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Original Article

Common viral respiratory infections in children with cancer during the COVID-19 pandemic: a multicenter study from Türkiye

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ABSTRACT

Background. Microbiologic confirmation of respiratory tract infections gained importance during the coronavirus disease 2019 (COVID-19) pandemic. This study retrospectively evaluated seasonal distribution, clinical presentation, and complications of respiratory viral infections (RVIs) other than COVID-19 in children with cancer during and after the pandemic lockdown.

Methods. Two hundred and sixty-five inpatient and outpatient RVI episodes in 219 pediatric cancer patients confirmed by multiplex reverse transcriptase polymerase chain reaction (RT-PCR) panels from 13 centers were enrolled.

Results. Eighty-six (32.5%) of the total 265 episodes occurred in 16 months corresponding to the lockdowns in Türkiye, and the remaining 67.5% in 10 months thereafter. Human rhinovirus/enterovirus (hRE) (48.3%) was the most common agent detected during and after lockdown. Parainfluenza virus (PIV) (23.0%), influenza virus (9.8%), and respiratory syncytial virus (RSV) (9.1%) were the other common agents. The 28.7% of episodes were

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lower respiratory tract infections (LRTIs), and complications and mortality were higher than upper respiratory tract infections (URTIs) (25.0% vs 5.3%). Bacteremia was identified in 11.5% of culture-drawn episodes. Treatment delay in one-third and death within four weeks after RVI in 4.9% of episodes were observed.

Conclusion. During the pandemic, fewer episodes of RVIs occurred during the lockdown period. Respiratory viruses may cause complications, delays in treatment, and even death in children with cancer. Therefore, increased awareness of RVIs and rapid detection of respiratory viruses will benefit the prevention and, in some cases, abrupt supportive and some antiviral treatment of RVI in children with cancer.

Key words: respiratory viral infections, children, cancer, COVID-19.

Respiratory viruses (RVs) are the most common infection agents in children and frequent causes of hospitalization in children with cancer.[1] After the first description of coronavirus disease 2019 (COVID-19) in December 2019, the pandemic mainly affected adults with immunosuppression and comorbidities. In March 2020, COVID-19 was first seen in our country, and the nationwide data of COVID-19 in children with cancer was reported.[2] Between January 2020 and May 2021, lockdowns and distance learning measures were taken, and the microbiologic confirmation of respiratory tract infections (RTIs) gained importance for extra precaution and isolation. Concurrently, our ability to ascertain RVs has improved with multiplex reverse transcriptase polymerase chain reaction (RT-PCR) platforms.

This study aimed to evaluate etiological agents, seasonal distribution, clinical pictures, complications, and mortality of non-COVID-19 respiratory viral infections (RVIs) during and after the pandemic lockdown in children with cancer in Türkiye.

Materials and Methods

In this retrospective multicenter study between January 1, 2020, and March 1, 2022, patients under 18 years of age with ongoing cancer chemotherapy or the ones who underwent hematopoietic stem cell transplantation (HSCT) with ongoing immunosuppressive therapy with viral upper respiratory tract infections (URTIs) or lower respiratory tract infections (LRTIs) were included. Episodes that occurred after four weeks from their last chemotherapy and following a year from HSCT without immunosuppression were excluded. Upper respiratory tract infections were defined as the presence of at least one of the following symptoms: fever, sore throat, rhinorrhea, nasal congestion, otitis media, and cough with normal chest examination findings. Lower respiratory tract infections were defined as the presence or absence of URTI symptoms accompanied by pathologic signs of auscultation or new pulmonary infiltrates observed on chest radiography or computed tomography (CT).

Viral respiratory infections were confirmed by multiplex RT-PCR panels from nasopharyngeal swabs. Assays could detect at least the following 19 viruses: influenza (A, H1N1, and B), human rhinovirus/enterovirus (hRE), coronavirus (229E, NL63, OC43, and HKU1), parainfluenza virus (PIV1, 2, 3, and 4), human metapneumovirus (A/B), human bocavirus (hBoV), respiratory syncytial virus (RSV A/B) and adenovirus. Some assays could also detect the following pathogens: *Mycoplasma pneumonia*, *Legionella pneumophila*, *Bordetella pertussis*, and severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Viral types under a common taxonomy were classified together. For instance, PIV1, 2, 3, and 4 were collected under PIV. Detection of more than one agent by the same or concurrent PCR panel study was accepted as coinfection. Clinical episodes occurring in the same patient with the same virus after one month with complete clinical resolution were enrolled as separate episodes and classified as recurrent infections.

