo-HCT patients with a follow-up >100 days)			<i>n</i> = 75	<i>n</i> = 6	<i>n</i> = 4	<i>n</i> = 8	0.002
Yes			12/75 (16)	3/12 (25)	3/12 (25)	5/12 (42)	
No			63/75 (84)	3/63 (5)	1/63 (2)	3/63 (5)	
Presence of comorbidity (not including lung disease)							0.2
Yes	14 (16)	0 (0)	14 (16)	3 (21)	1 (7)	3 (21)	
No	75 (84)	4 (100)	71 (84)	6 (8)	6 (8)	8 (11)	
Underlying lung pathology							0.3
Yes	7/88 (8)	0 (0)	7/84 (8)	0 (0)	0 (0)	0 (0)	
No	81/88 (92)	4 (100)	77/84 (92)	9 (12)	7 (9)	11 (14)	
Corticosteroids							0.06
Yes	24 (27)	0 (0)	24 (28)	6 (25)	3 (13)	6 (25)	
<2 mg/kg prednisone	9	-	9	3	2	3	
≥2 mg/kg prednisone	0	-	0	0	0	0	
missing data on dosage	15	-	15	3	1	3	
No	65 (73)	4 (100)	61 (72)	3 (5)	4 (7)	5 (8)	
Other immunosuppressive drugs							0.01
Yes	53 (60)	0	53 (62)	9 (17)	7 (13)	11 (21)	
Cyclosporine or tacrolimus	38 (43)	0	38 (45)	7 (18)	5 (13)	8 (21)	0.09
Sirolimus/everolimus	14 (16)	0	14 (17)	2 (14)	2 (14)	3 (21)	0.3
Janus kinase inhibitor	13 (15)	0	13 (15)	4 (31)	3 (23)	4 (31)	0.05
Mycophenolate	9 (10)	0	9 (11)	5 (56)	4 (44)	5 (56)	0.0002
other	9 (10)	0	9 (11)	1 (11)	0	1 (11)	0.9
No	36 (40)	4 (100)	32 (38)	0 (0)	0 (0)	0 (0)	
Immunodeficiency scoring index							
Low risk	19/32 (59)	1/1 (100)	18/31 (58)	0 (0)	0 (0)	0 (0)	0.002
Moderate risk	13/32 (41)	0/1 (0)	13/31 (42)	6 (46)	3 (23)	6 (46)	

ICU intensive care unit.

^aThe proportion of patients with ICU, mortality and severe course is presented within the group of allo-HCT patients with data available.

^b*p* value for comparison between malignant and non-malignant diseases.

^cOther malignancy: chronic myelocytic leukemia (2), Hodgkin lymphoma (2), B cell lymphoma (1).

^dInherited disorders included primary immune deficiencies (*n* = 11), two other diseases, and two not specified.

^eOther non-malignant diseases: Histiocytic disorders (3), autoimmune disease (1).

^fLansky score in patients with mild course was median (min-max) 100 (50–100).

^g*p* value for comparison between bone marrow and other sources.

^h*p* value for comparison between unrelated and other donors.

Bold entries indicate significant *p* values.

ongoing immune suppression predispose to a severe disease course has an important practical implication. Recent data in a general population demonstrate growing numbers of children infected with SARS-Cov-2, as well as a growing proportion of them requiring hospitalization [8]. Vaccination, recently approved from age 6 months, is an important protective measure. Vaccine efficacy, however, is impaired in patients with chronic GVHD and those receiving IST [9]. The fact that such children are at increased risk of severe disease course and mortality underscores the importance of additional precautions—among them, vaccination of family members, masks, and pre-exposure prophylaxis for eligible patients [10].

There are few treatment options for pediatric patients with SARS-Cov-2, especially for non-hospitalized children, with limited data on their efficacy and controversy over their recommended use as the course of COVID-19 is usually mild, even in children

with malignancies. Children with mild-to-moderate COVID-19 weighing at least 3.5 kg who are at high risk for progression to severe disease, including hospitalization or death, can be treated with remdesivir, as its indications for its use were expanded by the FDA [11], and our study helps identifying post-HCT children who are at higher risk for adverse outcomes. More severely ill children, such as those who require conventional oxygen, oxygen through high-flow device or non-invasive ventilation, shall receive treatment with remdesivir with or without dexamethasone, as recommended by the NIH [12]. These drugs were, however, rarely used in patients reported to our study, and none of the children with severe outcome was treated according to the current NIH guidelines.

