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Retrospective analysis of respiratory virus infections in adults with hematologic malignancies

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Abstract. – OBJECTIVE: The study aimed to evaluate respiratory virus infections in adult patients with hematological malignancies (HM).

PATIENTS AND METHODS: The medical records of patients who were followed up by the hematology clinic at Başakşehir Çam and Sakura City Hospital between March 2021 and March 2023 with a diagnosis of HM and who underwent real-time polymerase chain reaction (RT-PCR) testing for nasopharyngeal/oropharyngeal specimens taken with suspected respiratory tract infection constituted the study data.

RESULTS: Infections were symptomatic in 64.56% of patients, and the most common symptoms were fever (48.10%) and cough (18.99%). The mortality rate was 25.32% over a two-year period. When the samples were examined, positive test frequency was 43.04%, and the three most common pathogens were Influenza A (10.13%), SARS-CoV-2 (8.86%), and rhinovirus/enterovirus (7.59%). The frequency of positive tests from HMs was highest in patients with AML (p=0.042). Respiratory PCR kit positivity was higher in patients who had any symptoms (p=0.002) and cough (p=0.003). Test positivity was higher in patients with any pathological radiological finding (p=0.039) and ground glass appearance (p=0.010). The risk of death was found to be 5.848 times higher in patients with dyspnea compared to those without (OR: 5.848, 95% CI: 1.143-29.915, p=0.034).

CONCLUSIONS: Respiratory tract virus panel PCR test positivity is more common in patients with HM presenting with respiratory tract infection symptoms in the presence of AML diagnosis, symptomatic infection, cough, radiological findings, and ground glass appearance. Mortality risk is high in HM patients with respiratory tract virus infection who have shortness of breath.

Key Words:
Adult, Neoplasms, Hematologic malignancy, Respiratory tract infections, Virus diseases.

Introduction

Hematological malignancies (HM) represent a heterogeneous group of diseases that affect the blood, bone marrow, and lymph nodes, and can develop in people of all ages[1]. Due to severe impairment of cell-mediated and humoral immunity in patients treated for HMs, there is an increased risk of lower respiratory tract infections, which results from the reactivation of latent infections or progression of community-acquired upper respiratory tract infections. The presentation and diagnosis of these infections are often complex due to the high rate of co-infections with the association of bacterial, fungal, and other viral pathogens[2]. Viral infections of the respiratory system represent one of the most important complications in patients admitted to hematology departments, both in terms of severity of clinical presentation and impact on hospital stay and mortality[3].

Laboratory evaluation is essential for the definitive diagnosis of viruses, as most respiratory tract infections have similar clinical course. Although direct immunofluorescent antigen tests are advantageous in terms of being rapid and inexpensive in the evaluation of these viral infections, their sensitivity levels (50-93%) are relatively low. Viral culture has been accepted as the gold standard for diagnosing respiratory viruses. However,

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a delay of up to one week until results can be obtained is a particularly important problem for immunocompromised HM patients, especially considering that prompt diagnosis and treatment can prevent serious infection-related complications[4]. In the field of clinical microbiology, considerable advances have been made in the last decade due to new technologies that improve the diagnosis of infectious diseases[5]. Multiplex real-time polymerase chain reaction (RT-PCR) tests are often preferred for diagnosing viral infections because of their high sensitivity, specificity, and ability to successfully evaluate multiple viruses simultaneously[4]. Multiplex tests are revolutionary as they rapidly diagnose infections and allow timely clinical management decisions (such as isolation, antimicrobial therapy, and hospitalization)[5].

Respiratory syncytial virus (RSV), influenza virus, parainfluenza virus (PIV), and human metapneumovirus (hMPV) are responsible for the majority of virologically-diagnosed respiratory infections encountered in the population with HMs[4]. While it is well known that lower respiratory tract infections cause high mortality in immunocompromised patients with HMs, even respiratory viruses such as rhinovirus and coronavirus, which are typically thought to cause "mild colds", have been associated with serious outcomes[1]. Early diagnosis and treatment are important in these infections, as this approach reduces the risk of progression and increases survival[6].

The aim of this study was to evaluate the pathogen spectrum in viral infections of the respiratory tract among adult patients with HMs.

Patients and Methods

Ethics Approval

This retrospective study was carried out at Başakşehir Çam and Sakura City between March 2021 and June 2023. The ethical approval was obtained from Başakşehir Çam and Sakura City Ethical Committee (No.: 2023.05.207).

Study Population and Data Sources

The medical records of patients with a diagnosis of HM at Başakşehir Çam and Sakura City who underwent RT-PCR tests for suspected respiratory tract infection between March 2021 and March 2023 were evaluated. The research data were created by the detailed examination of medical records among patients with an indication for RT-PCR testing for viral pathogen screening due to receiving a preliminary diagnosis of respiratory tract infection based on the presence of symptoms such as fever, cough, runny nose, nasal congestion, headache, and fatigue.