Demographic characteristics, malignancy types, presence of fever or respiratory symptoms, hospitalization status, the last chemotherapy date, steroid or rituximab usage, influenza vaccination, detected RVs and other agents in multiplex RT-PCR, blood cultures, antibiotic-antiviral usage, absolute neutrophil, lymphocyte, monocyte counts and C-reactive protein (CRP) levels on the previous or following two days of RVI diagnosis, chemotherapy delays, clinical progression, complications, and mortality within four weeks were assessed.

Febrile neutropenia (FN) was defined as an absolute neutrophile count of < 500 cells/mm^3 or < 1000 cells/mm^3 with an anticipated decline to < 500 cells/mm^3 in the following 48-hour period with a single oral temperature of > 38.3 °C or 38 °C sustained for > 1 hour.[3] The temperature measurement routes varied between centres such as axillary, tympanic and forehead scanner while every center adopted the measured temperature to the classical definition. In patients with FN, appropriate antibiotics were taken immediately after cultures were drawn. The ethics committee of Ankara Bilkent City Hospital approved the study (date: Jan. 4, 2023; number: E2-23-3106).

Statistical analysis

Mean, standard deviation, median, minimum-maximum values, frequency, and percentage were used for descriptive statistics. The distribution of variables was checked with the Kolmogorov-Simirnov test. Independent samples t-test and Mann-Whitney U test were used to compare quantitative data. The chi-square test was used for the comparison of the qualitative data. All tests adopted a value of $p \leq 0.05$ for statistical significance. Analyses were conducted using SPSS (version 20.0).

Results

Patient characteristics

A total of 265 RVI episodes of 219 children from 13 centers located in six geographical regions of Türkiye were included in the study. Forty (18.3%) patients had recurrent (2-4) episodes and the median age was 4.9 (0.4-17.8) years during the RVIs. Most of the episodes (55.0%) occurred in children with leukemia followed by solid tumors (27.9%), lymphoma (9.9%) and HSCT recipients (7.2%). All HSCT procedures were allogeneic, and all patients were still on immunosuppressive therapy, 10 for graft versus host disease (GVHD) prophylaxis and 9 for confirmed GVHD. One hundred and ninety-two patients (72.5%) were detected with RVs while they were followed up with an inpatient status. Seventy-three children were outpatients, and 57.5% of them were hospitalized during RVIs. The characteristics of episodes are shown in Table I.

Seasonal distribution of respiratory viruses

Eighty-six (32.5%) episodes occurred between January 2020 and May 2021, corresponding to Türkiye's lockdowns and distance learning period. The remaining 179 (67.5%) episodes occurred between 1st May 2021 (end of lockdowns) and 1st March 2022. Human rhinovirus/enterovirus was the most common virus observed yearlong in 48.3% (*n*=128). The other common virus was PIV, detected yearlong in 23.0% (*n*=61, PIV2: 1, PIV3: 51, PIV4: 9) of episodes, followed by influenza virus in 9.8% (*n*=26, influenza A: 15, influenza A H1N1: 2, influenza B: 9) and RSV in 9.1% (*n*=24) of episodes, which were mainly observed during winter months. Adenovirus, coronaviruses other than SARS-CoV-2, and hBoV were also seen yearlong with ratios 8.7% (*n*=23), 7.5% (*n*=20, coronavirus OC43: 12, coronavirus 229E: 6, coronavirus HKU: 1, coronavirus NL63: 1), and 4.9% (*n*=13), respectively. Human metapneumovirus was observed in 1.5% (*n*=4) during winter months. The monthly distribution of RVs is shown in Fig. 1. Coinfection occurred in 14% (*n*=37) of episodes (Fig. 2). In 57 of 85 (67.1%) recurrent RVIs, a diverse virus was detected, while in 13 (15.3%) episodes, the previous virus was detected with a new co-partner agent. A prior virus was detected

Table I. Demographic, clinical, and laboratory details of patients and RVI episodes.