Comparison of data in our study to other pediatric multicenter studies and to the EBMT/GETH study [6] is presented in Table 4. To identify relevant studies, we searched PubMed at the end of June

Table 2. Clinical, laboratory and imaging findings at the time of SARS-CoV-2 infection (data is presented as percentage of children with information available).

	Total	Auto	Allo-HCT			P value	
			Allo total	ICU admission ^a	Died ^a		Severe course ^a
Numbers	89	4	85	9 (10)	7 (8)	11 (12)	
Clinical signs/symptoms at SARS-CoV-2 diagnosis							
Symptomatic							
Yes	52/89 (58)	0 (0)	52/85 (61)	9 (17)	6 (12)	10 (19)	0.06
No	37/89 (42)	4 (100)	33/85 (39)	0 (0)	1 (3)	1 (3)	
Fever							
Yes	37/88 (42)	0 (0)	37/84 (44)	8 (22)	5 (14)	9 (24)	0.01
No	51/88 (58)	4 (100)	47/84 (56)	1 (2)	2 (4)	2 (4)	
Cough							
Yes	26/89 (29)	0 (0)	26/85 (31)	8 (31)	4 (15)	8 (31)	0.004
No	63/89 (71)	4 (100)	59/85 (69)	1 (2)	3 (5)	3 (5)	
Upper respiratory symptoms ^b	13/88 (15)	0 (0)	13/84 (15)	1 (8)	0 (0)	1 (8)	
Fatigue	11/88 (13)	0 (0)	11/84 (13)	2 (18)	1 (9)	2 (18)	
Diarrhea	9/88 (10)	0 (0)	9/84 (11)	3 (33)	2 (22)	3 (33)	
Sputum production	4/88 (5)	0 (0)	4/84 (5)	2 (50)	1 (25)	2 (50)	
Other signs/symptoms ^c	7/88 (8)	0 (0)	7/84 (8)	3 (43)	2 (29)	3 (43)	
Time since start of symptoms to COVID-19 diagnosis in children symptomatic at diagnosis; median (range); days	2 (0–40) <i>n</i> = 39	<i>n</i> = 0	2 (0–40) <i>n</i> = 39	6(0–40) <i>n</i> = 9	3(0–10) <i>n</i> = 5	6(0–40) <i>n</i> = 9	0.1
Coinfection ^d							
No	64/88 (73)	3 (75)	61/84 (73)	3 (5)	2 (3)	4 (7)	0.009
Yes	24/88 (27)	1 (25)	23/84 (27)	6 (26)	5 (22)	7 (30)	
Laboratory parameters at the time of diagnosis							
Neutropenia <500 cells	63/70 (90)	3 (75)	60/66 (91)	9 (15)	6 (10)	10 (17)	0.3
Neutropenia <100 cells	9/70 (13)	0 (0)	9/66 (14)	2 (22)	3 (33)	3 (33)	0.1
Lymphopenia <500 cells	62/68 (91)	4 (100)	58/64 (91)	8 (14)	4 (7)	8 (14)	0.2
Lymphopenia <200 cells	49/69 (71)	3 (75)	46/65 (71)	6 (13)	3 (7)	6 (13)	0.4
C-reactive protein levels median (min-max), mg/L ^e	5 (0.0–234) <i>n</i> = 67	6 (2–16) <i>n</i> = 4	5 (0.0–234) <i>n</i> = 63	14 (1–234) <i>n</i> = 9	66 (5–234) <i>n</i> = 6	15 (1–234) <i>n</i> = 10	0.04
Pulmonary radiological findings							
Yes	18/62 (29)	0 (0)	18/60 (30)	8 (44)	4 (22)	8 (44)	0.004
No	44/62 (71)	2 (100)	42/60 (70)	1 (2)	3 (7)	3 (7)	

ICU intensive care unit.

^aThe proportion of patients with ICU, mortality and severe course is presented within the group of allo-HCT patients with data available.

