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MAJOR ARTICLE

SARS-CoV-2 Infection in the Pediatric Oncology Population: The Definitive Comprehensive Report of the Infectious Diseases Working Group of AIEOP

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Objective. The objective of this study was to assess the clinical impact and outcome of the SARS-CoV-2 infection on children with cancer or those who received a hematopoietic stem cell transplantation.

Methods. AIEOP (Italian Association of Pediatric Hematology and Oncology) performed a nationwide multicenter observational cohort study, including consecutive patients between April 2020 and November 2022.

Results. Twenty-five Italian centers participated and 455 patients were enrolled. We reported a significant increasing trend of symptomatic cases over the years, while the number of nonmild infections remained stable. Early infection after oncologic diagnosis (<60 days) and severe neutropenia were identified as independent risk factors for developing moderate, severe, or critical infections. The percentage of patients who were asymptomatic and mildly symptomatic and who stopped chemotherapy reduced over the years of the pandemic. Nine patients died, but no death was attributed to SARS-CoV-2 infection.

Conclusions. SARS-CoV-2 infection presented a self-limiting benign course in the Italian pediatric oncohematology population during the pandemic, and its main consequence has been the discontinuation of cancer-directed therapies. The rate of patients who were asymptomatic and stopped chemotherapy reduced over the years, suggesting that the continuation of chemotherapy is a feasible option.

Keywords. chemotherapy; hematopoietic stem cell transplantation; pediatric hematology; pediatric oncology; SARS-CoV-2.

The network of pediatric hematology and oncology centers belonging to AIEOP (Italian Association of Pediatric Hematology and Oncology) has been tracking SARS-CoV-2 infections and the related disease, named novel coronavirus disease 2019 (COVID-19), from the beginning of the pandemic in pediatric patients with cancer or those who received a hematopoietic stem cell transplantation (HSCT). In comparison with the adult population, children with immunocompetence presented a lower rate of mortality and a lower risk of severe illness, complications, hospitalization, and intensive care unit (ICU) admission from a SARS-CoV-2 infection [1, 2].

Studies conducted in the first months of the pandemic reported rare severe infections and almost no deaths solely

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related to the infection in children with cancer and COVID-19 [3–10]. After these reassuring initial reports, the data collected from larger cohorts of patients have enabled researchers to more precisely define the real risks faced by these children.

The Global Registry of COVID-19 in Childhood Cancer (GRCCC) [11] was created at the beginning of the pandemic, and it collects data from the global community to describe disease severity and identify factors associated with severe SARS-CoV-2 infection in pediatric patients with cancer. By March 2023, GRCCC reported 1814 cases from 51 countries. Among these patients, 10.7% had severe disease, 7.5% were in critical condition, 8.5% were admitted to the ICU, and 3.6% died from COVID-19 [12]. The last update from the Pediatric Oncology COVID-19 Case Report registry, in November 2022, included 2204 patients from 102 sites in the United States; it reported a hospitalization rate of 29% for patients with hematologic malignancies and 21% for patients with solid tumors, as well as ICU admission rates of 6% and 4%, respectively, and a mortality of 4% [13].

Aside from the direct impact that SARS-CoV-2 infection can have on the health of children with cancer, another important consequence of the infection is the discontinuation or delay in the treatment of the original disease [14]. In Mukkada et al study, more than half (55.8%) of the children in their cohort who were infected with the virus received some sort of modification in their treatment regimen: 80% suspended chemotherapy, 13.1% reduced the dosage, 6.6% postponed radiotherapy, and 6.7% postponed surgery [11].

Our report is a summary of the data collected during the years of the pandemic until November 2022 in an attempt to evaluate the characteristics and outcome of SARS-CoV-2 infection in a large Italian pediatric hematology and oncology population. We also considered the change of epidemiology over time due to the outbreak of new viral variants, the introduction of the vaccination, and all the restrictions applied to limit the spread of the infection.

