Evaluation of Possible Effects of the COVID-19 Pandemic on Febrile Neutropenia Episodes in Children With Acute Leukemia

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Summary: With the rapid spread of coronavirus disease 2019 (COVID-19) around the globe, concerns about the management of patients with malignancy have risen significantly. This study aimed to investigate the possible impact of the COVID-19 pandemic and prevention policies on the incidence and etiology of febrile neutropenia (FN) episodes in children with acute leukemia. Children who had acute leukemia and were diagnosed as FN in a tertiary center from March 2018 to March 2021 were included in the study. FN episodes were grouped as prepandemic and postpandemic based on the date that pandemic was declared. Relevant data were collected retrospectively. We evaluated 113 FN episodes (75.2% were prepandemic) of 46 patients, a median of 4.7 (2.6 to 12.6) years of age. The number of FN episodes per patient did not differ between prepandemic and postpandemic periods ($P = 0.476$). There was no significant difference among the 2 groups regarding the microbiologic causes, focus of fever, and clinical outcomes in FN episodes. Two of the patients were diagnosed as COVID-19 and recovered without any complications. In conclusion, we showed that the incidence and etiology of FN episodes were similar before and during the COVID-19 pandemic in children with acute leukemia.

Key Words: neutropenic fever, pediatrics, COVID-19

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Febrile neutropenia (FN) is one of the most common and fatal complications in pediatric patients with acute leukemia. It is an emergent clinical condition that requires immediate empirical antibiotic treatments in those individuals. FN causes prolonged hospitalization, increased risk of nosocomial infections, a delay in chemotherapy schedule, and even mortality.[1,2]

With the rapid spread of coronavirus disease 2019 (COVID-19) around the globe, concerns about the management of patients with malignancies and the possible impacts of this pandemic on those patients have arisen significantly.[3] Management of complications such as FN is particularly important to physicians and it is aimed to reduce the risk of infection and hospitalization in children with acute leukemia during the pandemic.[4] By this period, extraordinary measures such as wearing a mask, physical distance, strict hand hygiene, and stay-at-home orders were carried out all over the world to prevent the extension of COVID-19.[5] These policies can affect the transmission of not only severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) but also the other respiratory viruses or infections.[6] Considering the preventive measures, it is still unclear whether there has been a change in the frequency of bacterial or viral agents in the etiology of FN in the pandemic.

In this study, we aimed to investigate the possible impact of the COVID-19 pandemic and prevention policies on the incidence and etiology of FN episodes in children with acute leukemia.

MATERIALS AND METHODS

Patients diagnosed as FN in a tertiary center from March 2018 to March 2021, who were under 18 years of age and had acute leukemia, were included in the study. All phases of chemotherapy protocols including induction, consolidation, maintenance, and re-induction were evaluated retrospectively in all children from the medical records of the patients. FN episodes were grouped as prepandemic and postpandemic according to the period they observed, based on the date of March 11, 2020, that pandemic was declared. Relevant data were compared among the 2 groups.

FN was determined with an absolute neutrophil count of $< 500/mm^3$ or between 500 and $1000/mm^3$ and an expected absolute neutrophil count to decrease below $500/mm^3$ within 24 to 48 hours, in those with a fever as a single temperature of $\geq 38.3°C$ (101°F) or $\geq$ 38.0°C (100.4°F) sustained over an hour.[7] An FN episode was defined as the time from when the FN criteria were met, to the time that antibiotic treatment was discontinued, the patient was discharged, or chemotherapy was restarted whichever occurred earlier. According to this definition, FN episodes might be ended despite ongoing neutropenia, and a second FN episode could be diagnosed within a single neutropenia period.[8]

Fever without a known source was defined as failure to find a focus of fever with clinical and laboratory examinations. Bacterial agents were detected in blood, urine, and stool cultures. A bloodstream infection (BSI) was defined as bacterial growth in at least 1 blood culture. Identification for the agent was performed using an automated culture system (VITEK). Members of normal skin flora such as *Coagulase-negative staphylococci* (*CoNS*) were considered causative