Collecting and Studying Respiratory Tract Samples

In the routine application of the RT-PCR test, nasopharyngeal/oropharyngeal samples obtained from the patients were transferred to the laboratory under cold chain conditions after being placed in viral nucleic acid isolation buffer (vNAT, Biospeedy, Bioeksen, Istanbul, Turkey). The obtained samples were stored in the refrigerator at 2-8°C and analyzed within 24 hours. The nucleic acid extraction of the samples was performed using the magnetic bead-based total nucleic acid extraction kit (Bioeksen, Istanbul, Turkey) on the Zybio EXM 3000 device (Zybio, Shenzhen, China) according to the manufacturer's instructions. After nucleic acid extraction, respiratory tract pathogens were investigated using the Respiratory RT-qPCR MX-24S panel Kit (Bioeksen, Istanbul, Turkey) on the Bio-Rad CFX96 Touch device (Hercules, CA, USA). Positive, negative, and internal controls (RNase P gene) were included in each study. The results of the tests were evaluated in accordance with the manufacturer's recommendations. The respiratory PCR panel kit simultaneously screens for 23 respiratory pathogens, including SARS-CoV-2, human coronaviruses (CoV) 229E, 0C43, NL63 and HKU1, influenza A virus (FluA), influenza B virus (FluB), PIV 1, 2, 3, 4, rhinovirus/enterovirus, adenovirus, respiratory syncytial virus A/B (RSV), human metapneumovirus (MPV), human bocavirus (BoV), parechovirus, *Streptococcus pneumoniae, Haemophilus influenzae, Legionella pneumophilia, Mycoplasma pneumoniae, Chlamydophila pneumoniae* and *Bordetella pertussis*.

Statistical Analysis

All analyses were performed on IBM SPSS v. 25.0 (IBM Corp., Armonk, NY, USA). The conformity of quantitative variables to normal distribution was evaluated with the Shapiro-Wilk test. Since the quantitative variables did not demonstrate normal distribution characteristics, quantitative data were summarized with median (1st quartile - 3rd quartile), and qualitative variables were given as frequency (percentage). Quantitative variables were analyzed with the Mann-Whitney U test. Qualitative variables were analyzed with the chi-square test, the Fisher's exact test, or

the Fisher-Freeman-Halton test. Logistic regression analysis was used to identify factors associated with mortality. Variables were first evaluated with simple logistic regression analysis, and then statistically significant variables were included in a multiple logistic regression model. The statistical significance level was accepted as $p<0.05$.

Results

Of the patients in the study group, 48 (60.76%) were male, 31 (39.24%) were female, and the median age (min-max) was 52 (18-89) years. These patients with a diagnosis of HM included patients with acute myeloid leukemia (AML, 44.30%), non-Hodgkin lymphoma (NHL, 20.25%), acute lymphoblastic leukemia (ALL, 8.86%), Hodgkin lymphoma (HL, 7.59%), and patients with other HMs (18.99%). The majority of the patients (86.08%) in the study group consisted of inpatients admitted to wards.

When the samples were taken, 79.75% of the patients were receiving chemotherapy, and 77.22% were receiving steroid treatment. The three most common clinical comorbidities in patients were diabetes mellitus (DM, 18.99%), renal failure (7.59%) and congestive heart failure (5.06%), respectively. The infections were symptomatic in 64.56% of the study group, and the most common symptoms were fever (48.10%) and cough (18.99%). The most common radiological finding was ground glass appearance, with a frequency of 32.91%, while radiological findings were observed in 62.03% of the patients. The median duration of hospitalization among the patients in the study group receiving any treatment was found to be 18 (min-max: 0-81) days. During the two-year period in which the data were evaluated, the mortality rate among the patients was 25.32% (Table I).

The majority of the samples included in the study had been obtained in the winter (56.96%) and autumn (22.78%) seasons. Positive results were found in 43.04% of the examined samples, and more than one pathogen was detected in 11.39% (n=9) samples. The most common pathogens detected after the examination of the samples were Influenza A (10.13%), SARS-CoV-2 (8.86%), rhinovirus/enterovirus (7.59%), *Haemophilus influenzae* (5.06%) and Respiratory Syncytial Virus (RSV) A/B (5.06%). Among these patients, galactomannan positivity was 3.80%, Cytomegalovirus (CMV) positivity was 20.25%, the frequency of growth in blood culture was 6.33%, the presence of growth in tracheal culture was 7.5%, and the presence of growth in urine culture was 3.80% (Table II, Figure 1).

Among patients in which blood cultures were ordered, the most common growth was *Klebsiella pneumoniae*. Additionally, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* were the two most common pathogens detected in patients with

Table I. General characteristics of the patients, radiological examinations and laboratory findings.

Age	52 (32-66)
Sex	
Male	48 (60.76%)
Female	31 (39.24%)
Patient status	
Outpatient	11 (13.92%)
Inpatient	68 (86.08%)
Diagnosis	
ALL	7 (8.86%)
AML	35 (44.30%)
Hodgkin lymphoma	6 (7.59%)
Non-Hodgkin lymphoma	16 (20.25%)
Others	15 (18.99%)
Chemotherapy	63 (79.75%)
Steroid therapy	61 (77.22%)
Symptom[(1)]	51 (64.56%)
Fever	38 (48.10%)
Weakness	7 (8.86%)
Cough	15 (18.99%)
Sputum	6 (7.59%)
Dyspnea	8 (10.13%)
Others	10 (12.66%)
Pathological finding in radiology[(1)]	49 (62.03%)
Consolidation	14 (17.72%)
Frosted glass appearance	26 (32.91%)
Effusion	3 (3.80%)
Atelectasis	4 (5.06%)
Others	5 (6.33%)
White blood cell ($x10^3$)	1.66 (0.55-5.87)
Lymphocyte ($x10^3$)	0.50 (0.24-1.00)
Neutrophil ($x10^3$)	1.00 (0.15-2.73)
Neutrophil lymphocyte ratio	1.00 (0.25-6.14)
C-reactive protein (CRP), mg/dl	119.4 (47.9-175.4)
Length of stay in hospital, days	18 (6-34)
Mortality	20 (25.32%)

Since quantitative variables were not normally distributed, the median (1st quartile-3rd quartile) was used. Qualitative variables are given as frequency (percentage).
[(1)]Patients may have more than one of the findings.
AML: acute myeloid leukemia ALL: acute lymphoblastic leukemia.