METHODS

The AIEOP Infectious Diseases Working Group performed a multicenter prospective observational analysis of the clinical characteristics, treatment, and outcome of oncology and hematology cases of pediatric patients diagnosed with SARS-CoV-2 infection. Of the 53 centers that belong to the AIEOP network, 25 centers spread throughout the whole national territory participated in this study (16 in the north of Italy, 2 in the middle, and 7 in the south and islands). Each center collected data of all patients with confirmed SARS-CoV-2 infection diagnosed from April 2020 to November 2022. This report also includes 153 patients who were analyzed in the previous AIEOP study dated to May 2021 [15]. The study was approved by the ethics committee of the promoter center (25 May 2020, No. 29064) and subsequently by the local ethics committee of each participating center.

Data collection was performed by each local coinvestigator through an anonymous report for each patient at the moment of infection diagnosis per previous collection of the parents' consent. Patients were included if they were ≤18 years of age; had been treated with chemotherapy and/or other cancer-directed therapies, including radiotherapy, independent of treatment status, or had received HSCT; and were diagnosed with SARS-CoV-2 infection, as confirmed by molecular or antigen testing on nasopharyngeal swabs or bronchoalveolar lavage.

SARS-CoV-2 infections were classified as *asymptomatic* and *symptomatic*, the latter namely COVID-19 and defined by the presence of fever with or without symptoms or signs of the respiratory or gastrointestinal tract or any other organ involvement. Based on the clinical, laboratory, and radiologic characteristics, the severity of COVID-19 was graded as *mild* (upper respiratory or gastrointestinal symptoms) or *nonmild* (lower respiratory tract involvement). This latter subgroup included patients with infections classified according to published criteria: *moderate* (acute lower respiratory tract infection without hypoxemia), *severe* (hypoxia <94% with or without supplementary oxygen), or *critical* (need of ICU or organ support) [16].

In the cohort of patients receiving chemotherapy, SARS-CoV-2 infection was further classified as follows: *early*, if the time of occurrence from the day of diagnosis of the underlying disease and the infection was within 60 days (the time interval usually needed to obtain the remission of the underlying disease); *late*, if >60 days (the period to start the consolidation chemotherapy); and *infection during maintenance*. Maintenance chemotherapy was defined as low-medium intensity chemotherapy that follows the phases of induction and consolidation, as expected in the protocols for acute lymphoblastic leukemia and high-risk rhabdomyosarcoma [17, 18]. Among the HSCT recipients, the SARS-CoV-2 infection was defined as *early* if it occurred within the first 180 days after transplant and *late* if >180 days.

Recorded laboratory findings during the infectious episode included white blood cells and count, hemoglobin, platelets, and lactate dehydrogenase (LDH). Severe neutropenia was defined as an absolute neutrophil count <500/mm^3 and severe lymphopenia as an absolute lymphocyte count <300/mm^3 [11]. Collected data also included the need for hospitalization and for ventilatory, hemodynamic, or renal support; the types of treatments administered (eg, antibiotics, corticosteroids, antivirals, monoclonal antibodies, hyperimmune plasma, immunoglobulins); and the eventual modifications of the base disease treatment, particularly the necessity and timing of chemotherapy discontinuation. The collected data did not include detailed information on the concomitant invasive bacterial and fungal diseases or reactivation of systemic viral infections, except for the need for antibiotic, antiviral, or

Table 1. Demographic and Clinical Characteristics of Patients With SARS-CoV-2 Infection