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agents when isolated in at least two cultures.[9] A catheter-associated bloodstream infection (CLABSI) was defined according to The Clinical Practice Guidelines for the Diagnosis and Management of Intravascular Catheter-Related Infection, published in 2009.[10]

Viral agents were detected regarding a positive polymerase chain reaction test (PCR) result for herpes simplex virus-1, and -2 (HSV1-2), or using a reverse transcription PCR test (RT-PCR) for respiratory agents. Respiratory viruses (influenza, parainfluenza, respiratory syncytial virus [RSV], human metapneumovirus, seasonal coronavirus, rhinovirus, enterovirus, parechovirus, adenovirus, bocavirus) were studied from a nasopharyngeal swab sample. An RT-PCR for SARS-CoV-2 was tested on the nasopharyngeal swab, in all FN episodes after the pandemic.

Fungal infections were investigated in those with persistent fever and neutropenia lasting for more than 96 hours under broad-spectrum antibiotics. Invasive fungal disease (IFD) was evaluated by; (i) histopathologic, cytopathologic, or direct microscopic examination of a specimen obtained by needle aspiration or biopsy; (ii) culture from a sterile material from a clinically or radiologically abnormal site consistent with an infectious disease process; (iii) blood culture; (iv) radiologic and clinical findings; (v) other mycological evidence such as galactomannan antigen test. Using these criteria, IFD was classified as possible, probable, and proven according to the consensus.[11] Empirical antifungal therapy was initiated after 96 hours of fever without a known source and that was unresponsive to broad-spectrum antibacterial agents. Either liposomal amphotericin or caspofungin was used for this purpose.[12]

Polymicrobial infection was defined by the detection of more than 1 agent microbiologically.

Empirical therapy was admitted using an anti-pseudomonal penicillin agent or a carbapenem as monotherapy. A second-line treatment including antibiotics for gram-negative agents or a glycopeptide was used for clinically unstable patients or when a resistant infection was suspected.[13]

Severe complications were described as follows; a need for supplemental oxygen, hypotension, shock state, admission to the intensive care unit, a need for mechanical ventilation, and death.[14]

Ethics

This study was approved by the local ethics committee and performed according to the principles of the Declaration of Helsinki. An informed written consent form was not obtained because of the retrospective nature of the study.

Statistical Analysis

All statistical analyses were performed using the SPSS application for Windows version 24.0 (IBM Co., Armonk, NY). The distribution of data was evaluated using the Kolmogorov-Smirnov test. Clinical data were presented as counts and percentages, or medians with the respected 25 to 75th percentile values. Comparisons of medians were performed using the Mann-Whitney U test. The Pearson χ^2 test, or the Fisher exact test if any expected cell size numbered <5, was used for the comparison of categorical data. A P-value of <0.05 was considered statistically significant.

RESULTS

We evaluated 113 FN episodes (75.2% were prepandemic) of 46 patients (47.8% were female), a median of 4.7 (2.6 to 12.6) years old. The most common underlying disease was acute lymphoblastic leukemia (ALL) in 69.9% of the patients.

TABLE 1. Baseline Clinical Characteristics of Febrile Neutropenia Episodes in Children With Acute Leukemia in Prepandemic and Postpandemic Periods

	Prepandemic (n = 85, 75.2%), n (%)	Postpandemic (n = 28, 24.8%), n (%)	*P*
Underlying malignancy			
ALL	55 (64.7)	24 (85.7)	0.036
AML	30 (35.3)	4 (14.3)	
The number of episodes per patient	2 (1-3)	2 (1-3)	0.476
Duration of febrile days	2 (2-5)	2 (1-5)	0.385
Duration of neutropenia	16 (10-29)	12 (7-22)	0.142
Presence of a central venous catheter	48 (56.5)	27 (96.4)	**<0.001**
Administration of G-CSF	39 (45.9)	15 (53.6)	0.512
Mucositis	33 (38.8)	14 (50)	0.298
Fever without a known source	34 (40)	11 (39.3)	0.947
The frequency of bacterial agents	24 (28.2)	12 (42.9)	0.150
The frequency of viral agents	21 (24.7)	3 (10.7)	0.116
The frequency of fungal disease	7 (8.2)	4 (14.3)	0.461
Polymicrobial infection	3 (3.5)	3 (10.7)	0.160
Presence of resistant organisms	12 (14.1)	3 (10.7)	0.645
Duration of antibiotic therapy (days)	12 (7-21)	10.5 (7-18.5)	0.734