^bUpper respiratory symptoms included rhinorrhea, sinusitis, otitis, or pharyngitis.

^cOther: myalgia or arthralgia (4), conjunctivitis (3), vomiting (2), taste disturbance (1), smell disturbance (1), meningoencephalitis (1).

^dSpecified in Supplementary Table 1.

^eC-reactive protein in 53 allo-HCT patients with mild course was median (min-max) 3 (0–110) mg/L.

Bold entries indicate significant *p* values.

2022 for the following items: '(COVID OR SARS-CoV 2) AND (children OR adolescents OR pediatric) AND ((stem cell transplantation) OR (bone marrow transplantation)). The prospective EBMT/GETH study summarized data of 382 patients post-HCT, among them 32 children, reported until July 2020 [6]. Survival was presented separately for the pediatric and adult populations, whereas clinical manifestations and mortality risk factors were for the whole study population. Our current research presents data on children post-HCT reported to the EBMT registry from March 2020 until the end of 2021, including the 32 children from the EBMT/GETH study. Comparison of the current pediatric data with the overall EBMT/GETH cohort including predominantly adult population, reveals several differences. Amongst them are a higher

proportion of asymptomatic infections (42% vs. 9%), and a lower proportion of febrile patients and those requiring oxygen to maintain saturation (43 vs. 65% and 11 vs. 35%, respectively) in the current study; the difference between children and adults is probably even bigger, as data on 32 children is included in the EBMT/GETH report [6]. Ten percent of children in our study were admitted to the ICU and 8% died. Mortality rates in the EBMT/GETH study's overall patient population were 23% and 28% in allogeneic and autologous HCT recipients, respectively; survival in children was significantly higher. It should be noted that later in the pandemic, with improved COVID-19 management and effective medications and vaccines, and variant changes, lower mortality rates were observed in adults following HCT (PL, submitted to publication).

Table 3. Factors significantly associated with severe disease course (univariate analysis).

	Total	Events	Cumulative incidence (95% C.I.)	Hazard Ratio (95% C.I.)	P value
Diagnosis					
Malignant disease	52	3	6.12 (1.56–15.32)	1.00	
Non-malignant disease	33	8	26.98 (12.36–44.00)	4.70 (1.25–17.76)	0.02
Lansky (10-point effect)	84	11	-	0.96 (0.92–0.99)	0.01
Chronic GVHD (number of allo-HCT patients with a follow-up > 100 days)					
Yes	<i>n</i> = 12	<i>n</i> = 5	44.44 (13.97–71.59)	9.95 (2.37–41.73)	0.002
No	63	3	4.93 (1.28–12.49)	1.00	
Immunosuppressant drug(s)					
Yes	53	11	22.03 (11.58–34.60)		0.01
No	32	0	0.00		
Corticosteroids					
Yes	24	6	25.00 (9.90–43.57)	3.20 (0.98–10.51)	0.06
No	61	5	9.49 (3.39–19.42)	1.00	
Janus kinase inhibitor					
Yes	13	4	89.17 (78.44–94.73)	3.42 (1.00–11.73)	0.05
No	72	7	69.23 (37.34–87.18)	1.00	
Mycophenolic acid					
Yes	9	5	44.44 (13.59–71.93)	9.80 (2.94–32.62)	0.0002
No	76	6	91.07 (81.04–95.93)	1.00	
Symptomatic					
Yes	52	10	20.44 (10.39–32.86)	7.42 (0.95–58.15)	0.06
No	33	1	3.70 (0.26–16.23)	1.00	
Fever					
Yes	37	9	25.08 (12.28–40.16)	6.80 (1.46–31.61)	0.01
No	47	2	5.29 (0.92–15.81)	1.00	
Cough					
Yes	26	8	32.69 (15.07–51.66)	6.93 (1.83–26.20)	0.004
No	59	3	5.83 (1.46–14.81)	1.00	
Coinfection					
Yes	23	7	31.82 (13.61–51.81)	5.15 (1.50–17.62)	0.009
No	61	4	7.46 (2.31–16.72)	1.00	
C-reactive protein levels, mg/L (10-point effect)					
	63	10	-	1.10 (1.01–1.20)	0.04
Pulmonary radiological findings					
Yes	18	8	45.00 (20.91–66.54)	7.21 (1.91–27.28)	0.004
No	42	3	8.35 (2.01–20.62)	1.00	
Immunodeficiency scoring index					
Low	18	0	100.00		0.002
Intermediate	13	6	53.85 (24.77–75.99)	-	

Bold entries indicate significant *p* values.

