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Burden of Human Metapneumovirus Infections in Cancer Patients: Risk Factors and Outcomes

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Abstract

Background—Human metapneumovirus (hMPV) causes upper and lower respiratory tract infections (URI and LRI, respectively) in healthy and immunocompromised patients; however, its clinical burden in patients with cancer remains unknown.

Methods—In a retrospective study of all laboratory-confirmed hMPV infections treated at our institution between April 2012 and May 2015, we determined clinical characteristics, risk factors for progression to LRI, treatment, and outcomes in patients with cancer.

Results—We identified 181 hMPV infections in 90 (50%) patients with hematologic malignancies (HM), 57 (31%) hematopoietic cell transplantation (HCT) recipients, and 34 patients (19%) with solid tumors. Most patients (92%) had a community-acquired infection, presented with URI (67%), and 43% developed LRI (59 presented with LRI and 19 progressed from URI to LRI). On multivariable analysis, an underlying HM (adjusted odds ratio [aOR], 3.11(1.12-8.64); P=0.029), nosocomial infection (aOR, 26.9 (2.79-259.75); P=0.004), and hypoxia (SpO2 ≤ 92%) at presentation (aOR, 9.61(1.98-46.57); P = 0.005) were independent factors associated with LRI. All-cause mortality at 30 days from hMPV diagnosis was low (4%) and patients with LRI had a 10% mortality rate at day 30 from diagnosis; whereas, patients with URI had 0% mortality rate.

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Conclusions—hMPV infections in patients with cancer may cause significant morbidity, especially for those with underlying HM who may develop an LRI. Despite high morbidity and the lack of directed antiviral therapy for hMPV infections, mortality at day 30 from this infection remained low in this studied population.

Keywords

hMPV; stem cell transplantation; leukemia; cancer; respiratory virus; pneumonia; death

Introduction

In 2001, human metapneumovirus (hMPV), an enveloped nonsegmented negative RNA-Paramyxoviridae virus, was discovered in the Netherlands [1]. It has been reported in 4% of adults and 13% of children with community-acquired pneumonia [2-4]. The virus can affect all age groups with upper respiratory infections (URI) and lower respiratory tract infections (LRI); however, severe disease has been described in young children [5] and older adults [6]. The diagnosis of hMPV from respiratory specimens is dependent upon molecular assays (i.e., reverse transcriptase polymerase chain reaction), which are more sensitive than older methods such as direct fluorescent antibody, viral cultures, and serology.[7] In 2012, we adopted a new molecular assay (FilmArray Respiratory Panel, BioFire Diagnostics, LLC) which enhanced the diagnosis of patients with respiratory viral infections secondary to hMPV and other respiratory viruses from respiratory specimens.

hMPV infections in immunocompromised hosts have been described in small case series. In patients with cancer, hMPV incidence is similar to that in the immunocompetent population (approximately 7%) [8,9]. hMPV-associated LRI has been reported in as many as 41% of patients with cancer [8] and 100% of children undergoing hematopoietic cell transplantation (HCT) [10]. Yet hMPV-associated mortality remains low [8,9,11] unless bronchoalveolar lavage (BAL) findings are positive for the virus [12]. These studies were limited by small sample size and inadequate power to determine risk factors and outcomes of hMPV infections in patients with cancer and associated mortality and morbidity.[13] Although supportive measures may be in place, hMPV treatment remains a challenge because the only in vitro active drug choice is ribavirin for inhibition of hMPV replication.[14,15]. In addition, intravenous immunoglobulins (IVIGs) with or without ribavirin have been used in patients with hMPV infections[16-18] with lack of systematic evaluation for efficacy. The ECIL 4 European Conference on Infections in Leukemia addressed community-acquired respiratory viruses, including hMPV; however, this therapy lacks systematic evaluation[19].

In this large retrospective study, we aimed to determine the clinical characteristics and outcomes of hMPV infections in patients with cancer who are immunocompromised. We attempted to characterize the risk factors associated with development of hMPV-associated LRI, hMPV-associated mortality, and all-cause mortality to identify patients with specific underlying malignancies who are at higher risk for these outcomes and who may be suitable targets for antiviral therapy.