	No. (%) or Median (Range)			
	Asymptomatic	Symptomatic	Total	*P* Value
Patients	196 (43.1)	259 (56.9)	455 (100.0)	
Sex				.3
Female	80 (40.8)	117 (45.3)	197 (43.3)	
Male	116 (59.2)	141 (54.7)	257 (56.7)	
Age, y	7.0 (0.0–18.0)	9.0 (0.0–18.0)	7.4 (0.0–18.0)	**.004**
Weight, kg	25 (7.9–100)	30 (3.4–100)	27 (3.4–100)	**.02**
Underlying disease				.6
Acute leukemia, myelodysplasia, lymphoma	114 (58.2)	166 (64.1)	280 (61.5)	
Solid tumor	65 (33.2)	74 (28.6)	139 (30.5)	
Histiocytosis	6 (3.1)	7 (2.7)	13 (2.9)	
Nonmalignant disease	11 (5.6)	11 (4.2)	22 (4.8)	
Chemotherapy	164 (83.7)	211 (81.5)	375 (82.4)	.5
Early (<60 d from diagnosis)	32 (19.5)	30 (14.2)	62 (16.5)	.4
Late (>60 d from diagnosis)	84 (51.2)	115 (54.5)	199 (53.1)	
During maintenance	46 (28.0)	66 (31.3)	112 (29.9)	
Diagnosis to infection, d	217 (19–4398)	319 (19–4228)	277 (19–4398)	**.02**
HSCT	32 (16.3)	48 (18.5)	80 (17.6)	
HSCT to infection, d	399 (32–3910)	364 (8–4209)	363 (8–4209)	.8
Allogenic	25 (78.1)	35 (72.9)	60 (75.0)	.6
Autologous	7 (21.9)	13 (27.1)	20 (25.0)	
Immunosuppressive therapy				.7
No	22 (68.7)	30 (62.5)	52 (65)	
Yes	10 (31.3)	18 (37.5)	28 (35)	
At diagnosis				
Neutropenia, <500/mm^3	29 (14.8)	47 (18.2)	76 (16.7)	.3
Lymphopenia, <300/mm^3	12 (12.0)	32 (19.4)	44 (16.6)	.1

Bold indicates $P < .05$.

Abbreviation: HSCT, hematopoietic stem cell transplantation.

antifungal treatments during the episode. Data were also collected on the SARS-CoV-2 vaccination status at the moment of infection, the timing of SARS-CoV-2 testing negativization, and serologic status after the infection. As for the patients who were deceased, the cause of death was determined by the primary caregivers and registered in the patients' medical records.

Statistical Analysis

The main patients' characteristics were reported by descriptive statistics. Median, minimum, and maximum values were used for continuous variables, while absolute and percentage frequencies were used for categorical variables. Comparisons among categorical variables were performed by the chi-square or Fisher exact test, as appropriate, while continuous variables were compared by *t* test or Mann-Whitney test. The identification of factors potentially associated with moderate, severe, or critical infection was performed by logistic regression analysis. The factors assessed were age, gender, weight, type of underlying disease, time of SARS-CoV-2 infection (early, late, maintenance, after HSCT), severe neutropenia, and antifungal prophylaxis, as well as levels of D-dimer, pro-BNP, troponin, and fibrinogen. In the subgroup of patients with SARS-CoV2 infection after the introduction of vaccination, the vaccination state was assessed as a possible impact factor. The median follow-up was computed by reverse Kaplan-Meier methods. $P \leq .05$ was considered statistically significant. All *P* values are 2-sided. All statistical analyses were performed with SAS version 9.4 (SAS Institute).

RESULTS

A total of 518 patients were enrolled, 63 of which did not match the inclusion criteria and were consequently excluded, leaving 455 patients (Supplementary Figure 1). Table 1 shows the main demographic and clinical characteristics according to the presence or not of symptoms. Interestingly, the median age was significantly higher in the group of patients with symptoms.

No significant difference in clinical and demographic features was detected in the asymptomatic and symptomatic groups. Among the 259 (56.9%) patients who were symptomatic, fever was the most common symptom, reported in 60.6% of cases, followed by cough, rhinitis, pharyngitis, and others. Two patients (0.8%) had hemodynamic complications with systemic hypotension and shock. Multisystemic inflammatory syndrome in children was reported in only 1 patient.