Data were given as median (25-75p) for continuous variables.
Bold value indicates $P < 0.05$.
ALL indicates acute lymphoblastic leukemia; AML, acute myeloid leukemia; FN, febrile neutropenia; G-CSF, granulocyte colony-stimulating factor.

FN episodes in the postpandemic period were more frequent in children with ALL than those with acute myeloid leukemia ($P = 0.036$). Remission rates and risk groups were similar between the 2 groups ($P = 0.689$ and 0.054, respectively) (Table 1). 34.1% of the episodes before the pandemic and 50% after the pandemic were diagnosed by admission to the outpatient clinic ($P = 0.133$), whereas the remaining ones were already hospitalized. The number of FN episodes per patient did not differ among the 2 groups ($P = 0.476$). Baseline clinical characteristics of the episodes were shown in Table 1. Although a mild increase in the frequency of bacterial agents and a slight decrease in the frequency of viral agents were found at the postpandemic period, this did not account for a statistically significant difference ($P = 0.150$ and 0.116, respectively). Similarly, the incidence of IFD was similar in both groups (8.2% vs. 14.3%, $P = 0.461$).

While the most common focus of fever in FN episodes was respiratory tract and BSI in the prepandemic period; BSI and urinary tract infection were found as the most common ones in the postpandemic period, respectively. However, there was no significant difference between the 2 groups regarding the focus of fever, clinical diagnoses, and complications in FN episodes (Table 2). Mortality was observed in only 1 patient because of the underlying disease in the postpandemic period.

Isolated bacterial agents in FN episodes were presented in Table 3. Among them, *Enterobacteriaceae* spp. was the most common etiologic cause in either prepandemic and

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TABLE 2. The Comparison of Focus of Fever, Clinical Diagnoses, and Complications in Febrile Neutropenia Episodes of Children With Acute Leukemia in Prepandemic and Postpandemic Periods

	Prepandemic (n = 85, 75.2%), n (%)	Postpandemic (n = 28, 24.8%), n (%)	*P*
Lower respiratory tract infection	13 (15.3)	1 (3.6)	0.183
Upper respiratory tract infection	10 (11.8)	1 (3.6)	0.287
UTI	8 (9.4)	4 (14.3)	0.488
BSI			
non-CLABSI	5 (5.9)	5 (17.9)	0.117
CLABSI	4 (4.7)	3 (10.7)	0.362
Acute gastroenteritis	4 (4.7)	1 (3.6)	1.000
Others	4 (4.7)	2 (7.2)	0.636
Complications			
Need of supplemental oxygen	7 (8.2)	2 (7.1)	1.000
Need of mechanical ventilation	2 (2.4)	0	1.000
Shock state	4 (4.7)	0	0.570
Followed-up at the intensive care unite	4 (4.7)	1 (3.6)	1.000
Death	0	1 (3.6)	0.248

BSI indicates bloodstream infections; CLABSI, catheter-associated bloodstream infections; UTI, urinary tract infections.

postpandemic periods. When we documented viral respiratory tract pathogens; the most frequent ones were Rhinovirus, RSV, and Parainfluenza before the pandemic, while SARS-CoV-2, Rhinovirus, and Adenovirus after the pandemic, respectively (Table 4). One of the patients diagnosed as COVID-19 was a 12-year-old girl with high-risk ALL, who presented with fever and diarrhea. She recovered without any complications after 21 days of hospitalization. The other patient was a 12-year-old girl with high-risk acute myeloid leukemia. She received hydroxychloroquine treatment for 5 days and was discharged without complications after 12 days of hospitalization. Both patients did not have any sign of pneumonia and did not need oxygen support. Regarding other viral pathogens, HSV1 was confirmed in only 1 patient in the prepandemic period.