Patients and methods

This study was conducted at the University of Texas MD Anderson Cancer Center in Houston, Texas. The Infection Control database was searched to identify all patients with laboratory-confirmed hMPV infections between April 2012 and May 2015. The BioFire FilmArray Respiratory Panel at our institution was used to diagnose respiratory viral infections including hMPV. The institutional review board approved the protocol, and the waiver for informed consent was granted.

Data collection

We reviewed patient medical records and collected these data: demographics including age, gender, and race; smoking history; cancer type; and cancer status (complete remission or active disease) at the time of infection. For HCT recipients, we reviewed the underlying cancer, the type of transplant (matched-related donor, matched-unrelated donor, haploidentical, mismatched, and autologous), the source (marrow, cord, or peripheral), date of HCT, use of myeloablative versus nonmyeloablative conditioning regimens and type of immunosuppressive therapy used, time of engraftment, history and type of graft-versus-host-disease (GVHD) (acute or chronic), grade and organ involvement, and cytomegalovirus (CMV) serostatus. For hMPV infection episodes, we included coinfections within 30 days prior to and after the hMPV episode, if any; date of symptom onset; type of infection at the time of presentation (community-acquired versus nosocomial acquisition); infection site at presentation (URI versus LRI); absolute neutrophils count (ANC); absolute lymphocytes count (ALC); and gamma globulin levels (when available) up to 30 days before presentation. Systemic steroid use and doses were recorded within 30 days before the infection diagnosis. We also collected data on outcomes and therapy, including whether patients required hospitalization, length of stay if admitted, intensive care unit admission (at onset or later), use of mechanical ventilation, use of ribavirin (oral versus aerosolized form), IVIGs, and date and cause of death. Oxygen saturation at presentation was recorded as well as the lowest oxygen saturation during the infection and the type of oxygen supplementation (nasal cannula, venti-mask, face-mask, vapotherm, or bilevel positive airway pressure).

Definitions

hMPV cases were defined in this study as situations in which a patient with cancer developed acute symptomatic respiratory illness and had a positive nasal wash result and/or BAL finding indicating hMPV. Community-acquired cases occurred when patients developed symptoms while they were outpatients and/or before hospitalization or within the first 5 days after admission [20,21]. Symptomatic hMPV infections that develop > 5 days after hospitalization of patients are considered nosocomially-acquired. URI was defined as the development of rhinorrhea, nasal or sinus congestion, otitis media, pharyngitis, cough, or shortness of breath with no hypoxemia or infiltrates on chest radiographic imaging in patients with a positive hMPV test result in a nasal wash. LRI was defined when new or worsening pulmonary infiltrates were seen on chest radiograph and/or when hMPV was detected in a lower respiratory specimen such as endotracheal tube aspirate, sputum, or BAL. Neutropenia was defined as ANC<500/mL and lymphopenia was defined as

ALC<200/mL. All-cause mortality was assessed within 30 days and 90 days from hMPV diagnosis and was attributed to hMPV if a patient had persistent or progressive hMPV LRI with respiratory failure at the time of death.

Statistical analysis

We evaluated patient characteristics using descriptive statistics. Categorical variables were compared using the χ^2 test or Fisher's exact test, and continuous variables were compared using the Student *t* test or Wilcoxon rank sum test. Multivariable logistic regression analyses were used to identify risk factors associated with LRI and reported as adjusted odds ratios (aOR) and 95% confidence intervals (CI). A secondary model restricted to those patients who presented with URI (n=122) was also constructed to identify risk factors for progression from URI to LRI. The probability of progression from URI to LRI between 3 cancer groups (hematologic malignancies [HM], HCT, and solid tumor) was compared using a Kaplan-Meier failure curve. A 2-sided *P* value of 0.05 was considered statistically significant. All statistical analyses were performed with Stata Software Version 13 (Statacorp, College Station, Texas).