	n	%	p-value
Median age (years)	4.9 (0.4-17.8)	56.6	
Male	150	43.4	
Female	115	72.5	
Inpatient	192	27.5	
Outpatient	73	57.5	
Hospitalization needs	42/73		
Diagnosis			
Leukemia[a]	146	55.0	
Solid tumors[b]	74	27.9	
Lymphoma[c]	26	9.9	
HSCT recipients[d]	19	7.2	
URTIs	189	71.3	
LRTIs	76	28.7	
Mean age (years)			
URTIs	6.5±4.5		0.319
LRTIs	5.9±4.4		
LRTIs at admission			
Leukemia	47	32.2	0.186
Solid tumors	17	23.0	
Lymphoma	5	19.2	
HSCT recipients	7	36.8	
Bacteremia			
URTIs	10/115	8.7	0.125
LRTIs	11/67	16.4	
Bacteremia			
FN	18/115	15.7	0.026
Non-FN	3/67	4.5	
Laboratory findings at diagnosis			
ANC (mm^3)			
URTIs	1200 (0-29860)		0.003
LRTIs	430 (0-33740)		
ALC (mm3)			
URTIs	680 (0-10760)		0.034
LRTIs	400 (0-11740)		
AMC (mm3)			
URTIs	225 (0-5400)		0.007
LRTIs	70 (0-21350)		
CRP (mg/L, N:0-5)			
URTIs	7 (0-300)		<0.0001
LRTIs	20 (0-208)		
Complications and mortality			
URTIs	10/189	5.3	<0.0001
LRTIs	19/76	25.0	
Complications and mortality			
Inpatients	23/192	12.0	0.381
Outpatients[e]	6/73	8.2	

Quantitatie data were presented as mean ± standard deviation, or median (min-max). ALC, absolute lymphocyte count; AMC, absolute monocyte count; ANC, absolute neutrophil count; CRP, C-reactive protein; FN, febrile neutropenia; HSCT, hematopoietic stem cell transplantation; LRTI, lower respiratory tract infection;
RVI, respiratory viral infection; URTI, upper respiratory tract infection.

[a] 130 acute lymphoblastic leukemia, 13 acute myeloid leukemia, 3 juvenile myelomonocytic leukemia

[b] 27 embryonal tumors, 19 central nervous system tumors, 18 bone and soft tissue tumors, 3 germ cell tumors, 7 others

[c] 22 non-Hodgkin lymphoma, 4 Hodgkin lymphoma

[d] 11 acute lymphoblastic leukemia, 4 juvenile myelomonocytic leukemia, 3 acute myeloid leukemia, 1 non-Hodgkin lymphoma

[e] at admission

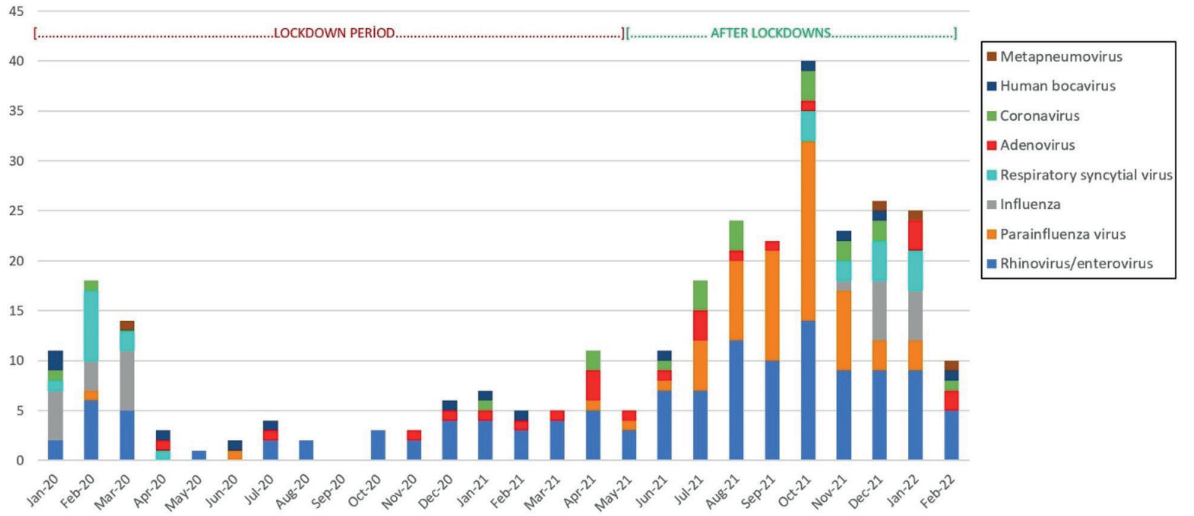

Fig. 1. Monthly distribution of detected viruses.