Table II. Features related to microbiological examination.

Sample acceptance time, season	
Spring	11 (13.92%)
Summer	5 (6.33%)
Autumn	18 (22.78%)
Winter	45 (56.96%)
Inpatient sample acceptance time, day	2 (1-8)
Positive pathogens (1)	
Adenovirus	1 (1.27%)
Bordetella pertussis	0 (0.00%)
Chlamydophila pneumoniae	0 (0.00%)
Haemophilus influenzae	4 (5.06%)
Human Bocavirus (HBoV)	1 (1.27%)
Human Coronavirus 229E	0 (0.00%)
Human Coronavirus HKU1	1 (1.27%)
Human Coronavirus NL63	0 (0.00%)
Human Coronavirus OC43	1 (1.27%)
Human Metapneumovirus (HMPV)	1 (1.27%)
Human Parechovirus (HPeV)	2 (2.53%)
Influenza A virus (FluA)	8 (10.13%)
Influenza B virus (FluB)	1 (1.27%)
Legionella pneumophila	0 (0.00%)
Mycoplasma pneumoniae	0 (0.00%)
Parainfluenza virus 1	0 (0.00%)
Parainfluenza virus 2	1 (1.27%)
Parainfluenza virus 3	2 (2.53%)
Parainfluenza virus 4	0 (0.00%)
Respiratory Syncytial Virus (RSV) A/B	4 (5.06%)
Rhinovirus/Enterovirus	6 (7.59%)
SARS-CoV-2	7 (8.86%)
Streptococcus pneumoniae	3 (3.80%)
Respiratory kit results	
Negative	45 (56.96%)
Positive for one virus	25 (31.65%)
Positive for one bacterium	2 (2.53%)
Positive for two viruses	2 (2.53%)
Positive for one virus and one bacterium	3 (3.80%)
Positive for two viruses and one bacterium	2 (2.53%)
Galactomannan	
Not Evaluated	6 (7.59%)
Negative	70 (88.61%)
Positive	3 (3.80%)
CMV	
Not Evaluated	5 (6.33%)
Negative	58 (73.42%)
Positive	16 (20.25%)
Blood culture	
Not Evaluated	16 (20.25%)
Negative	58 (73.42%)
Positive	5 (6.33%)
Tracheal culture	
Not Evaluated	36 (45.57%)
Negative	37 (46.84%)
Positive	6 (7.59%)
Urine culture	
Not Evaluated	21 (26.58%)
Negative	55 (69.62%)
Positive	3 (3.80%)

Since quantitative variables were not normally distributed, median (1st quartile-3rd quartile) was used. Qualitative variables are given as frequency (percentage). (1)Patients may have more than one of the findings.

tracheal cultures. In patients with urine cultures, three pathogens were detected: *Enterococcus cloaca*, *Enterococcus feacium,* and *Klebsiella pneumoniae* (Table III).

Positive results from respiratory tract PCR kit tests were not correlated with age (p=0.289), sex (p=0.590), congestive heart failure (p=0.309), renal failure (p=1.000), and DM (p=0.980). Among the HMs evaluated, the majority of positive tests were of patients with AML (p=0.042). Respiratory kit positivity was unassociated with chemotherapy (p=0.729) and steroid treatment (p=0.136). The frequency of respiratory tract PCR kit positivity was higher in patients who had any symptoms (p=0.002) and specifically in those with coughing symptoms (p=0.003). Additionally, positivity was found to be higher in patients with any pathological findings in radiology (p=0.039) and ground glass appearance (p=0.010). Respiratory tract PCR kit test positivity was not correlated with white blood cell (p=0.280), lymphocyte (p=0.470), neutrophil (p=0.127) counts, neutrophil-to-lymphocyte ratio (p=0.219) and C-reactive protein (CRP, p=0.100) level. Finally, hospital stay (p=0.275), mortality (p=0.641), season of sampling (p=0.802), blood culture result (p=0.315), tracheal culture result (p=0.572), and urine culture result (p=0.083) were also unassociated with respiratory tract PCR kit positivity (Table IV).

As a result of the multivariable logistic regression analysis performed to elucidate the factors affecting mortality in the patients in the study group, it was found that the risk of death in patients with dyspnea was 5.848 times higher than in those without (OR: 5.848, 95% CI: 1.143-29.915, p=0.034). No significant relationships were found between mortality and other variables included in the multivariable model, kidney failure (p=0.117) and CMV positivity (p=0.108) (Table V).

Discussion

Respiratory viral pathogens remain a common cause of morbidity and mortality in patients with HMs. The continuous development of diagnostic tools increases the detection of respiratory tract viruses by facilitating them[7]. In this study, the results of a two-year viral respiratory RT-PCR panel in patients with a diagnosis of HM were evaluated.

Factors associated with the acquisition and progression of respiratory tract virus infections include male sex, lymphopenia, myeloablative

Table III. Distribution of pathogens reproduced in blood, trachea and urine cultures.