Results

Patients' characteristics

Between April 2012 and May 2015, 181 laboratory-confirmed hMPV infections were identified in patients with cancer; 34 (19%) patients had solid tumors, 57 (31%) patients were HCT recipients (in remission), and 90 (50%) patients had HM. Patients with relapsed HM after HCT were included in the HM group. Patients' characteristics are depicted in **Table 1.** The median age was 59 years (range, 1-88 years), and 60% were men. Most patients were non-Hispanic whites (111, 61%) and never smoked (126, 70%). Among patients with HM or post-HCT status, multiple myeloma was the most common underlying malignancy (30%). The majority of patients (92%) had community-acquired infections that were detected throughout the year with a peak during April and May **(Figure 1)** and had occurred with URI (67%). The overall LRI rate was 43%, and patients with HM had the highest rate of LRI (54%). All-cause mortality at days 30 and 90 from infection diagnosis was 4% and 7%, respectively.

hMPV-associated LRI

Patient characteristics associated with LRI are depicted in **Table 2.** Patients with LRI were more likely than patients with URI to have HM (adjusted odds ratio [aOR], 3.11; 95% confidence interval [CI], 1.12-8.64; $P = 0.029$), nosocomially-acquired hMPV(aOR, 26.9; 95% CI, 2.79-259.75; $P = 0.004$), and hypoxia (SpO2 ≤ 92%) at presentation (aOR, 9.61; 95% CI, 1.98-46.57; $P = 0.005$). When the logistic model was restricted to only patients who presented with URI, having an underlying HM was a significant predictor for progression to LRI (aOR, 27.23; 95% CI, 1.44-514.82; $P = 0.028$), as did having nosocomially-acquired infections(aOR, 500.41; 95% CI, 15.79-15854.59; $P < 0.001$). The Kaplan-Meier failure curve showed a significantly higher incidence of LRI in the HM group versus the solid tumor or HCT groups ($P = 0.016$) **(Figure 2).** Age, gender, smoking status,

immunodeficiency status based on ANC and ALC values, steroid use, and presence of pulmonary copathogens prior to hMPV diagnosis did not significantly affect progression to LRI in this cohort.

Among the 78 patients with LRI, BAL was performed on 33 (42%) and hMPV was detected in 23 (70%). *Escherichia coli (E. coli)* was detected in 1 patient, and no pathogens were detected in the remaining 9 patients. Copathogens were recovered from BAL samples of only 7 patients with LRI and hMPV positivity and included *Cytomegalovirus* (1), *E. coli* (1), methicillin-resistant *Staphylococcus aureus (S. aureus)* (1), methicillin-sensitive *S. aureus* (1), parainfluenza virus (PIV) 3 (1), respiratory syncytial virus (RSV) (1), coronavirus 229E (1), and *Arthrographis* (1).

All-cause and hMPV-associated mortality

Twelve patients died at a median of 15 days (range, 1-45 days) within their hMPV diagnosis, and mortality rates were similar for all 3 cancer groups. Of these, 4 patients had probable hMPV attributed death (3 with relapsed or refractory HM and 1 matched unrelated donor [MUD] HCT recipient) after progression to respiratory failure within 18 days of hMPV diagnosis (range, 5-36 days). Only 2 patients with hMPV-associated death had pulmonary coinfections, 1 with *Stenotrophomonas maltophilia* and the other with *Aspergillus terreus*. The remaining 8 patients died from cancer relapse (4) and other causes (4) at a median of 22 days (range, 1-45 days).

Antiviral therapy (ribavirin and IVIG)

Five patients received ribavirin therapy (2 at the URI stage and 3 at the LRI stage), and 31 patients received IVIG (14 at the URI stage and 17 at the LRI stage). Of the 4 patients who died with respiratory failure, 1 received IVIG and 1 received aerosolized ribavirin with IVIG at the LRI stage, while the others had not received antiviral therapy.