solely after complete recovery in 15 episodes (17.6%). SARS-CoV-2 PCR was examined in 220 episodes (83%) and detected in four episodes (1.8%) as a co-partner agent, which were all after the lockdown period. *Bordetella pertussis* in two episodes and *Legionella pneumophila* in one were also detected with concomitant hRE. Adenovirus was detected in 23 episodes, seven (30.4%) in HSCT recipients. It was the most common detected agent in HSCT recipients (36.8%).

Clinical presentations

Seventy-six episodes (28.7%) were diagnosed as LRTIs at first admission, and all virus types were related to LRTIs (Fig. 2). Lower respiratory tract infections were not associated with malignancy type, age, and coinfection (Table I). In 29.4% (*n*=78) of episodes, steroids had been used in the preceding two weeks, LRTI ratio was 32.1% in this group which was not higher than that of the steroid-free group (*p*=0.433). Rituximab was not used in any of the patients.

Fever accompanied 66% (*n*=175) of episodes, 43.4% (*n*=115) were classified as FN, and all those patients were treated in clinics. Antibiotics were used in 75.8% (*n*=201) via intravenous route in 182. Oseltamivir was used in all patients with influenza. Other antiviral agents were not used in any of the episodes. During the four weeks of follow-up, 94.7% (*n*=179) of URTIs and 75% (*n*=57) of LRTIs resulted in full recovery. The median chemotherapy delay was seven (2-80) days in 74 of 237 episodes (31.2%).

Laboratory and radiological results

At diagnosis of RVI, the median absolute neutrophil, lymphocyte, and monocyte counts were lower in LRTIs than in URTIs ($p<0.05$), whereas the median CRP level was significantly higher in LRTIs than in URTIs ($p<0.0001$) (Table I).

Blood cultures were obtained in 68.7% (*n*=182) of episodes, and bacteremia was identified in 11.5% (*n*=21), mostly in FN episodes. Five of the 21 bacteremia episodes were catheter-related bloodstream infections in FN episodes. There was no relation between bacteremia and the RVI site (Table I). The microbiological agents detected in blood cultures during episodes were as follows: *Klebsiella pneumoniae*, *Staphylococcus epidermidis*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Enterococcus faecium*, *Staphylococcus hominis*, *Staphylococcus lugdunensis*, *Streptococcus pneumonia*, *Streptococcus oralis*, and *Candida albicans*.

Radiologic imaging, either posteroanterior chest radiography (*n*=113) or CT (*n*=43), was performed in 58.9% (*n*=156) at diagnosis. The