Blood culture	Tracheal culture	Urine culture
P. Montei	*K. pneumoniae*	*E. Cloaca*
K. pneumoniae	*K. Pneumoniae-A. baumani*	*E. Feacium*
K. pneumoniae	*P. aeruginosa*	*K. Pneumoniae*
K. pneumoniae	*S. maltophilia*	
P. aeruginosa	*P. aeruginosa*	
	Pneumocystis carinii	

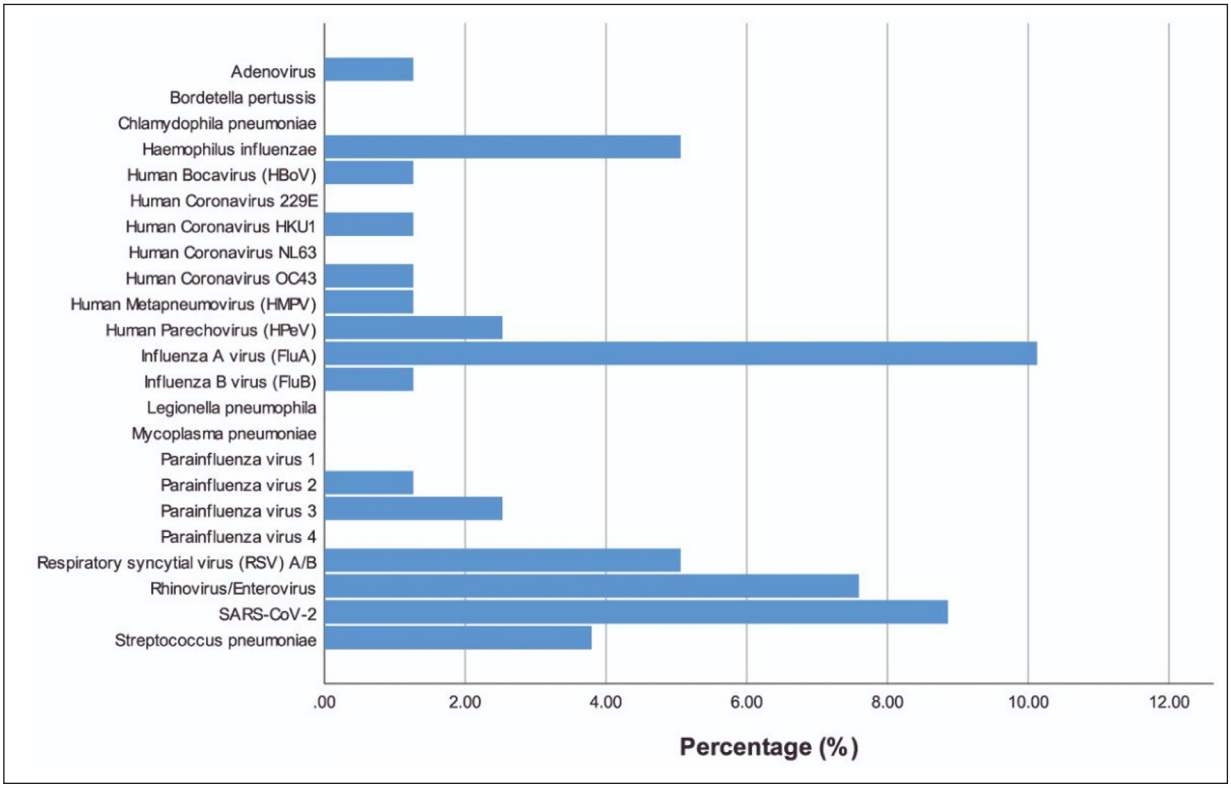

Figure 1. Distribution of pathogens detected in the respiratory tract RT-PCR panel.

and T-cell-depleted chemotherapy, graft-versus-host disease (GVHD), allogeneic HSCT (hematopoietic stem cell transplantation) from an unrelated donor, and CMV seropositivity[4,8]. In a prospective study by Legoff et al[9], it was reported that respiratory virus test positivity in hematology patients admitted to intensive care was associated with lymphoproliferative disorders, hematopoietic stem cell transplantation, treatment with steroids or other immunosuppressants, acute renal failure, and death in the intensive care unit. In a prospective study in which pulmonary infiltrates were evaluated bronchoscopically in granulocytopenic patients with HMs, it was reported that the majority of patients were diagnosed with AML[10]. In a study by Hong et al[11] in which they evaluated lower respiratory tract infections in hematopoietic stem cell transplant recipients, the most frequently diagnosed HM was AML (37.3%). Similarly, in the current study, it was found that the majority of patients who underwent RT-PCR tests had a diagnosis of AML (44.30%). The incidence of leukemia is higher than other HMs examined in the study[12].

Table IV. Analysis of variables according to respiratory PCR kit results.