TABLE 3. The Distribution of Isolated Bacterial Pathogens in Infections With a Documented Focus of Fever in Febrile Neutropenia Episodes of Children With Acute Leukemia in Prepandemic and Postpandemic Periods

	Prepandemic (n = 24 for Those With Positive Blood Cultures), n (%)	Postpandemic (n = 12 for Those With Positive Blood Cultures), n (%)	*P*
Gram-negative bacteria	19 (22.3)	9 (32.1)	0.298
Enterobacteriaceae spp.	14 (16.5)	6 (21.4)	0.574
Escherichia coli	8 (9.4)	4 (14.3)	0.488
Klebsiella spp.	5 (5.9)	2 (7.1)	1.000
Salmonella spp.	1 (1.2)	0	1.000
Pseudomonas aeruginosa	4 (4.7)	0	0.570
Stenotrophomonas maltophilia	1 (1.2)	1 (3.6)	0.436
Ralstonia piketti	0	2 (7.1)	0.060
Gram-positive bacteria	5 (5.8)	3 (10.7)	0.407
Coagulase-negative staphylococci	4 (4.7)	1 (3.6)	1.000
Enterococcus spp.	0	2 (7.1)	0.060
Streptococcus viridans	1 (1.2)	0	1.000

Percentages were calculated according to the whole groups (n = 85 and n = 28 for prepandemic and postpandemic periods, respectively).

TABLE 4. The Distribution of Isolated Viral Pathogens in Infections With a Documented Focus of Fever in Febrile Neutropenia Episodes of Children With Acute Leukemia in Prepandemic and Postpandemic Periods

	Prepandemic (n = 85, 75.2%), n (%)	Postpandemic (n = 28, 24.8%), n (%)	*P*
Rhinovirus	12 (14.1)	1 (3.6)	0.180
RSV	3 (3.5)	0	0.573
Parainfluenza	3 (3.5)	0	0.573
Bocavirus	2 (2.4)	0	1.000
Seasonal coronavirus	1 (1.2)	0	1.000
Human metapneumovirus	1 (1.2)	0	1.000
Adenovirus	0	1 (3.6)	0.248
SARS-CoV-2	0	2 (7.1)	0.060

Two viral agents were found together in 2 and 1 episodes in prepandemic and postpandemic periods, respectively.

RSV indicates respiratory syncytial virus; SARS-CoV-2, severe acute respiratory syndrome.

Two of 7 IFD in the prepandemic and 3 of 4 IFD in the postpandemic period were classified as proven. Both 2 proven IFD were caused by *Aspergillus* spp. before the pandemic, while *Candida* spp., *Aspergillus* spp., and *Blastoschizomyces capitatus* were observed after the pandemic.

DISCUSSION

We evaluated 113 FN episodes of children with acute leukemia in 2 groups as before (75.2%) and after (24.8%) the COVID-19 pandemic, to find out possible impacts of this extraordinary period on these episodes. By this study, we demonstrated that frequencies of FN episodes per patient, etiologic causes, and clinical courses of FN episodes were similar in both prepandemic and postpandemic timeframes in the pediatric population.

FN is one of the most common and mortal complications that requiring urgent empirical antibiotic therapy in pediatric patients with malignancy.[2] It is known that approximately half of the children with cancer who received chemotherapy experience at least 1 FN episode.[15] Zermatten et al[16] reported the median number of FN episodes per patient with malignancy in childhood as 2. Management of patients with cancer such as acute leukemia is particularly important to physicians during this pandemic, especially in pediatrics.[4] Some new preventive measures started to take an important place in our daily lives to reduce the spread of COVID-19. The most widely accepted ones are strict hand hygiene, wearing a mask, physical distance, and stay-at-home orders.[5] Several studies demonstrated that the frequency and etiology of some diseases changed in children during this period.[17,18] However, it is still unknown that how this pandemic affects children with malignancy and whether it has an impact on related complications about

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their diagnosis.[19,20] In our study, the frequency of FN episodes per patient was consistent with the previous literature data and it was similar in the 2 groups. This result may be related to the fact that patients with malignancy had already been wearing masks and paying attention to hygiene or isolation rules before the pandemic occurred.