Airflow decline

Pulmonary function tests after infection were performed in 22 HCT recipients (16 allogeneic HCT and 6 autologous HCT) at an average of 60 days (range, 18-520 days) from hMPV diagnosis. Evidence of airflow decline, defined as a drop of at least 15% in forced expiratory volume (FEV1) from pre-HCT to post-infection, was observed in 8 (36%) patients (4 who had matched related donor HCT, 3 who had matched unrelated donor, and 1 who had autologous HCT). The median delta drop in FEV1 was 26% (range, 16%-49%) within a median of 56 days (range, 33-307 days) after hMPV infection. Five of these patients had LRI; however, all patients survived.

Gamma globulin levels

In a subgroup of 39 HCT recipients who had gamma globulin levels checked at the time of presentation, significantly higher levels of gamma globulin levels were observed in patients with URI (1032 mg/dL ± 561) versus patients with LRI (566 mg/dL ± 197; $P = 0.01$).

Discussion

In this retrospective study of hMPV infections in 181 patients with cancer, we report a high incidence of LRI (43%) and low overall mortality (7%) following these infections. Risk factors associated with LRI were underlying HM, nosocomially-acquired infection, and hypoxia at presentation. Patients with HM were more likely to progress from URI to LRI than HCT recipients or patients with solid tumors. All patients who died within 30 days from hMPV diagnosis had developed LRI (a 10% mortality rate in patients with LRI versus 0% in patients with URI).

An overall LRI rate of 43% was observed in these patients with cancer. This finding is higher when measured against previous studies, which reported an LRI rate of 28% to 41% in patients with cancer and an hMPV diagnosis [22]. Incidence of hMPV LRI was consistent with that reported for other respiratory viruses among HCT recipients and patients with HM [22,23]. Several risk factors associated with LRI were identified. Hypoxia at the time of diagnosis was a substantial risk factor in the multivariable analysis. Hypoxia and a supplemental oxygen requirement at diagnosis are associated with a higher rate of LRI and death in patients with cancer who have RSV, PIV, and influenza [23]. Oxygen use may be a surrogate marker of the extent of lung injury, which may lead to poor outcomes [24]. Of interest, an underlying diagnosis of HM significantly increased risk for LRI. Currently, there are limited data on hMPV infections in patients with HM and their impact; however, underlying HM was reported as a significant risk factor for progression to LRI in PIV-associated respiratory infections [25]. Patients with HM might have a high level of immunosuppression owing to active chemotherapy at the time of hMPV infection or due to their underlying relapse or refractory disease with subsequent prolonged cytopenias when compared to engrafted HCT recipients in remission.[26,27] Nosocomial acquisition of hMPV was associated with significantly higher risk for hMPV-associated LRI. A substantial number of nosocomial hMPV infections also was described in a previous hMPV study of patients with HM [8]. Respiratory viruses can be transmitted from either asymptomatic or symptomatic patients, family members, or healthcare workers. This highlights the importance of infection control measures because nosocomial infections were associated with higher morbidity rates in this study's population.

Neutropenia and/or lymphopenia have been described as major risk factors for LRI and death associated with other respiratory viruses [22,23]. This was not observed in our study or other studies examining patients with cancer who had hMPV and can be explained by the fact that only a few patients had these risk factors [8]. Similarly, other risk factors for progression to LRI and death (i.e., older age, smoking history, and steroid use) reported with other respiratory viruses were not observed in this population with hMPV infection.

An overall mortality rate of 4% at day 30 and 7% at day 90 is consistent with previous smaller case series in patients with cancer [8,9,11,28,29]. Also, hMPV-associated death was only 2%. When evaluated against other respiratory viral infections in patients with cancer (i.e., RSV or PIV), the lower incidence of mortality associated with hMPV infections in our patients with cancer suggests a difference in viral factors (genotype, viral fitness, or virulence) rather than host factors, and further study is warranted.

Ribavirin, which is mainly used to treat RSV infections in HCT recipients [23,30-32], has shown in vitro activity against hMPV by a direct antiviral effect [14] and in mouse models by reducing viral replication [15]. In a few case reports, the use of ribavirin was associated with good outcomes following severe hMPV infections in patients with cancer [17,33-35]. In our study, the mortality rate remained low despite the lack of ribavirin use in most of the patients and those with LRI in particular.