	Respiratory kit results		
	Negative (n=45)	Positive (n=34)	p
Age	51 (32-64)	54 (35-68)	0.289
Sex			
Male	29 (64.44%)	19 (55.88%)	0.590
Female	16 (35.56%)	15 (44.12%)	
Congestive heart failure	1 (2.22%)	3 (8.82%)	0.309
Kidney failure	3 (6.67%)	3 (8.82%)	1.000
Diabetes mellitus	8 (17.78%)	7 (20.59%)	0.980
Diagnosis			
ALL	4 (8.89%)	3 (8.82%)	0.042
AML	24 (53.33%)	11 (32.35%)	
Hodgkin lymphoma	2 (4.44%)	4 (11.76%)	
Non-Hodgkin lymphoma	11 (24.44%)	5 (14.71%)	
Others	4 (8.89%)	11 (32.35%)	
Chemotherapy	37 (82.22%)	26 (76.47%)	0.729
Steroid therapy	38 (84.44%)	23 (67.65%)	0.136
Symptom (1)	22 (48.89%)	29 (85.29%)	0.002
Fever	17 (37.78%)	21 (61.76%)	0.059
Weakness	2 (4.44%)	5 (14.71%)	0.133
Cough	3 (6.67%)	12 (35.29%)	0.003
Sputum	3 (6.67%)	3 (8.82%)	1.000
Dyspnea	3 (6.67%)	5 (14.71%)	0.280
Others	3 (6.67%)	7 (20.59%)	0.090
Pathological finding in radiological imaging(1)	23 (51.11%)	26 (76.47%)	0.039
Consolidation	9 (20.00%)	5 (14.71%)	0.755
Frosted glass appearance	9 (20.00%)	17 (50.00%)	0.010
Effusion	2 (4.44%)	1 (2.94%)	1.000
Atelectasis	2 (4.44%)	2 (5.88%)	1.000
Others	3 (6.67%)	2 (5.88%)	1.000
White blood cell ($x10^3$)	1.38 (0.50-4.73)	2.63 (0.56-6.38)	0.280
Lymphocyte ($x10^3$)	0.44 (0.24-1.00)	0.57 (0.33-1.04)	0.470
Neutrophil ($x10^3$)	1.00 (0.08-2.03)	1.17 (0.44-3.62)	0.127
Neutrophil lymphocyte ratio	0.71 (0.24-4.27)	1.23 (0.43-7.13)	0.219
C-reactive protein (CRP), mg/dl	102.95 (36.8-149.3)	134.25 (71.0-200.5)	0.100
Patient status			
Outpatient	8 (17.78%)	3 (8.82%)	0.335
Inpatient	37 (82.22%)	31 (91.18%)	
Length of stay in hospital, days	21 (6-38)	10.5 (6-28)	0.275
Mortality	10 (22.22%)	10 (29.41%)	0.641
Sample acceptance time, season			
Spring	6 (13.33%)	5 (14.71%)	0.802
Summer	4 (8.89%)	1 (2.94%)	
Autumn	10 (22.22%)	8 (23.53%)	
Winter	25 (55.56%)	20 (58.82%)	
Sample acceptance time in hospitalized patients, days	1 (1-12)	3 (1-5)	0.418
Galactomannan			
Not Evaluated	4 (8.89%)	2 (5.88%)	0.869
Negative	39 (86.67%)	31 (91.18%)	
Positive	2 (4.44%)	1 (2.94%)	

Continued

Table IV *(continued)*. Analysis of variables according to respiratory PCR kit results.

	Respiratory kit results		
	Negative (n=45)	Positive (n=34)	p
CMV			
Not Evaluated	3 (6.67%)	2 (5.88%)	
Negative	35 (77.78%)	23 (67.65%)	0.447
Positive	7 (15.56%)	9 (26.47%)	
Blood culture			
Not Evaluated	11 (24.44%)	5 (14.71%)	
Negative	30 (66.67%)	28 (82.35%)	0.315
Positive	4 (8.89%)	1 (2.94%)	
Tracheal culture			
Not Evaluated	23 (51.11%)	13 (38.24%)	
Negative	19 (42.22%)	18 (52.94%)	0.572
Positive	3 (6.67%)	3 (8.82%)	
Urine culture			
Not Evaluated	16 (35.56%)	5 (14.71%)	
Negative	27 (60.00%)	28 (82.35%)	0.083
Positive	2 (4.44%)	1 (2.94%)	

Since quantitative variables were not normally distributed, median (1st quartile-3rd quartile) was used. Qualitative variables are given as frequency (percentage). (1)Patients may have more than one of the findings. AML: acute myeloid leukemia ALL: acute lymphoblastic leukemia, CMV: Cytomegalovirus.

In addition, it is conceivable to associate this result with the fact that AML was the most common leukemia in the adult population and constitutes approximately 80% of all cases[13]. In the current study, the frequency of respiratory panel positivity was higher among patients with HM who were found to have any respiratory tract infection symptoms, cough, and any radiological findings or ground glass appearance. In the study group, the three most common comorbidities among patients who underwent PCR testing were DM (18.99%), renal failure (7.59%), and congestive heart failure (5.06%). In a 5-year prospective study of transplantation patients by Kumar et al[14], the three most common comorbidities associated with influenza infection were DM (30.5%), chronic renal failure (18.3%), and obesity (12.3%), respectively. When any respiratory tract infection symptom is observed in patients with HM, including patients with a common diagnosis of AML or with any comorbidity, it would be useful to obtain samples for evaluation to identify the infectious agent, particularly considering the importance of early diagnosis and treatment.

The incidence of respiratory virus infections varies greatly as a result of differences in screening parameters, study population, and testing methodology. Seasonal trends in patients with HM and HSCT recipients sometimes produce significant year-to-year variations in disease incidence and severity, reflecting the respiratory virus infection profile in the population[15]. In a multicenter, comprehensive prospective cohort study examining the nasal-swab PCR tests of hematology patients in 7 intensive care units, it was reported that viruses were detected in 21.3% of cases: 56.4% had rhinovirus/enterovirus and 30.7% had influenza/PIV/RSV[9]. In a prospective study[16] evaluating the main causes of morbidity and mortality in HSCT recipients, the three most common agents were reported as being influenza A and B, RSV, and human MPV, respectively. Viruses such as RSV, PIV, Influenza virus, and hMPV are reported[17] to be important factors causing pneumonia in HSCT recipients. In the study of Chemaly et al[4], it was reported that the incidence of RSV (2-17%) in HSCT recipients was higher than influenza (1.3-2.6%), PIV (4-7%), or hMPV (3-9%). In a study evaluating upper respiratory tract virus infections in patients with HMs, the frequency of infection was reported as 29.0%[18]. In a retrospective study[19] evaluating upper respiratory tract viral infections in patients with HMs after

Table V. Risk factors associated with mortality, logistic regression analyses.