Table 2. Blood Count Values in Asymptomatic and Symptomatic Groups at the Beginning of SARS-CoV-2 Infection

	Median (Range)			
	Asymptomatic	Symptomatic	Total	*P* Value
WBC, N × e9/L	2.93 (0.43–424.00)	3.36 (0.01–125.80)	3.07 (0.01–424.00)	.6
Neutrophils, N × 10e9/L	1.30 (0.00–9.79)	1.50 (0–23.98)	1.40 (0–23.98)	.6
Lymphocytes, N × 10e9/L	0.93 (0.00–12.74)	0.85 (0.00–21.80)	0.91 (0.00–21.8)	.4
Monocytes, N × 10e9/L	0.37 (0.00–3.00)	0.36 (0–12.40)	0.37 (0–12.40)	.8
Hemoglobin, g/dL	10.7 (7–15.6)	10.9 (4.5–17.8)	10.8 (4.5–17.8)	.7
Platelets, N × 10e9/L	204.00 (13.00–738.00)	176.00 (2.00–1569.00)	196.00 (2.00–1569.00)	.1
LDH, mU/mL	0.27 (0.15–2.09)	0.28 (0.12–12.91)	0.27 (0.12–12.91)	.6
CRP, mg/dL	0.47 (0.01–106)	1.44 (0–359)	0.93 (0–359)	**.0006**
Troponin, mg/L	6 (0–164)	6 (0–289)	6 (0–289)	.5
Pro-BNP, pg/mL	26 (7–2580)	106 (2–18 095)	64 (2–18 095)	.3
Fibrinogen, mg/dL	293 (52–768)	379 (52–1036)	338 (52–1036)	**.001**
D-dimer, µg/dL	473 (0.15–5690)	966 (0.34–29 520)	816 (0.15–29 520)	**.05**

Bold indicates $P < .05$.

Abbreviations: BNP, brain natriuretic peptide; CRP, C-reactive protein; LDH, lactate dehydrogenase; WBC, white blood count.

Table 3. Symptomatic and Asymptomatic Infections During the Years 2020–2022

	Patients, No. (%)			
	2020	2021	2022	*P* Value
Asymptomatic	63 (66.3)	54 (47.0)	79 (32.2)	<.0001
Symptomatic	32 (33.7)	61 (53)	166 (67.8)	
Mild	26 (81.3)	51 (83.6)	158 (95.2)	.004
Nonmild	6 (18.8)	10 (16.4)	8 (4.8)	

Disease was classified as mild in 235 cases (90.7% among the patients with symptoms) and nonmild in 24 cases (9.3%). This latter group included 3 children with a moderate infection (1.2% among the patients with symptoms), 8 with a severe infection (3.1%), and 13 with a critical infection (5%). Most patients who developed asymptomatic or mildly symptomatic COVID-19 had infected late (>60 days) after diagnosis of the underlying disease (51.9% and 55.7%, respectively) or during maintenance therapy (28.4% and 33.3%), while the majority of patients with moderate, severe, or critical COVID-19 had early infections (47.4%; Supplementary Table 1).

Radiologic investigations were performed in 92 patients (20.2%): in 70 cases, chest radiograph; in 12 cases, lung computed tomography scan; and in 8 cases, chest radiograph and lung computed tomography scan. Blood count assessment at the time of SARS-COV-2 infection did not show any significant quantitative difference between the asymptomatic and symptomatic cohorts in the blood counts, while C-reactive protein ($P = .0006$), fibrinogen ($P = .001$), and D-dimer ($P = .05$) were all statistically higher in symptomatic cases (Table 2).

Over the years, we observed an increasing rate of symptomatic cases vs the asymptomatic ones ($P = .0001$; Table 3). Interestingly, the number of nonmild infections did not increase significantly during the years ($P = .004$).

A total of 154 patients (34.2%) were hospitalized: 45 (29.2%) asymptomatic and 109 (70.8%) symptomatic. Figure 1 depicts the trend over the pandemic years for the percentage of patients with an asymptomatic, mild, or nonmild (moderate, severe or critical) infection who required hospitalization. Patients with a mild infection had the most marked reduction of hospitalization rate during the years.