Demonstrating the focus of fever can be challenging in most FN episodes in children with malignancy. Regarding this, fever without a known source was reported in 22% to 79% of FN episodes in those individuals.[1,2,21–24] Costagnola et al[22] showed that fever without a known source was the most common diagnosis in those patients, followed by documented BSI, gastrointestinal tract infections, skin and soft tissue infections, and respiratory tract infections. Likewise, we found fever without a known source as the most common cause of fever in FN episodes of children with acute leukemia in both prepandemic and postpandemic periods. Also, other clinical diagnoses for the focus of fever in those patients were similar among the 2 groups. For the effective treatment of patients diagnosed as FN, it is substantial to identify microbiologic agents during fever.[22] However, in the literature, most of the infections in those individuals could not be confirmed microbiologically.[2] Bacterial agents are the most common organisms detected in children with FN, with an incidence ranging between 10% and 20%.[7,22,25] According to the recently published data, *Enterobacteriaceae* spp. (*Escherichia coli*, *Klebsiella* spp., *Enterobacter* spp.) and *CoNS* were reported as the most common organisms in pediatric patients with FN.[22,26] We found that the frequency and distribution of bacterial agents before and after the pandemic did not differ significantly in each other. Our findings were compatible with the literature data and a previous study from our center.[27] These findings showed that the COVID-19 pandemic did not appear to be affecting the focus of fever or even causative bacterial agents in FN episodes of children with acute leukemia. This may be related to that, bacterial infections in these patients are mostly caused by invasive procedures and their own intestinal and skin floras, rather than environmental contamination. Therefore, they may not be affected by the measures taken in the pandemic. In addition, the frequency of fungal agents, which corresponds to a small proportion in the etiology of FN episodes in children (with a range of 2% to 37%), were similar in the 2 groups of our study.[21,28–30] This result can also be explained by the fact that IFDs also stem from patients' floras or nosocomially.

Considering viruses in the etiology of FN episodes in children, varying results up to an incidence of 76% have been reported in the literature.[1,31–34] The estimated incidence of respiratory viruses has a wide range because of the variability in screening and diagnostic methods as well as study designs. Respiratory viral agents such as influenza and parainfluenza virus, RSV, adenovirus, rhinovirus, coronavirus, and rarely human metapneumovirus or bocavirus are known to play a role in those infections.[35] Pathogens other than respiratory tract viruses, such as EBV, VZV, and HSV also can cause serious illness in pediatric patients with FN, which may be caused by initial contact with the virus or reactivation of the virus because of immunosuppressive conditions.[36,37] Rhinovirus was shown to be the most common virus detected in patients with respiratory tract infections and was reported in 33.9% of children with leukemia.[38,39] To reduce the transmission of viral respiratory agents, it is important to carry out a series of measures such as paying attention to hand hygiene, screening family members for respiratory symptoms, educating the health care staff, and isolating the patients with respiratory symptoms.[40,41] Because of the COVID-19 pandemic, these preventive measures have taken an important place in our daily lives. As a result, some researchers reported a significant reduction in viral infectious diseases in the general pediatric population after the pandemic such as cold, gastroenteritis, and bronchiolitis, which are all spread by droplet and close contact.[42–44] In our study, the incidence of viral infections before and after the pandemic was similar and the distribution of confirmed viral agents was consistent with the previous literature. The reason for a lack of reduction in these infections may be that children with cancer had already been following the relevant isolation and hygiene rules before the pandemic.