	Univariate		Multivariable	
	OR (95% CI)	p	OR (95% CI)	p
Age	1.011 (0.983-1.040)	0.440		
Sex, female	1.376 (0.493-3.842)	0.542		
Congestive heart failure	0.982 (0.096-10.019)	0.988		
Kidney failure	7.125 (1.195-42.490)	**0.031**	4.790 (0.674-34.038)	0.117
Diabetes mellitus	1.091 (0.304-3.910)	0.894		
Diagnosis, Non-Hodgkin lymphoma	2.100 (0.649-6.790)	0.215		
Chemotherapy	1.021 (0.288-3.621)	0.974		
Steroid therapy	3.349 (0.697-16.090)	0.131		
Symptom	0.581 (0.206-1.637)	0.304		
Fever	0.846 (0.306-2.343)	0.748		
Weakness	0.000 (0.000-N/A)	0.999		
Cough	2.381 (0.724-7.834)	0.153		
Sputum	0.568 (0.062-5.180)	0.616		
Dyspnea	6.222 (1.333-29.042)	**0.020**	5.848 (1.143-29.915)	**0.034**
Others	0.708 (0.137-3.652)	0.680		
Pathological finding in radiological imaging[(1)]	1.187 (0.412-3.416)	0.751		
Consolidation	1.852 (0.538-6.375)	0.329		
Frosted glass appearance	0.836 (0.279-2.505)	0.749		
Effusion	1.500 (0.129-17.487)	0.746		
Atelectasis	0.000 (0.000-N/A)	0.999		
Others	2.074 (0.321-13.408)	0.444		
White blood cell ($x10^3$)	1.013 (0.996-1.032)	0.139		
Lymphocyte ($x10^3$)	0.994 (0.929-1.062)	0.850		
Neutrophil ($x10^3$)	1.012 (0.937-1.092)	0.768		
Neutrophil lymphocyte ratio	1.072 (0.999-1.151)	0.052		
C-reactive protein (CRP), mg/dl	1.001 (0.996-1.006)	0.735		
Respiratory kit results, Virus positive	1.682 (0.605-4.678)	0.319		
Respiratory kit results, Bacteria positive	2.426 (0.493-11.931)	0.275		
Respiratory kit results, positive	1.458 (0.526-4.040)	0.468		
Galactomannan, Positive	1.500 (0.129-17.487)	0.746		
CMV, Positive	4.250 (1.326-13.617)	**0.015**	2.897 (0.793-10.584)	0.108
Blood culture, positive	0.724 (0.076-6.883)	0.778		
Tracheal culture, positive	0.568 (0.062-5.180)	0.616		
Urine culture, positive	6.444 (0.552-75.281)	0.137		
Nagelkerke R^2	-	0.221		

OR: Odds ratio, CI: Confidence interval, N/A: not applicable, CMV: Cytomegalovirus. [(1)]Patients may have more than one of the findings.

allogeneic HSCT, it was reported that 64% of the patients had a positive viral panel 140 days after transplantation, and the most common agents were RSV (32%) and PIV (32%). In a retrospective study of adults with HMs, it was reported that influenza, PIV, and RSV were responsible for most cases, and their frequencies were approximately equal[20]. In a prospective study[21] of respiratory tract virus infections in adult patients with HMs, hMPV was detected in 9% of acute infections, which was found to be similar to the frequency of RSV in the cohort. In the study of Mikulska et al[22], it was reported that 22% of 264 swabs taken in a hematology clinic gave positive results, and the most frequently detected agents were influenza (32.8%), RSV (34.4%), rhinovirus (19.7%), coronavirus (6.5%). In a study of adult HM patients diagnosed with viral respiratory infections by Cardenas et al[23], the most common viruses detected in multiplex PCR samples were rhinovirus/enterovirus (25%, 43.8%), Influenza

A/B (14%, 24.5%) and RSV A/B (7%, 12.2%), respectively. In the current study, one or more infectious agents were detected in 43.04% of the patients who underwent PCR testing for respiratory infection. After examining the samples, the three most common pathogens were found to be Influenza A virus (10.13%), SARS-CoV-2 (8.86%), and rhinovirus/enterovirus (7.59%). The high frequency of SARS-CoV-2 in this study due to the pandemic may have caused the virus distribution to be different from other studies. On the other hand, in this study, only tests performed with a preliminary diagnosis of respiratory tract infection who were hospitalized or had symptoms were evaluated. The results of patients who had not sought treatment due to being asymptomatic or having mild symptoms could have been different. Additionally, the possible differences between measurement tools used in the studies, the clinical conditions of the patients in the research groups, and the infectious agents in the communities they live in may have caused the variations in the results.

While some of the viruses that cause respiratory infections typically have a defined seasonality, most can occur throughout the year and at overlapping time periods[6]. While the incidence of some viruses, such as influenza and RSV, shows significant seasonal variation, rising particularly during the winter months, other viruses, such as PIV and adenovirus, tend to cause illness throughout the year[2]. Most of the samples examined in this study were taken in the winter (56.96%) and autumn (22.78%) seasons. In a retrospective study[20] evaluating respiratory virus infections in adults with HMs, it was reported that infections caused by influenza, RSV, and picornaviruses show a seasonal trend, occurring between November and April, while PIV infections occur throughout the year. It is often difficult to clearly distinguish the virus type by seasonal trend, clinical presentation, or radiological findings. This makes it important to use comprehensive diagnostic strategies, such as multiplex PCR, in which the virus type is clarified by direct examination of the sample[6].