In the symptomatic group, 20 (7.8%) patients required respiratory support (12 with nasal cannula, 4 with noninvasive ventilation, 4 with invasive ventilation) and 8 (3.1%) were admitted to the ICU. Antibiotics (25.3%) and steroids (9.1%) were the most used therapies, particularly in patients who were symptomatic. Other therapies were antivirals for coronavirus 2 (4.2%), antispike monoclonal antibodies (4.2%), polyclonal immunoglobulins (1.6%), and convalescent plasma (2%).

The course of the infection was generally self-limiting and benign: 9 (2%) patients died, 7 for disease progression and 2 for concomitant sepsis (Supplementary Table 2). In our cohort, no death was solely related to SARS-CoV-2 infection, and the mean time between SARS-CoV-2 infection diagnosis and death was 170 days. Of the 9 patients who were deceased, 2 stopped their chemotherapy, and they both died because of their disease progression. The median time to SARS-CoV-2 negativization on nasopharyngeal swab was 16 days (range, 1–116), with no significant differences between patients who were asymptomatic and symptomatic.

Of the 375 patients undergoing active chemotherapy, 175 (47.2%) withdrew the treatment, 71 (40.6%) were asymptomatic, and 104 (59.4%) were symptomatic for a median 12 days (range, 1–82). Figure 2 shows the percentage of patients with an asymptomatic, mild, or nonmild (moderate, severe, or critical) infection who stopped their chemotherapy over the years of the pandemic.

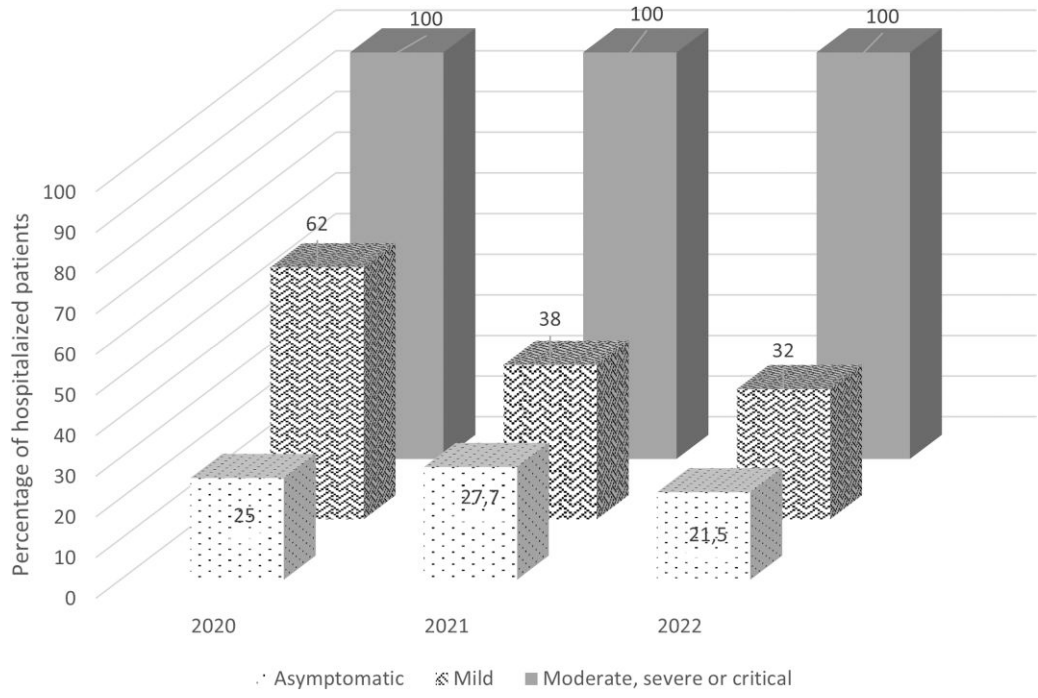

Figure 1. Percentage of patients with asymptomatic, mild, or nonmild (moderate, critical, or severe) infection who required hospitalization, each year of the pandemic.