The COVID-19 incidence of our center was reported as 13.4% in a recently published study,[45] which was similar to other reports from different regions of our country.[46,47] Slightly below these ratios, we observed an incidence of COVID-19 as 7.1% in the postpandemic period among FN episodes of children with acute leukemia. On the basis of the scientific evidence published to date, it is still unknown whether the COVID-19 infection increases the risk of serious outcomes in pediatric patients with cancer. A meta-analysis demonstrated no association between the COVID-19 infection and mortality rates in children with malignancy.[48] Supporting these findings, our 2 patients with COVID-19 infection did not need any supplemental oxygen and recovered without any complications. This may be related to the recent thoughts that children are less experience severe disease with this novel virus, because of an unknown pathophysiological mechanism. Therefore, the management of COVID-19 as a cause of FN in pediatric patients with acute leukemia may not differ from other individuals. However, there is a need for future prospective studies with large cohorts and guidelines including recommendations to manage COVID-19 infections in such special patient groups.

To the best of our knowledge, this is the first study to evaluate the possible impacts of the COVID-19 pandemic on FN episodes in children with acute leukemia. However, there are several limitations to be noted. First of all, this was a retrospective study and we included a small number of patients. Although it is hard to make a precise conclusion with such a limited sample size, there is an urgent need for reports regarding the effects of this pandemic to guide future studies. Randomized-controlled prospective trials with larger cohorts are needed to elucidate the underlying mechanisms between measures related to the COVID-19 pandemic and infections caused by varying agents in pediatric patients with cancer.

In conclusion, we showed that the incidence and etiology of FN episodes were similar before and during the COVID-19 pandemic in children with acute leukemia. This result might be explained by the fact that similar preventive rules had already been taken by the patients with malignancy before the pandemic came into our lives. In addition, the possible reason for the lack of change in the etiology of FN might be that FN is mostly caused by bacterial pathogens which usually stem from the own floras of patients or nosocomially.

REFERENCES

1. Meena JP, Brijwal M, Seth R, et al. Prevalence and clinical outcome of respiratory viral infections among children with