The clinical presentation in respiratory tract virus infections is nonspecific, and the severity is variable. There is a spectrum ranging from asymptomatic disease to respiratory failure. Clinically, upper respiratory tract infections present with symptoms such as fever, rhinorrhea, sore throat, malaise, nasal congestion, headache, earache, and/or fever, which may present in varying degrees and combinations. In addition to these symptoms, they can also be detected as lower respiratory tract infections with localized or widespread pneumonia findings[6]. In the prospective study by Kumar et al[14], the most common symptoms of influenza infection were reported to be cough, fever, and flu-related findings. In the current study, 64.56% of patients undergoing PCR testing for respiratory tract virus infection were symptomatic, and the most commonly reported symptoms were fever (48.10%) and cough (18.99%). Considering these frequencies, it is noteworthy that 35.44% of the patients were asymptomatic, and 51.9% of them did not have fever as one of the symptoms. It is, therefore, vital not to overlook patients with asymptomatic infections in this population, in which patients are often immunocompromised due to HM and the treatments applied, and thus, even a seemingly simple infection causes mortality.

When respiratory tract virus infection is suspected in immunocompromised patients, radiological examinations are performed in the majority of subjects, and radiographic abnormalities can be detected at the time of diagnosis in slightly more than half of these examinations. These radiographic abnormalities include diffuse bilateral ground-glass infiltrates, small multifocal nodules, bronchial vascular thickening, and/or airspace consolidation. However, these findings may overlap with some other clinical entities[6]. Therefore, although chest imaging techniques may aid the diagnosis in these cases, they are usually nonspecific[8]. In this study, 62.03% of patients with HMs who underwent RT-PCR test had a radiological finding, and the most common radiological finding was ground glass appearance, with 32.91%. However, with these radiological findings, it is not possible to clarify the presence of a viral respiratory tract infection. Since imaging findings cannot differentiate between different viral etiologies, the presence of other viral, bacterial, and fungal co-infections and the type of virus can be confirmed by direct examination of obtained samples[2].

Viral respiratory infections can cause irreversible airway damage by contributing to persistent inflammation or activation of an inflammatory process. The susceptibility to other viral, bacterial, and fungal infections is increased as a result of respiratory virus infection, epithelial damage, impaired ciliary function, altered immune response, or upregulation of infected bacterial receptors. In addition, respiratory virus infections are often associated with bacterial or fungal pathogens and contribute to the development of pneumonia[11,24,25]. In a study[26] evaluating bronchoalveolar lavage samples of patients with

HM, it was reported that polymicrobial etiology was detected in 20.5% of the patients, and allogeneic HSCT was found to be a predictor of polymicrobial infection. CMV and RSV coinfection is an important factor in allogeneic HSCT patients with HMs and negatively affects the prognosis by facilitating the development of severe pneumonia. For instance, it has been reported[27] that while severe pneumonia was detected in 61% of cases with coinfection, it was diagnosed in only 10% of cases with or without mono-infection, and co-infection with CMV and RSV was detected in all patients who died of severe pneumonia. In a retrospective study[19] evaluating upper viral respiratory infections in patients with HMs after allogeneic HSCT, it was reported that patients with concurrent bacterial or fungal infections were more likely to have pneumonia. In the study of Yue et al[27], patients with HM who were found to have CMV and RSV coinfection had poor response to antiviral treatment and had greater risks for more severe infection and death. More than one pathogen was detected in 11.39% of the samples examined in this study. Polymicrobial respiratory tract infections are frequently encountered in patients with HM. Since the clinical course of these infections may be worse than in monoinfections, close monitoring for additional pathogens and early treatment can be valuable in immunocompromised patients.

Viral respiratory infections are common infections in the general population, but they can often lead to serious morbidity and mortality in patients with HMs[1]. In a study[18] evaluating the prevalence and clinical course of viral upper respiratory tract infections in critically ill patients with HMs, the overall in-hospital mortality rate was reported to be 65.9%. In a prospective cohort study[9] evaluating hematology patients in intensive care units, mortality associated with viral respiratory infection was reported as 26%. A similar mortality rate (25%) was found for adults with HMs who suffered from RSV-caused lower respiratory tract infection. In addition, it was reported[28] that neutropenia, lymphopenia, high-grade immunodeficiency, and RSV detection from bronchoalveolar lavage fluid were associated with 60-day mortality in multivariable analysis. In a retrospective study by Atilla et al[19] evaluating viral infections of the upper respiratory tract after allogeneic HSCT in patients with HMs, the mortality rate was 40%, and lymphopenia and high CRP levels were reported as risk factors for mortality. Vakil et al[28] reported a mortality rate of 25% in HM patients and demonstrated that neutropenia and lymphopenia were associated with 60-day mortality in RSV infections.

Allogeneic HSCT recipients who experience any respiratory virus infection after the procedure are known to have a higher risk of all-cause death compared to patients without infection[29]. In a study[11] evaluating lower respiratory tract viral diseases in HSCT recipients, high-dose steroid use and lymphopenia were reported as independent risk factors for mortality within 30 days after lower respiratory tract infection. In a retrospective review of respiratory viral infections in adults with HMs by Chemaly et al[20], the mortality rate from viral pneumonia was reported to be only 15%, and having an absolute lymphocyte count of $\leq$200 while suffering from influenza pneumonia was determined to be the only independent predictor of fatal outcome. In the current study, during the two-year period for which the data were evaluated, the mortality rate among patients was 25.32%. The current study found that patients with dyspnea had a 5.848-fold higher risk of death than those without. In multivariable logistic regression analysis, no relationship was found between mortality risk and factors such as renal failure and CMV positivity.