In a subgroup analysis of 39 HCT recipients who had gamma globulin levels checked at the time of presentation, we observed significantly higher levels of gamma globulins in patients with URI than in those with LRI. Gamma globulin levels are much lower in patients with chronic lymphocytic leukemia (CLL) who have a history of any infection than in patients with CLL with no history of infection [36]. This suggests that higher gamma globulin levels can protect against worse outcomes. Standard IVIG administration can inhibit hMPV replication in vitro [14], so we hypothesize that IVIG administration may be beneficial in HCT recipients to prevent progression from hMPV URI to LRI; however, an association between IVIG administration and LRI prevention could not be shown in our study and needs to be systematically determined in future trials. We did not identify other significant risk factors such as age, smoking status, levels of immunodeficiency (ANC, ALC), type of conditioning regimen, and CMV serostatus of the donor or recipient, GVHD, time of engraftment, HCT cell source, or HCT recipient exposure to steroids. In a 2015 study, use of at least 1mg/kg of steroids within 2 weeks leading to diagnosis was the only significant risk factor identified for progression to LRI according to a multivariate regression analyses of 118 HCT recipients [37].

This retrospective study has many limitations including the lack of hMPV quantification in respiratory secretions, which can indicate disease severity as seen in hMPV studies in populations for which higher viral loads have been associated with increased risk for LRI and hospitalization [38,39]. Several studies suggest that severity of disease and symptom manifestations varies with hMPV genotype [40,41], but this information was not available in our cohort.

For patients with cancer, the burden of hMPV infection is similar to the burden associated with other respiratory viral infections. However, the mortality rate following hMPV infections is lower than mortality associated with other related viruses such as RSV. Patients with HM, nosocomial infections, and hypoxia at presentation should be closely monitored for risk of progression to LRI. Because hMPV may be acquired nosocomially, leading to worse outcomes and high morbidity, strict adherence to infection control measures and universal hand hygiene should be underscored. The significance of gamma globulin levels and the role of IVIG in prevention of hMPV-associated LRI and/or mortality should be determined in future studies, especially among HCT recipients and patients with HM.

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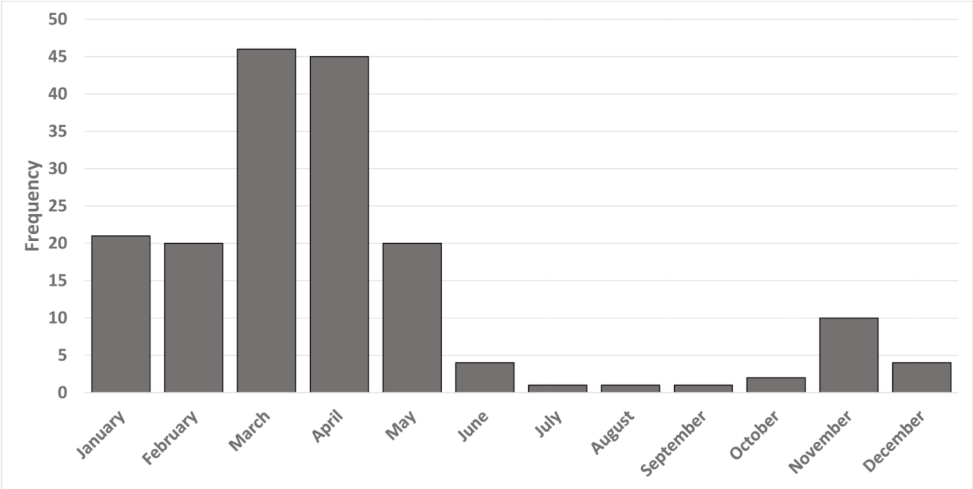

Fig 1. Seasonal distribution of hMPV infections between April 2012 and May 2015 (n = 181)
Abbreviation: hMPV, human metapneumovirus.