Similarly, CIBMTR study including 29 children and 289 adults reported a 22% and 19% mortality rates in allogeneic and autologous HCT recipients, respectively [13]. Another CIBMTR study that summarized data on 135 children following allo-HCT and 32 children following auto-HCT, reported 6% mortality rate and 4% rate of mechanical ventilation [14]. A multicenter Brazilian study found higher mortality rates in children post-HCT—5/24 (21%) [15]—with mortality rates in adults post-HCT comparable with those in the EBMT/GETH study (21/62, 34%). A summary of 54 post-allogeneic pediatric HCT recipients with COVID-19 described in case series and case reports yields figures of 7/27 (26%) ICU admissions and 5/54 (9.3%) mortality [16]. Additional reports on SARS-Cov-2 in children

with cancer, including some HCT recipients, found an 0 to 18% rate of ICU admission, and 0 to 5% mortality rate [17–23]. The rates of the ICU admission and mortality in the Pediatric Oncology COVID-19 Case Report (POCC) registry at the pre-Omicron time period (1584 children registered up to January 2022) were 5% and 7%, respectively, in children with solid tumors; and 8% and 3% in children with hematological malignancies [24]. In another registry, Global Registry of COVID in Childhood cancer, (1814 children registered at November 2022), 8.5% were admitted to the ICU and 3.6% died [25].

The proportion of patients in our study requiring oxygen (11%), as well as in the CIBMTR pediatric study (10%) was considerably

Table 4. COVID-19 in children following HCT: Comparison of the current study to other multicenter studies that reported at least some data on children following HCT (including at least 10 patients).