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cancer and febrile neutropenia. *Pediatr Hematol Oncol*. 2019; 36:330–343.
2. Hakim H, Flynn PM, Knapp KM, et al. Etiology and clinical course of febrile neutropenia in children with cancer. *J Pediatr Hematol Oncol*. 2009;31:623–629.
3. Minotti C, Tirelli F, Barbieri E, et al. How is immunosuppressive status affecting children and adults in SARS-CoV-2 infection? A systematic review. *J Infect*. 2020;81:e61–e66.
4. Bochennek K, Luckowitsch M, Lehrnbecher T. Recent advances and future directions in the management of the immunocompromised host. *Semin Oncol*. 2020;47:40–47.
5. Susana Rodríguez M. Bronchiolitis in the year of COVID-19. *Arch Argent Pediatr*. 2020;118:222–223.
6. Fricke LM, Glöckner S, Dreier M, et al. Impact of non-pharmaceutical interventions targeted at COVID-19 pandemic on influenza burden—a systematic review. *J Infect*. 2020;82:1–35.
7. Freifeld AG, Bow EJ, Sepkowitz KA, et al. Infectious Diseases Society of America. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 Update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2011;52:56–93.
8. von Allmen AN, Zermatten MG, Leibundgut K, et al. Pediatric patients at risk for fever in chemotherapy-induced neutropenia in Bern, Switzerland, 1993-2012. *Sci Data*. 2018;5:180038.
9. Wisplinghoff H, Seifert H, Wenzel RP, et al. Current trends in the epidemiology of nosocomial bloodstream infections in patients with hematological malignancies and solid neoplasms in hospital in the United States. *Clin Infect Dis*. 2003;36:1103–1110.
10. Mermel LA, Allon M, Bouza E, et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 Update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2009;49:1–45.
11. Donnelly JP, Chen SC, Kauffman CA, et al. Revision and Update of the Consensus Definitions of Invasive Fungal Disease From the European Organization for Research and Treatment of Cancer and the Mycoses Study Group. Education and Research Consortium. *Clin Infect Dis*. 2020;71:1367–1376.
12. Groll AH, Pana D, Lanternier F, et al. 8th European Conference on Infections in Leukaemia: 2020 guidelines for the diagnosis, prevention, and treatment of invasive fungal diseases in paediatric patients with cancer or post-haematopoietic cell transplantation. *Lancet Oncol*. 2021;22:e254–e269.
13. Lehrnbecher T, Robinson P, Fisher B, et al. Guideline for the management of fever and neutropenia in children with cancer and hematopoietic stem-cell transplantation recipients: 2017 update. *J Clin Oncol*. 2017;35:2082–2094.
14. Ortega M, Rovira M, Almela M, et al. Bacterial and fungal bloodstream isolates from 796 hematopoietic stem cell transplant recipients between 1991 and 2000. *Ann Hematol*. 2005; 84:40–46.
15. Zhang J, Wang X, Jia X, et al. Risk factors for disease severity, unimprovement, and mortality in COVID-19 patients in Wuhan, China. *Clin Microbiol Infect*. 2020;26:767–772.
16. Zermatten MG, Koenig C, von Allmen A, et al. Episodes of fever in neutropenia in pediatric patients with cancer in Bern, Switzerland, 1993-2012. *Sci Data*. 2019;6:180304.
17. Vukomanovic VA, Krasic S, Prijic S, et al. Differences between pediatric acute myocarditis related and unrelated to SARS-CoV-2. *Pediatr Infect Dis J*. 2021;40:e173–e178.
18. Van Brusselen D, De Troeyer K, Ter Haar E, et al. Bronchiolitis in COVID-19 times: a nearly absent disease? *Eur J Pediatr*. 2021;180:1969–1973.
19. Balduzzi A, Brivio E, Rovelli A, et al. Lessons after the early management of the COVID-19 outbreak in a pediatric transplant and hemato-oncology center embedded within a COVID-19 dedicated hospital in Lombardia, Italy. Estote parati. *Bone Marrow Transplant*. 2020;10:1–6.
20. Dong Y, Mo X, Hu Y, et al. Epidemiology of COVID-19 among children in China. *Pediatrics*. 2020;145:e20200702.
21. Ariffin H, Navaratnam P, Lin HP. Surveillance study of bacteraemic episodes in febrile neutropenic children. *Int J Clin Pract*. 2002;56:237–240.
22. Castagnola E, Fontana V, Caviglia I, et al. A prospective study on the epidemiology of febrile episodes during chemotherapy-induced neutropenia in children with cancer or after hemopoietic stem cell transplantation. *Clin Infect Dis*. 2007;45:1296–1304.
23. Lehrnbecher T, Varwig D, Kaiser J, et al. Infectious complications in pediatric acute myeloid leukemia: analysis of the prospective multi-institutional clinical trial AML-BFM 93. *Leukemia*. 2004;18:72–77.
24. Meena JP, Gupta AK, Seth R. Outcomes of febrile neutropenia in children with cancer managed on an outpatient basis: a report from Tertiary Care Hospital from a resource-limited setting. *J Pediatr Hematol Oncol*. 2020;42:467–473.
25. Lee JH, Kim SK, Kim SK, et al. Increase in antibiotic-resistant gram-negative bacterial infections in febrile neutropenic children. *Infect Chemother*. 2016;48:181–189.
26. Mikulska M, Viscoli C, Orasch C, et al. Aetiology and resistance in bacteraemias among adult and paediatric haematology and cancer patients. *J Inf Dis*. 2014;68:321–331.
27. Yilmaz S, Oren H, Demircioğlu F, et al. Assessment of febrile neutropenia episodes in children with acute leukemia treated with BFM protocols. *Pediatr Hematol Oncol*. 2008;25:195–204.
28. Aytaç S, Yildirim I, Ceyhan M, et al. Risks and outcome of fungal infection in neutropenic children with hematologic diseases. *Turk J Pediatr*. 2010;52:121–125.
29. Bakhshi S, Padmanjali KS, Arya LS. Infections in childhood acute lymphoblastic leukemia: an analysis of 222 febrile neutropenic episodes. *Pediatr Hematol Oncol*. 2008;25:385–392.
30. Gupta A, Singh M, Singh H, et al. Infections in acute myeloid leukemia: an analysis of 382 febrile episodes. *Med Oncol*. 2010;27:1037–1045.
31. Koskenvuo M, Mottonen M, Rahiala J, et al. Mixed bacterial-viral infections in septic children with leukemia. *Pediatr Infect Dis J*. 2007;26:1133–1136.
32. Torres JP, Labraña Y, Ibañez C, et al. Frequency and clinical outcome of respiratory viral infections and mixed viral-bacterial infections in children with cancer, fever and neutropenia. *Pediatr Infect Dis J*. 2012;31:889–893.
33. Söderman M, Rhedin S, Tolfvenstam T, et al. Frequent respiratory viral infections in children with febrile neutropenia–a prospective follow-up study. *PLoS One*. 2016;11:e0157398.
34. Torres JP, De la Maza V, Kors L, et al. Respiratory viral infections and coinfections in children with cancer, fever and neutropenia. *Pediatr Infect Dis J*. 2016;35:949–954.
35. Popescu CM, Ursache AL, Feketea G, et al. Are community acquired respiratory viral infections an underestimated burden in hematology patients? *Microorganisms*. 2019;7:521.
36. Han SB, Shin JA, Kim SK, et al. Respiratory viral infections in children and adolescents with hematological malignancies. *Mediterr J Hematol Infect Dis*. 2019;11:e2019006.
37. Gabutti G, De Motoli F, Sandri F, et al. Viral respiratory infections in hematological patients. *Infect Dis Ther*. 2020;9:495–510.
38. Aydin Köker S, Demirağ B, Tahta N, et al. A 3-year retrospective study of the epidemiology of acute respiratory viral infections in pediatric patients with cancer undergoing chemotherapy. *J Pediatr Hematol Oncol*. 2019;41:e242–e246.
39. Koskenvuo M, Möttönen M, Rahiala J, et al. Respiratory viral infections in children with leukemia. *Pediatr Infect Dis J*. 2008;27:974–980.
40. Dykewicz CA. Hospital infection control in hematopoietic stem cell transplant recipients. *Emerg Infect Dis*. 2001;7:263–267.
41. Dignan FL, Clark A, Aitken C, et al. Haemato-oncology Task Force of the British Committee for Standards in Haematology; British Society for Blood and Marrow Transplantation and the UK Clinical Virology Network. BCSH/BSBMT/UK clinical virology network guideline: diagnosis and management of common respiratory viral infections in patients undergoing treatment for haematological malignancies or stem cell transplantation. *Br J Haematol*. 2016;173:380–393.
42. Yeoh DK, Foley DA, Minney-Smith CA, et al. The impact of COVID-19 public health measures on detections of influenza and respiratory syncytial virus in children during the 2020 Australian winter. *Clin Infect Dis*. 2021;72:2199–2202.