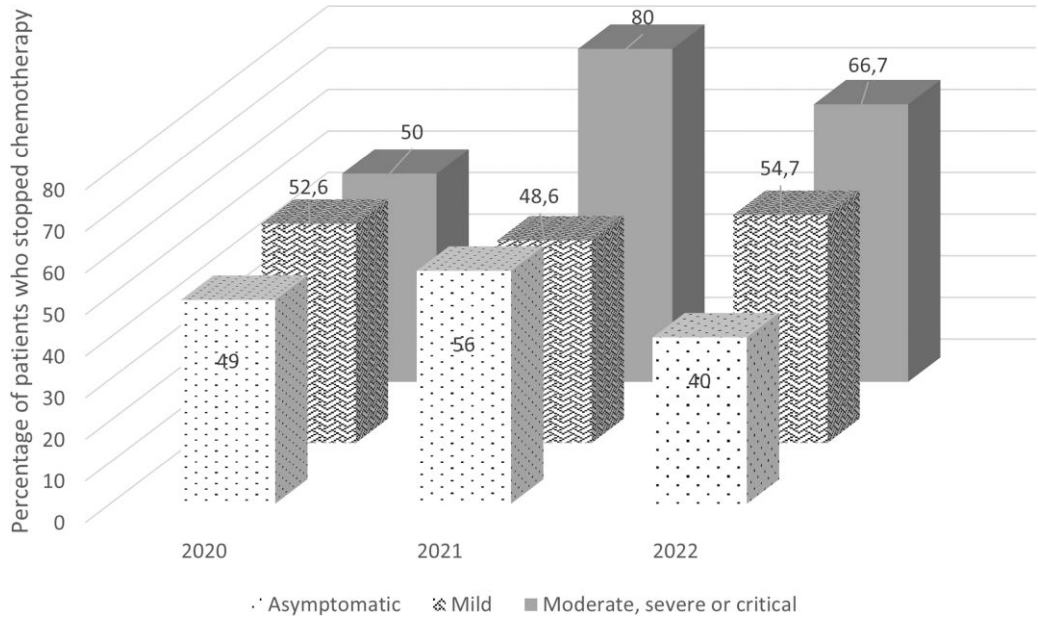

Figure 2. Percentage of patients with an asymptomatic, mild, or nonmild (moderate, severe, or critical) infection who stopped chemotherapy, each year of the pandemic.

Among the 215 patients who were infected after March 2021 and consequently had access to vaccination, only 58 (17.7%) were vaccinated: 9 with 1 dose, 35 with 2 doses, and 5 with 3 doses. Among the vaccinated patients, 56 (96.6%) developed an asymptomatic or mild infection; just 2 (3.4%) developed a moderate or severe infection (both patients received 2 doses). The median time of infection after the vaccine was 21 days (range, 4–179) after the first dose, 102 days (range, 7–296) after the second, and 51 days (range, 13–112) after the third. Among the patients who did not receive a vaccine, 95.7% developed an

Table 4. Univariate Analysis: Factors Associated With Moderate, Severe, or Critical Disease

	No. (%) or Median (Range)		
	Asymptomatic or Mild (n = 431)	Moderate, Severe, or Critical (n = 24)	*P* Value
Sex			.3
Male	241 (93.8)	16 (6.2)	
Female	189 (95.9)	8 (4.1)	
Underlying disease			.1
Leukemia-lymphoma	261 (93.2)	19 (6.8)	
Solid tumor	136 (97.8)	3 (2.2)	
Histiocytosis	12 (92.3)	1 (4.5)	
Nonmalignant hematologic disease	21 (95.5)	0 (0.0)	
Age, y	7.0 (0–18)	11.5 (1–18)	.2
Weight, kg	26.3 (3.4–100.0)	34.0 (9.4–100)	.6
HSCT			.6
Yes	75 (93.8)	5 (6.3)	
No	356 (94.9)	19 (5.1)	
Time between diagnosis/HSCT and infection			**.01**
Early	76 (88.4)	10 (11.6)	
Late	352 (96.2)	14 (3.8)	
Severe neutropenia at diagnosis			**.002**
Yes	66 (98.5)	1 (1.5)	
No	365 (96.6)	13 (3.4)	
Antifungal prophylaxis			**.005**
Yes	39 (84.8)	7 (15.2)	
No	391 (96.1)	16 (3.9)	
LDH, mU/mL	271 (120–2086)	329 (156–12 906)	**.04**
CRP, mg/dL	0.8 (0.0–359.0)	9.6 (0.07–43.4)	**<.0001**
Troponin, mg/L	6 (0–289)	6 (0–93)	.7
Pro-BNP, pg/mL	36 (2–2580)	190 (48–18 095)	**.004**
Fibrinogen, mg/dL	327 (52–797)	529 (282–1036)	**<.0001**
D-dimer, µg/dL	777 (0.15–29 520)	1268 (0.74–7346)	.1