	Current study	Bhatt TCT 2022 (14)	Daudt BMT 2021 (15)	Zama Ann Hem 2022 (30)	Mukkada Lanc Onc 2021 (22)	Bailey Curr Onc 2022 (16)	Ljungman Leuk 2021 (6)
Location	Multinational EBMT study	North and South America CIBMTR	Brazil	Multicenter Italian study	Multinational Global Registry	Review, 18 case reports and case series	Multinational EBMT study
Study period	March 2020–16th December 2021	March 27 2020 - May 7 2021	29th March–1st September 2020	March 2020–August 2021	15th April 2020–February 2021	Until June 2021	Until 31st July 2020
Patient population	Children post-HCT	Children post-HCT	Children and adults post-HCT	Children with cancer and post-HCT	Children with cancer and post-HCT	Children and adults post-HCT	Children and adults post-HCT
Non-malignant disease proportion	33/89 (37%)	50/135 (37%) in allo-HSCT	11/24 (46%)	8/23 (35%)	12/81 (14.8%)	NA	28/382 (7.3%) (T)
Number of patients	89	167	24 children; 62 adults	153 children, 23/153 post-HSCT	81 children post-HSCT; 1419 children with cancer	54 children; 1285 adults	32 (8.4% <18 years) 350 adults
Median age (min-max) years in children	9 (1–18)	Allo: 15 (range <1-21) Auto: 7 (range 1-21)	6.5 (0–17)	7 (0–17) (T)	8 (IQR 4–13) (T)	0.6–17	9.5 (1.0–16.9)
Males	52 (58%)	106 (64%)	14 (58.3%)	86 (56.2%) (T)	891/1500 (59.4%) (T)	19/30 (63%)	236/382 (61.8%) (T)
HCT type	85 (96%) allo; 4 (4%) auto	135 allo; 32 auto	22 (92%) allo; 2 (8%) auto	19 (83%) allo; 4 (17%) auto	allo and auto, numbers NA	allo	236 allo T (29 children); 146 auto T (3 children)
Time since HCT to COVID (min-max)	7 months (0–181)	Allo: 15 (IQR 7-45); Auto: 16 (IQR 6-59) months	7 (0–216) (T) months	219 (50–3910) days	6/81 (7.4%; <30 days); 13/81 (16%; 31–99 d); 20/81 (24.7%; 100–300 d); 31/81 (38.3%; >300 d); 11/81 (13.6% unknown)	0–41 months	17.9 (–0.9 to 350.3) (T) months
Fever	36/84 (43%)	NA	5 (21%)	40 (75%) (T)	619/1500 (41.3%) (T)	17/30 (57%)	257/382 (67.3%) (T)
Respiratory symptoms	26/85 (31%) cough	NA	URT 10 (42%), LRT 4 (17%)	10 (19%) (T)	356/1500 (23.7%) cough (T)	8/30 (27%) cough	209/382 (54.7%) (cough 209 (54.7%); URT 106 (27.7%) (T)
Diarrhea/Gastrointestinal symptoms	9/84 (11%)	NA	1 (4%)	11 (21%) (T)	152/1500 (10.2%) (T)	3/30 (10%)	52/382 (13.6%) (T)
Asymptomatic	35/85 (41%)	146/167 (87%) mild/asymptomatic	8 (33%)	9/19 (47.4%) allo 3/4 (75%) auto	30/76 (39.5%)	NA	34/382 (8.9%) (T)
Severe disease	9 (10%) ICU care	6/167 (4%) severe disease (mechanical ventilation)	8 (33%) severe/critical	3/23 (13%) moderate/severe/critical; 2/23 (8.7%) ICU	16/76 (21.1%) severe/critical	7/27 (26%) ICU care	80/356 (22.5%) ICU care (T)
Death	7 (8%)	10/167 (6%)	5 (21%)	3/153 (1.9%; due to disease progression), 0/23 in HSCT	83/1500 (6.3%) (T)	5/54 (9.3%)	3/32 (9.4%)
Risk factors for mortality or severe disease	Severe disease course in allo-HCT (ICU/mortality); chronic GVHD, non-malignant disease, immune suppressive treatment; and specifically mycophenolic acid (MMF), moderate risk based on immunodeficiency scoring index (vs. low risk), fever, cough, coinfection, pulmonary radiological findings, low Lansky score, high C-reactive protein levels	45-day survival lower among recipients transplanted in the US centers outside the US and those transplanted between 2014-2020 versus 2000-2013	Mortality: male sex in children; symptomatic infection and Eastern Cooperative Oncology Group Performance Status (ECOG) (T); higher survival in children vs. adults;	Factors associated with moderate, severe, and critical disease: Infections occurring early (<60 days) after the diagnosis or after SCT	Severe disease: low-income or lower-middle-income or upper-middle income country, age 15–18 years vs. younger children, lymphopenia, neutropenia, intensive immune suppressive treatment (among them recent HCT) (T)	NA	No difference in age between the children who died or survived; higher survival in children vs. adults; Mortality (T): older age, higher ISI group, worse performance status. In allo-HCT and auto-HCT separately: older age

EBMT European Blood and Marrow Transplantation Society, CIBMTR Center for International Blood and Marrow Transplant Research, NA non-available for HCT children, URT upper respiratory tract symptoms, LRT low respiratory tract symptoms, ICU intensive care unit, ISI immune suppression index, GVHD Graft versus host disease, T total cohort, including children and adults in the mixed studies; or children following HCT together with children with other diagnoses in the pediatric studies including children with malignant diseases and HCT. Percentages are presented in pediatric population HCT if available; and if not – in total population (T)

lower than the 32% of 87 pediatric cancer patients reported in a review of 20 studies [14, 23]. This is most likely due to the large number of asymptomatic infections in our series.

The proportion of children post-HCT with a severe COVID-19 course is markedly higher than in the general pediatric population. The Centers for Disease Control and Prevention 2021 Morbidity and Mortality Weekly Report (MMWR) reports that 0.8% of 0- to 17-year-olds in the US need ICU care, with a mortality <0.1% [2]. We found a higher proportion of children with radiological evidence of pneumonia (29%) than that reported among SARS-Cov-2 -infected children who sought emergency care in a nationwide Israeli study [26]. These high rates of severe disease due to respiratory viruses in HCT children are not unique to SARS-Cov-2. Similar rates of ICU admission (9–19%) and mortality (1–10%) were reported in children post-HCT infected with other respiratory viruses, such as influenza and respiratory syncytial virus [27–29].