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43. Angoulvant F, Ouldali N, Yang DD, et al. COVID-19 pandemic: impact caused by school closure and national lockdown on pediatric visits and admissions for viral and non-viral infections, a time series analysis. *Clin Infect Dis*. 2021;72:319–322.
44. Friedrich F, Ongaratto R, Scotta MC, et al. Early Impact of social distancing in response to COVID-19 on hospitalizations for acute bronchiolitis in infants in Brazil. *Clin Infect Dis*. 2021;72:2071–2075.
45. Şık N, Duman M, Yılmaz D, et al. Evaluation of COVID-19 disease and the effect of trends in intervention measures: the pediatric perspective from a tertiary care hospital in Turkey. *Balkan Med J*. 2021;38:222–228.
46. Önal P, Kılınç AA, Aygün F, et al. COVID-19 in Turkey: a tertiary center experience. *Pediatr Int*. 2021;63:797–805.
47. Cura Yayla BC, Özsürekçi Y, Aykaç K, et al. Characteristics and management of children with COVID-19 in Turkey. *Balkan Med J*. 2020;37:341–347.
48. Dorantes-Acosta E, Ávila-Montiel D, Klünder-Klünder M, et al. Survival and complications in pediatric patients with cancer and COVID-19: a meta-analysis. *Front Oncol*. 2021;10:608282.

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