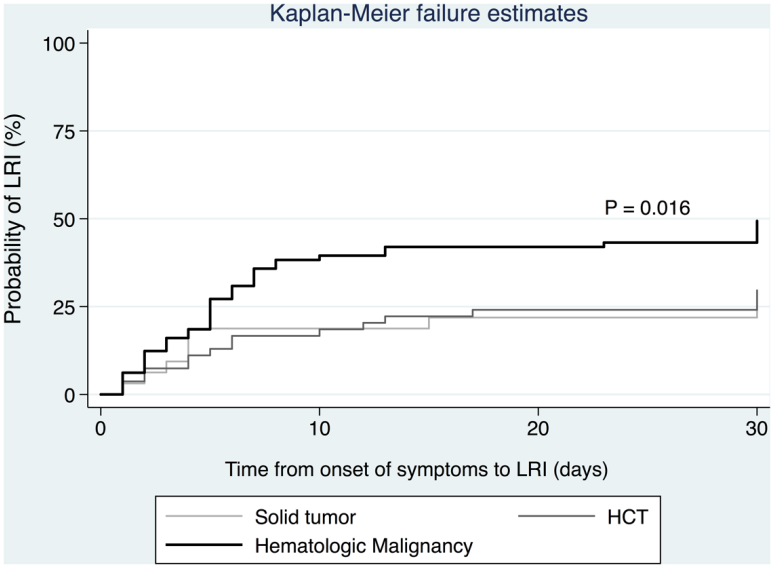

Fig 2. Kaplan-Meier failure curve for progression to LRI over time (restricted to patients presenting with URI)

Abbreviations: HCT, hematopoietic cell transplantation; LRI, lower respiratory tract infection.

TABLE 1

Characteristics and Outcomes of 181 Patients With Cancer and Human Metapneumovirus Infections

	No. of Patients (%)			
Characteristic	**Solid Tumors**	**HCT, Remission**	**HM**	**Total**
Total cohort	34 (19)	57 (31)	90 (50)	181 (100)
Age: Median [range] y	62 [3-86]	56 [16-76]	59 [1-88]	59 [1-88]
Sex				
Male	16 (47)	30 (53)	63 (70)	109 (60)
Female	18 (53)	27 (47)	27 (30)	72 (40)
Race[a]				
Non-Hispanic white	16 (47)	36 (63)	59 (66)	111 (61)
Hispanic	11 (32)	12 (21)	16 (18)	39 (22)
Black	5 (15)	6 (11)	8 (9)	19 (11)
Asian	1 (3)	2 (3)	2 (2)	5 (3)
Other	1 (3)	1 (2)	4 (4)	6 (3)
Smoking[a]				
Never smoker	22 (65)	40 (70)	64 (71)	126 (70)
Former smoker	11 (32)	16 (28)	22 (24)	49 (27)
Current smoker	1 (3)	1 (2)	3 (3)	5 (3)
Type of malignancy				
AML	0 (0)	12 (21)	14 (16)	26 (14)
ALL	0 (0)	9 (16)	13 (14)	22 (12)
CML	0 (0)	2 (4)	6 (7)	8 (4)
CLL	0 (0)	3 (5)	4 (4)	7 (4)
Hodgkin lymphoma	0 (0)	1 (2)	5 (6)	6 (3)
NHL	0 (0)	11 (19)	10 (11)	21 (12)
MDS	0 (0)	2 (4)	4 (4)	6 (3)
MM	0 (0)	14 (25)	30 (33)	44 (24)
AA	0 (0)	2 (4)	0 (0)	2 (1)
Other	34 (100)	1 (2)	4 (4	39 (22)
Type of HCT				
None	34 (100)	0	64 (71)	98 (54)
MRD	0 (0)	20 (35)	2 (2)	22 (12)
MUD	0 (0)	16 (28)	3 (33)	19 (10)
Haploidentical	0 (0)	3 (5)	1 (1)	4 (2)
Cord	0 (0)	2 (4)	2 (2)	4 (2)
Mismatched	0 (0)	1 (2)	0	1 (1)
Autologous	0 (0)	15 (26)	18 (20)	33 (18)