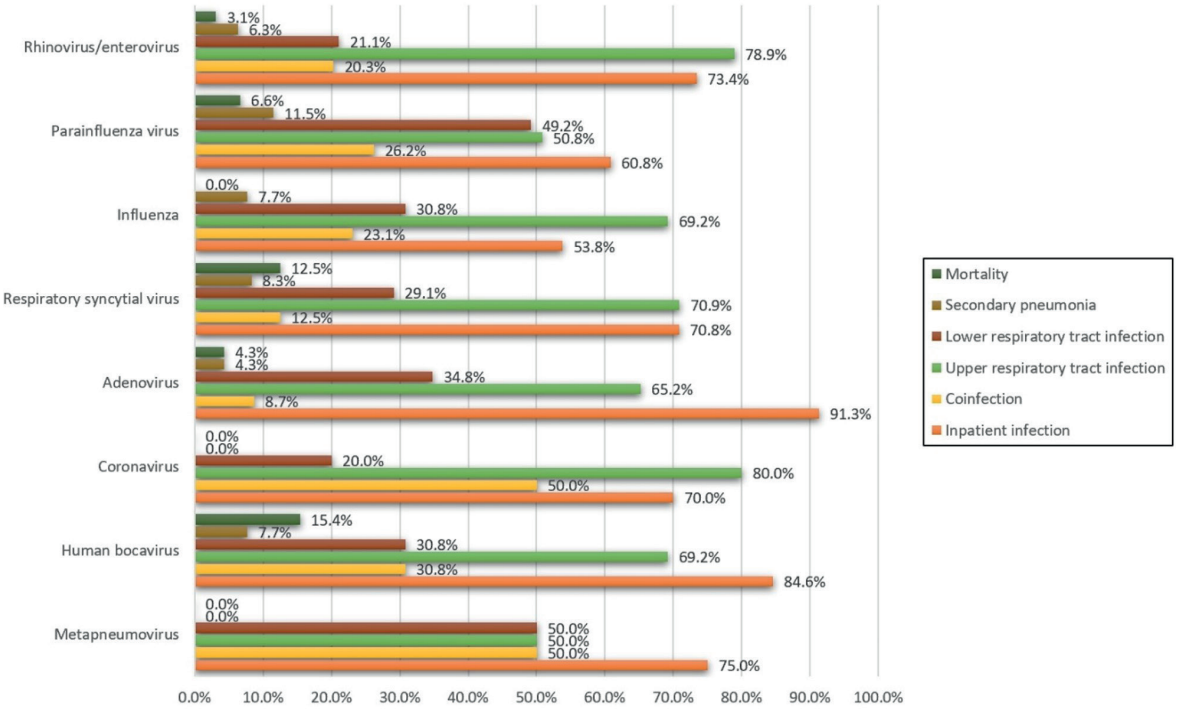

Fig. 2. Virus-specific clinical and prognostic characteristics.

most common findings were peribronchial thickening (35 episodes), ground-glass opacities (30 episodes), nodules (11 episodes), and consolidations (11 episodes).

Complications and mortality

During the follow-up, 5.3% of URTIs and 25.0% of LRTIs had complications or mortality (p<0.0001). The most common complication was secondary pneumonia, observed in 7.5% of the episodes (n=20). Secondary pneumonia was observed related with all the virus types except metapneumovirus and coronaviruses (Fig. 2). In these episodes, one hRE with *Legionella pneumophila* and one hRE with PIV were detected; the remaining 18 were single agents. These complicated 20 episodes were accompanied by bacteremia (n=4) (*S. epidermidis*, *E. faecium*, *S. lugdunensis, S. pneumonia)*, multiple organ failure (n=4), and myocarditis (n=2). Another critical complication, Guillian Barre Syndrome, was observed in two patients, in a relapsed acute lymphoblastic leukemia (ALL) patient after an adenovirus episode and in an ALL patient following an hRE episode complicated by *K. pneumonia* sepsis and myocarditis. Two URTIs were complicated by sinusitis (influenza virus, RSV), and one URTI by otitis media (hRE).

Overall, the mortality rate was 4.9% (n=13). The details of fatal episodes are shown in Table II. Most patients were either relapsed leukemia or at induction of leukemia with severe neutropenia and lymphopenia. The mortality rates of RVs are shown in Fig. 2.

Discussion

Viruses are important causes of RTIs in children with cancer and often cause similar clinical manifestations. Multiplex PCR is a sensitive method to detect viruses and fits with the "multi-etiological" nature of viral RTIs.[4] The COVID-19 pandemic has underscored the effects of RVIs, and the use of PCR for the diagnosis of RVIs has become more established. Besides, the diversity and prevalence of RVs changed because of the infection control measures taken during the pandemic.[5] Before the pandemic, the most

Table II. Clinical and laboratory details of mortal episodes.