Bold indicates $P < .05$.

Abbreviations: BNP, brain natriuretic peptide; CRP, C-reactive protein; HSCT, hematopoietic stem cell transplantation; LDH, lactate dehydrogenase.

Table 5. Multivariate Analysis: Factors Associated With Moderate, Severe, or Critical Disease

	Odds Ratio (95% CI)	*P* Value
Time between diagnosis/HSCT and SARS-CoV-2 infection		.01
Early	3.28 (1.34–8.03)	
Late	1.00	
Severe neutropenia at diagnosis, <500/mm^3		.002
Yes	4.02 (1.64–9.87)	
No	1.00	

Abbreviation: HSCT, hematopoietic stem cell transplantation.

asymptomatic or mild infection and 4.3% a moderate or severe infection.

We performed univariate analysis to identify factors associated with a nonmild infection (ie, moderate, severe, or critical disease; Table 4). Age, sex, weight, and underlying disease were similar between asymptomatic and mild cases and those with moderate, severe, or critical disease. Patients with early infection from diagnosis (<60 days) or HSCT (<180 days) had higher risk of developing a nonmild infection ($P < .05$). Two other associated factors were severe neutropenia and antifungal prophylaxis at the time of infection ($P < .05$). Multivariate analysis confirmed early infection and severe neutropenia as independent risk factors for developing a moderate, severe, or critical infection (Table 5). Among the laboratory parameters, levels of LDH, C-reactive protein, pro-BNP, and fibrinogen were higher in patients with moderate, severe, or critical infection ($P < .05$).

DISCUSSION

We herein described a prospective cohort of 455 patients collected by the AIEOP Infectious Diseases Working Group regarding the clinical characteristics and outcome of SARS-CoV-2 infections in cases of hematology and oncology among pediatric patients during the pandemic in Italy since the beginning to November 2022 [3, 4, 15].

We collected data from the entire national territory and started the enrollment since the first phase of the pandemic.

In our previous reports, we described a generally benign and self-limiting course of infection in this category of patients, similar to the general pediatric population. In the present report, we expanded the cohort of patients and confirmed this benign clinical course, also considering the change in the epidemiology of the pandemic and the emergence of new viral variants (Supplementary Figure 2) [19, 20].

In our cohort, just 24 patients (5.3% of the total) experienced a moderate, severe, or critical form of COVID-19, while the majority were asymptomatic or had only mild symptoms. These data are consistent with our previous studies that analyzed smaller cohorts of patients during the first 3 waves of the pandemic until May 2021 [3–7]. According to our data, it seems that the percentage of symptomatic infections increased over the years of the pandemic, while the percentage of moderate, severe, or critical infections remained stable. This probably is in line with the observation that more recent SARS-CoV-2 variants have a greater contagiousness but, at the same time, a tendency to cause mildly symptomatic infections [8, 9].

In our study, the most frequently reported symptoms were the well-known fever, rhinitis, cough, pharyngitis, and gastrointestinal symptoms such as vomiting and diarrhea. Twenty patients (7.8%) needed oxygen and 8 (3.1%) were admitted to the ICU. Hospitalization rates for patients with mildly symptomatic infections were 62% in 2020, 38% in 2021, and 32% in 2022. This significant reduction derives from a progressive confidence in treating this type of patient at home, supported by advancing knowledge of the characteristics of the course of this infection.