	No. of Patients (%)			
Characteristic	**Solid Tumors**	**HCT, Remission**	**HM**	**Total**
HCT cell source				
Bone marrow	0 (0)	7 (12)	0 (0)	7 (4)
Cord	0 (0)	2 (4)	2 (2)	4 (2)
Peripheral	0 (0)	48 (84)	24 (27)	72 (40)
Type of infection				
Community-acquired	32 (94)	52 (91)	82 (91)	166 (92)
Nosocomial	2 (6)	5 (9)	8 (9)	15 (8)
Site of infection at the time of presentation				
URI	25 (74)	43 (75)	54 (60)	122 (67)
LRI	9 (26)	14 (25)	36 (40)	59 (33)
Progression from URI to LRI				
No	24 (71)	38 (67)	41 (46)	103 (57)
Yes	1 (3)	5 (9)	13 (14)	19 (10)
Time to progression from URI to LRI: Median [range], d[b]	1	12 [1-30]	8 [1-30]	8 [1-30]
Overall LRI				
No	24 (71)	38 (67)	41 (46)	103 (57)
Yes	10 (29)	19 (34)	49 (54)	78 (43)
Steroids within 30 d before hMPV				
No	25 (74)	39 (70)	52 (58)	116 (64)
Yes	9 (26)	18 (32)	38 (42)	65 (36)
Lymphopenia[a]				
No	31 (91)	54 (95)	75 (83)	160 (88)
Yes	2 (6)	3 (5)	15 (17)	20 (11)
Neutropenia[a]				
No	29 (85)	56 (98)	69 (77)	154 (85)
Yes	4 (12)	1 (2)	21 (23)	26 (14)
Hypoxia at presentation				
>92%	29 (85)	53 (93)	82 (91)	164 (91)
≤92%	5 (15)	4 (7)	8 (9)	17 (9)
Ribavirin				
URI stage	0	1 (2)	1 (1)	2 (1)
LRI stage	0	2 (4)	1 (1)	3 (2)
IVIG				
URI stage	1 (3)	7 (13)	6 (7)	14 (8)
LRI stage	0 (0)	3 (5)	16 (18)	19 (11)
Coinfection before hMPV				

	No. of Patients (%)			
Characteristic	**Solid Tumors**	**HCT, Remission**	**HM**	**Total**
Pulmonary	5 (15)	11 (19)	15 (7)	31 (17)
Extrapulmonary	1 (3)	1 (2)	6 (7)	8 (4)
Coinfection after hMPV				
Pulmonary	3 (9)	2 (4)	4 (4)	9 (5)
Extrapulmonary	0 (0)	1 (2)	2 (2)	3 (2)
Hospital admission secondary to infection[c]	15/29 (52)	21/30 (70)	44/78 (56)	80/137 (58)
Length of hospital stay: Median [range], d[c]	4 [2-20]	6 [3-17]	6 [2-29]	6 [2-29]
ICU at onset	2 (6)	1 (2)	1 (1)	4 (2)
ICU later during the illness	1 (3)	1 (2)	4 (4)	6 (3)
Mechanical ventilation	3 (9)	2 (4)	3 (3)	8 (4)
Oxygen supplement	10 (29)	12 (21)	26 (29)	48 (27)
All-cause mortality, 30 d	1 (3)	1 (2)	6 (7)	8 (4)
All-cause mortality, 90 d	2 (6)	2 (4)	8 (9)	12 (7)

Abbreviations: AA, aplastic anemia; ALL, acute lymphoblastic leukemia; AML, acute myelogenous leukemia; CLL, chronic lymphocytic leukemia; CML, chronic myelogenous leukemia; HCT, hematopoietic cell transplantation; HM, hematologic malignancy; hMPV, human metapneumovirus; ICU, intensive care unit; IVIG, intravenous immunoglobulin; LRI, lower respiratory tract infection; MDS, myelodysplastic syndrome; MM, multiple myeloma; MRD, matched-related donor; MUD, matched-unrelated donor; NHL, non-Hodgkin lymphoma; URI, upper respiratory tract infection.

[a] One patient was missing information.