Risk factors for severe COVID-19 disease post HCT are poorly defined in children. Consistent with our data, low performance status was associated with inferior outcomes in the overall EBMT/GETH study cohort, and ongoing immunosuppression increased the risk of ICU admission in allogeneic HCT recipients [6]. In a pediatric CIBMTR study, 45-day survival was lower among recipients transplanted in the centers outside the US and those transplanted between 2014 and 2020 versus 2000–2013 [14]. In a Brazilian study of 62 adults and 24 children, Eastern Cooperative Oncology Group Performance Status and severity of clinical presentation were associated with mortality in the overall study population, and male gender was associated with mortality in children [15]. In contrast to our data, other studies also reported a higher proportion of males among immunocompromised children with severe COVID-19 [15, 17, 19]. Higher risk of severe clinical course in children with non-malignant diseases was not reported previously. Higher rate of T-cell depletion and comorbidities in these children could probably contribute to this, and shall be assessed in the multivariate analysis. In a multicentre Italian study, infections occurring early (<60 days) after the diagnosis or after SCT were associated with higher risk of moderate/severe/critical disease [30]. We, however, did not observe higher rate of severe disease course during the early pre-HCT period. Literature data on factors associated with a severe disease course in immunocompromised children are presented in Table 4. It should be mentioned that mortality in our study was multifactorial, as five out of seven children who died had coinfections that could contribute to adverse outcome.

The median period from HCT to SARS-Cov-2 infection (6 months) in our study is far shorter than that in the overall EBMT/GETH study cohort (17.9 months) and in the CIBMTR reports [6, 13, 14]. This difference is probably attributable to the mild course of pediatric COVID-19 and a high proportion of asymptomatic infections, that could mean that many pediatric SARS-Cov-2 infections occurring late after HCT go undiagnosed or unreported to the HCT center, especially if more time has elapsed since HCT.

Our study has limitations. First, most of the patients included are from the pandemic's early waves, with clinical presentation and outcome sometimes differing with subsequent variants. The patients also represent a large and non-vaccinated cohort and the more widespread use of vaccines also in children both before and after HCT might ameliorate the seriousness of COVID-19 further. Second, our sample size, and, fortunately, low rate of severe disease, precludes multivariate analysis of risk factors, and identification of independent risk factors for a severe disease course in children. Univariate analysis revealed several risk factors, but these results should be interpreted with caution due to small numbers. Third, there are data on treatment only for a minority of children, and we cannot conclude on the correlation between treatment and disease outcome. Fourth, cases were not

consecutively collected but were based on voluntary reporting and hence are subject to reporter bias.

Our study also, however, has important strengths. It represents a large cohort of children infected with SARS-Cov-2 following HCT. Its clinical, laboratory and outcome data are detailed. In addition, it is the first study that has enabled risk factor analysis for a severe clinical course in children with SARS-Cov-2 post-HCT, with potential clinical implications.

To conclude, SARS-Cov-2 following HCT in children was frequently asymptomatic. The rates of ICU admission (10%) and mortality (8%) was lower than in immunocompromised adults; they are, however, higher than those reported in immunocompetent children, and comparable to these risks reported for post-HCT children infected with other respiratory viruses. HCT and underlying disease related factors (non-malignant disease, chronic GVHD, IST and specifically MMF exposure, moderate risk based on immunodeficiency scoring index (vs. low risk), low Lansky score), as well as SARS-Cov-2 related factors (fever, cough, pulmonary radiological findings, high CRP, and coinfections) are associated with ICU admission and mortality in a univariate analysis and should be confirmed in a bigger study.

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AUTHOR CONTRIBUTIONS

Conceptualization and design: DA, PL. Collection and assembly of data: NK. Data analysis: DA, GT. All authors helped with data interpretation, critical review of manuscript, appropriate revisions and approved the final version of the manuscript.

COMPETING INTERESTS

RC: advisor for AstraZeneca in EVUSHELD pre-exposure prophylaxis for SARS-CoV-2. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

ADDITIONAL INFORMATION

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