No death was solely associated to SARS-CoV-2 infection during the entire observational period: out of the 9 patients who were deceased, 7 died because of their underlying disease progression and 2 died with concomitant sepsis.

In our experience, rates of severe infection, ICU admission, and mortality were lower than those reported by Mukkada et al in the GRCCC [11]. At the March 2023 update, severe or critical illness was reported in 330 of 1814 patients (18.2%) with a mortality rate of 3.6%, higher than the general pediatric population. However, other studies reported variable results, with severe infection ranging from 6.6% to 21% and mortality from 0% to 10%, likely depending on the socioeconomical context of the country [21, 22].

C-reactive protein and fibrinogen levels were the only laboratory factors associated with the presence of symptoms, which are the expression of a stronger inflammatory response related to the infection. In addition, severe neutropenia at diagnosis and levels of LDH, C-reactive protein, pro-BNP, and fibrinogen were associated to moderate, severe, or critical disease, which is in line with previous reports [11, 23]. The timing of infection is also related to the development of moderate, severe, or critical disease in patients with COVID-19. Patients who experienced COVID-19 early after the diagnosis/beginning chemotherapy or early after HSCT have a higher risk of developing moderate, severe, or critical disease, potentially due to a higher immunosuppression level and an increased susceptibility to severe respiratory complications. At the multivariate analysis, severe neutropenia and an early infection after diagnosis/HSCT were confirmed as the only risk factors for developing moderate, severe, or critical forms of infection. These findings align with those from global studies that identified lymphopenia, neutropenia, active treatment, and HSCT as the main risk factors for developing severe infection in this population [11, 23, 24].

Our attention is now focused on the high percentage of patients undergoing chemotherapy withdrawal. The discontinuation of cancer-directed therapies represents a serious concern for the pediatric oncologic global community [25]. In the aforementioned GRCCC study, factors associated with treatment change were different from those associated with severity of disease [11]. The mild course of the disease described in our cohort suggests that we consider regular continuation of the scheduled therapy, particularly in patients undergoing low- to medium-intensity chemotherapy, consolidation chemotherapy, and maintenance therapy or in patients infected late after diagnosis of the underlying disease. National and international recommendations on the possible continuation of cancer therapy in patients with hematologic malignancies during SARS-CoV-2 infection have also recently been published [9, 26].

Our data are encouraging, with a gradually and constantly reducing rate of patients who were asymptomatic and stopped chemotherapy during the years of the pandemic. In any case, further studies are still necessary to properly investigate the impact of the pandemic on therapy delay and the possibility to continue cancer-directed therapy in specific conditions, as in patients with a mild course of the disease or those with a high risk of relapsing disease, perhaps with the concomitant use of specific antiviral drugs.

The limited number of patients who underwent vaccination in our cohort did not allow us to draw any significant conclusion regarding its efficacy in the prevention of severe forms of infection. Regarding its safety, no patient who was vaccinated in our cohort developed moderate or severe adverse reactions to the vaccine.

Further studies are needed to implement the knowledge on specific clinical features that can represent a relevant issue in children with cancer, such as multisystemic inflammatory syndrome in children, immune-mediated hematologic manifestations, and coagulative disorders [27–29].

CONCLUSION

We reported a benign course of SARS-CoV-2 infection in cases of oncology and hematology among pediatric patients during the first 3 years of the pandemic in Italy. In particular, in our

large and nationwide cohort, no deaths were solely correlated to SARS-CoV-2 infection.

We argue that the main consequence of COVID-19 in this category of patients was the modification of their underlying disease treatment, in particular the discontinuation of cancer-directed therapies such as chemotherapy, with a possibly negative impact on the dose intensity of treatment (cumulative dose of chemotherapy/time) and consequently their general outcome. Specific recommendations on treatment and management on oncohematologic cases of pediatric patients who are infected with SARS-CoV-2 would be helpful at shepherding the clinician's decision over the continuation or withdrawal of cancer-directed therapies.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online (http://jid.oxfordjournals.org/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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