Acute respiratory failure is the leading cause of intensive care hospitalization in patients with HMs and causes high mortality. The need for mechanical ventilation is the main determinant of prognosis[30]. Early detection of respiratory virus infections in patients with HM, early initiation of treatment, and providing respiratory support when necessary are of vital importance in this patient group with immunodeficiency.

In a study[31] evaluating 3,702 immunocompromised patients from 6 continents, the most frequently reported risk factors for immunodeficiency were steroid use (45%), hematological cancer (25%), and chemotherapy (22%). Chemotherapy and steroid use in patients with HMs may increase both the risk of developing infection and the risk of mortality. Vakil and Evans[8] reported that T-cell-depleting chemotherapy increases the risk of life-threatening viral pneumonia in patients with HMs. In a study[11] evaluating common respiratory viruses in HSCT recipients, steroid use was reported to be an independent risk factor for mortality within 30 days of infection. In this study, 79.75% of patients were receiving chemotherapy, and 77.22% were receiving steroids when the samples were obtained. Positivity for respiratory viruses was not associated with HMs or treatment (chemotherapy, steroids). In addition, neither steroid nor chemotherapy administration during viral in-

fections were risk factors associated with mortality. There are other studies reporting no association between corticosteroid use and mortality[28].

CMV is one of the most important infections that occurs after allogeneic HSCT, and CMV has also been reported[32] to be a potentially important pathogen in patients treated with recently released drugs for HMs. CMV reactivation remains a major problem in high-risk HM patients. In this study, the frequency of CMV positivity was found to be 20.25%, and although CMV positivity was found to increase mortality in univariate logistic regression analysis, no correlation was found between mortality risk and CMV positivity in multivariable analysis. CMV is the most common cause of viral pneumonia after allogeneic HSCT[2]. In the study by George et al[33], at 43 months follow-up after HSCT, it was reported that patients without CMV reactivation (57.3%) had significantly higher survival compared to patients with CMV reactivation (45.5%), and CMV seropositivity or reactivation was associated with increased morbidity and mortality.

While the global incidence of hematologic malignancy is increasing, survival times are increasing with recent successes in diagnosis and treatment strategies. As these patients with increased survival are treated with new agents that may result in secondary immunodeficiency, viral respiratory infections will be encountered at an increased frequency. The use of strategies to identify patients in the early stages of the disease course is crucial to reducing morbidity and mortality caused by viral infections of the respiratory tract[1]. Although multiplex PCR panels offer clear advantages in diagnostic sensitivity and speed compared to conventional methods, these tests need to be carefully integrated into clinical practice. We believe that it would be beneficial to establish permanent strategies for routine use, as multiplex tests have various limitations, such as costs, risk of contamination, panel composition variations between manufacturers, uncertainties about integrating panels into laboratory workflows, and the need for expertise when performing tests[5].

Given the high cost of antiviral therapies, the lack of clear evidence for drug efficacy in this patient population, and the high morbidity/mortality, it is worth emphasizing the need for effective vaccines against respiratory viruses. Vaccines have not yet been produced for all relevant viruses, and the effectiveness of antiviral treatments is insufficient[4]. Apart from influenza, currently available antivirals have limited efficacy and/or potential for toxicity[6]. For these reasons, preventive measures, including vaccinations with current vaccines, hand hygiene, contact isolation, and face masks remain the best approach to reduce the burden of viral infections in HM patients[4,34].

Limitations

Due to the retrospective nature of the study, the data should be interpreted with caution. The results obtained in the research need to be tested with prospective studies. Stronger evidence could, in fact, be obtained with a population-based and prospective study. On the other hand, the design of the study included data from only medically-followed respiratory infection cases. This may mean that data on mildly symptomatic or asymptomatic cases were not included in the study and may affect the results. Another limitation is that data related to vaccines for influenza or SARS-CoV-2 were not included in the study. The lack of detailed data on the treatment features of the infections and the stage/prognosis of HMs is another limitation. Moreover, since the length of stay in the intensive care unit is an important factor with respect to infections, the lack of data in this regard is also a limitation.

Conclusions

As a result of the analyses, the frequency of PCR test positivity for respiratory tract viruses was 43.04% in patients with HM who presented with symptoms associated with respiratory virus infections. AML, symptomatic infection, cough, and presence of any radiological findings and ground glass appearance were found to be associated with a higher likelihood of having PCR test positivity for respiratory tract viruses. The most common symptom was fever, and the most common radiological finding was ground glass appearance. Mortality risk was greater in the presence of dyspnea among HM patients with viral infection of the respiratory tract. It is important to carefully monitor the trends of respiratory virus infections in patients with HMs and to regulate diagnosis and treatment guidelines accordingly. There is a need for population-based and prospective studies focusing on these infections in patients with HM.

Conflict of Interest

The authors declare that they have no conflicts of interest.

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Authors' Contributions
K. Şanlı, N. Karabulut, M. Ayer; concept, design, supervision, data collection, literature search, writing manuscript, critical review, analysis and interpretation, and resources. S. Alaçam, A. Gümüş; concept, design, data collection, analysis, literature review, manuscript writing, critical review, resources, materials, and editing

Ethics Approval
This study was conducted in accordance with the principles of the Declaration of Helsinki. The ethical approval was obtained from Başakşehir Çam and Sakura City Ethical Committee (No.: 2023.05.207).

Informed Consent
Not applicable, due to the retrospective nature of the study.

Data Availability
All data used in this study can be obtained from the author upon request.

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