viral agent/ agents	diagnosis	malignancy status/ post-HSCT duration	laboratory at the time of RVI				accompanying complications, comorbidities
			ANC/ mm^3	ALC/ mm^3	AMC/ mm^3	CRP mg/L (N:0-5)	
hRE	ALL	Remission	40	110	20	185	*Legionella pneumophila* coinfection
	ALL	Relapsed-refractory	20	220	0	183	Secondary pneumonia, invasive fungal infection
	HL	Relapsed	1100	10	10	204	Secondary pneumonia, multiple organ failure
RSV	ALL	Relapsed	20	70	0	125	Down S., secondary pneumonia, *S. epidermidis* bacteremia
	AML	Remission	210	20	0	4	
	ALL	Induction	100	290	0	3	
PIV3	ALL	Induction	760	380	150	0	Secondary pneumonia, myocarditis
	ALL	Relapsed-refractory	360	100	0	24	*K. pneumoniae* sepsis
	Osteosarcoma	Relapsed-refractory	8740	1260	490	208	Secondary pneumonia
hBoV	HSCT recipient (ALL)	Remission/ 122 days	80	430	20	40	*S. epidermidis* bacteremia, GI tract GVHD, adenoviremia
	HSCT recipient (JMML)	Remission/ 67 days	240	310	90	70	
Adenovirus	HSCT recipient (ALL)	Remission/ 50 days	120	30	20	204	Secondary pneumonia, multiple organ failure, *E. faecium* bacteremia, GI tract GVHD, adenoviremia
PIV3, hRE	HSCT recipient (ALL)	Remission/ 201 days	390	130	10	190	*S. pneumoniae* bacteremia, GI tract GVHD, adenoviremia

ALL, acute lymphoblastic leukemia; ALC, absolute lymphocyte count; AMC, absolute monocyte count; AML, acute myeloid leukemia; ANC, absolute neutrophil count; CRP, C-reactive protein; GI, gastrointestinal; GVHD, graft versus host disease; hBoV, human bocavirus; HL, Hodgkin lymphoma; hRE, human rhinovirus/enterovirus; HSCT, hematopoietic stem cell transplantation; JMML, juvenile myelomonocytic leukemia; PIV3, parainfluenza virus type 3; RSV, respiratory syncytial virus; RVI, respiratory viral infection.

common RVs were hRE, RSV, PIV, and influenza in pediatric cancer patients in our country.[6,7] A recent cohort showed rhinovirus was the most common RV agent in patients who were negative for SARS-CoV-2, and the frequency of influenza significantly decreased in the year 2020.[8] The significant findings observed in our study were that hRE viruses affect cancer patients yearlong despite lockdown and distance learning. SARS-CoV-2 had a low ratio of 1.9%, and influenza was not detected in any of the cases of children with cancer during the lockdown period. The lower rate of SARS-CoV-2 compared to other viruses can be attributed to frequent screening in patients, their caregivers, and health care providers, and those who test positive were immediately isolated. Srinivasan et al. detected rhinovirus in over 60% of pediatric cancer patients with URTI/LRTI, coinfection in 24% of patients, and coinfection did not increase the risk for LRTI.[9]

In our study, LRTIs were mostly related to hMPV, PIV, adenovirus, and RSV, which might be related to their high virulence. PIV was frequently associated with LRTIs and complicated with secondary pneumonia, in which mortality was higher. A study conducted with 74 pediatric cancer patients with PIV revealed the LRTI was present in 20.3% of these patients at the initial presentation, 20.3% of URTI progressed to LRTI, PIV-associated mortality was 18.5%, and 80% of infections were nosocomial.[10] PIV-3-related LRTIs in patients with hematologic malignancy were noted more frequently with higher viral loads than non-hematologic patients.[11]

RSV was reported as the third most common viral agent after hRE and PIV in children undergoing HSCT, with 10% mortality.[12] In adult HSCT recipients, ribavirin-based therapy was associated with decreased progression to LRTIs and improved mortality rates.[13] RSV was another frequent and mortal agent in our study; however, ribavirin was not used in any of the RSV episodes. Of interest, we didn't observe any RSV episodes in HSCT recipients. Adenovirus was the prominent agent with viremia in most HSCT patients. Following HSCT, activation of adenovirus and respiratory tract involvement may cause respiratory failure and death.[14]

An unexpected agent, hBoV, was detected in two mortal episodes in our HSCT recipients. A study from Türkiye revealed that one-third of pediatric patients with hBoV required intensive care due to severe acute LRTI.[15] However, in another study, hBoV was reported as an infrequent and non-serious respiratory pathogen in adult and pediatric HSCT recipients.[16]

According to the 2013 Infectious Diseases Society of America Guidelines, influenza vaccine is recommended for all immunocompromised patients aged six months or older[17] —none of the enrolled patients were known to be vaccinated against influenza. However, the vast usage of oseltamivir may have helped to no mortality from influenza.

Respiratory viruses are documented in 76.5% of FN attacks with respiratory symptoms and cause more extended hospitalization with antibiotic usage and higher mortality.[18] In the current study, almost half of the RVIs were seen during FN episodes, and the mortality was high in these patients. Koskenvuo et al. reported that half of the septic episodes in children with leukemia had an accompanying virus infection, mostly rhinovirus and RSV, and they had more severe clinical profiles.[19] However, Shinn et al. found that despite a high prevalence of RVIs in children with FN, the result of a respiratory multiplex PCR panel did not impact the length of hospital stay or bacteremia.[20] In our study, the bacteremia ratio was 15.7% in FN episodes, comparable with the reported ratios of 12.9-23.3% in children with FN.[21-23] The bacteremia ratio in non-FN episodes was 4.5%, higher than the reported ratios of 1.3-2.5% in community-acquired pneumonia but with similar agents like *S. pneumonia* and *S. aureus*.[24-26] Lymphopenia, corticosteroids, GVHD, and cytomegalovirus reactivation in HSCT recipients are also risk factors for viral LRTIs in hematological

patients.[27-30] In the present study, LRTIs were significantly associated with lower lymphocyte and monocyte counts but not higher in patients under steroids. The T cell-mediated immune response is fundamental in protection from viral infections. The patients notably lack T or B cell immunity due to immunosuppressive therapies and are susceptible to viral infections and related complications.[28]

Influenza, PIV, adenovirus, hMPV, measles, RSV, and coronavirus disrupt the mucosal barrier, impair ciliary and macrophage phagocytic functions, and have viral effects on the cytokine milieu commonly increasing the susceptibility of other viral, bacterial, and fungal infections and the development secondary pneumonia.[31] We observed secondary possible bacterial pneumonia as the most common complication. Indicating the bacterial infection predisposition of RVs, Peltola et al. found an association between rhinovirus circulation in the community and invasive pneumococcal disease in children younger than five years of age.[32]

In our study, 4.9% of episodes resulted in death. It is difficult to attribute these mortalities to viral infections because of other comorbidities. Furthermore, RVs can lead to delays in treatment. In one-third of episodes, approximately a week of planned cancer therapy delay was observed, similar to those reported in 22-33% and 6-9 days in other studies.[7,33]

Our study is a multicenter study, in which the changed frequency and seasonal distribution of RVIs with the pandemic were reported in a patient group with high morbidity and mortality. But it has some limitations. Firstly, it was retrospective, and it was challenging to detect patients' previous microbiological and clinical patterns, which might be related to morbidity and mortality. Also, the other risk factors and related clinical conditions leading to LRTI progression were unclear. The time between the onset of initial findings and admission may affect the need for hospitalization and the prognosis of outpatients. In addition, most RVs acquired through the community can also lead to nosocomial viral spread and outbreaks of centers. The epidemics of the centers were not investigated in our study.

Respiratory viruses may cause complications overlapping with other opportunistic infections and cause morbidity and mortality in children with cancer. Although the prevalence of RVs has changed since the COVID-19 pandemic, the distribution of RVs in pediatric cancer patients remain similar. Determining RVs may contribute to proper use of currently available antiviral drugs, isolation measures, reducing unnecessary antibiotics, and increasing appropriate therapy for complications. Specific recommendations for each virus will be possible by prospective studies revealing viral loads along with the development of vaccines and drugs.

Ethical approval

This study was approved by the Institutional Ethics Committee of Ankara Bilkent City Hospital (approval number: E2-23-3106). All procedures were under the Declaration of Helsinki and its later amendments or with comparable ethical standards. The local ethics committee did not require informed consent for this retrospective, non-invasive study. The local ethics committee permitted access to the raw data in the hospital database.

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: DK, RK, DT, NE; data collection: DK, RK, DÖ, DT, AB, ZCÖ, AAÖ, MFO, ATY, CA, İK, NS, HT, MA, ACA, NE, SA, VHÜ, BZ, ÜMY, MB, HG, ET, ÖB, NYÖ, İEİ, NY; analysis and interpretation of results: DK, RK, DT, NE. NY; draft manuscript preparation: DK, RK, NY. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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