[b] This analysis was restricted to patients who progressed from URI to LRI (n = 19).

[c] Analysis of the time to progression excluded patients who were admitted before hMPV diagnosis.

TABLE 2

Patient Characteristics Associated With Human Metapneumovirus Lower Respiratory Tract Infection

	No. (%)		Total Cohort, n = 178[a]				Restricted to Patients who Presented With URI, n = 122	
Characteristic	**URI**	**LRI**	**Unadjusted OR [95% CI]**	***P***	**Adjusted OR [95% CI]**	***P***	**Adjusted OR [95% CI]**	***P***
All patients	103 (57)	78 (43)						
Age: Median/range, y[b]	59/1-84	59/7-88	1.08/0.93-1.26	.288	1.15/0.94-1.39	.167	1.06/0.77-1.45	.718
Sex								
Men	59 (54)	50 (46)	1.00					
Women	44 (61)	28 (39)	0.75 [0.41-1.38]	.354				
Race								
Non-Hispanic white	55 (50)	56 (50)	1.00				1.00	
Hispanic	27 (69)	12 (31)	0.44 [0.2-0.95]	.036	0.46 [0.18-1.13]	.091	0.54 [0.08-3.51]	.521
Black	12 (63)	7 (37)	0.57 [0.21-1.56]	.277	0.64 [0.2-2.10]	.464	4.6 [0.84-25.38]	.079
Asian/other	9 (82)	2 (18)	0.21 [0.05-1.06]	.058	0.15 [0.03-0.87]	.035	0.56 [0.05-6.3]	.635
Smoking								
Never	71 (56)	55 (44)	1.00				1.00	
Former/current smoker	31 (57)	23 (43)	0.96 [0.5-1.82]	.896	0.75 [0.34-1.65]	.475	1.19 [0.3-4.77]	.804
Underlying condition								
Solid tumor<zaq;4>	24 (71)	10 (29)	1.00				1.00	
HCT, in remission	38 (67)	19 (33)	1.2 [0.48-3.01]	.698	1.09 [0.37-3.23]	.877	4.35 [0.23-83.51]	.33
HM	41 (46)	49 (54)	2.89 [1.23-6.69]	.015	3.11 [1.12-8.64]	.029	27.23 [1.44-514.82]	.028
Type of infection								
Community-acquired	102 (61)	64 (39)	1.00		1.00		1.00	
Nosocomial	1 (7)	14 (93)	22.31 [2.86-173.79]	.003	26.9 [2.79-259.75]<zaq;5>	.004	500.41 [15.79-15,854.59]	< .001
Steroids								

	No. (%)		Total Cohort, n = 178[a]				Restricted to Patients who Presented With URI, n = 122	
Characteristic	**URI**	**LRI**	**Unadjusted OR [95% CI]**	***P***	**Adjusted OR [95% CI]**	***P***	**Adjusted OR [95% CI]**	***P***
No	70 (60)	46 (40)	1.00				1.00	
Yes	33 (51)	32 (49)	1.48 [0.8-2.72]	.213	0.89 [0.42-1.90]	.769	0.35 [0.08-1.64]	.184
Immunodeficiency								
None	86 (61)	56 (39)	1.00		1.00		1.00	
Neutropenia	9 (50)	8 (50)	1.54 [0.57-4.11]	.393	0.47 [00.12-1.79]	.268	0.16 [0-5.11]	.299
Lymphopenia	5 (42)	7 (58)	2.15 [0.65-7.11]	.210	1.16 [0.24-5.62]	.853	1.59 [0.13-19.44]	.717
Both	2 (25)	6 (75)	4.61 [0.89-23.64]	.067	3.39 [0.44-26.43]	.244	3.21 [0.13-79.16]	.476
Hypoxia at presentation								
>92%	89 (58)	64 (42)	1.00				1.00	
≤92%	3 (25)	9 (75)	4.17 [1.09-16.02]	.037	9.61 [1.98-46.57]	.005	10.08 [0.55-184.45]	.119
IVIG at URI stage								
No	92 (55)	75 (45)	1.00		—	—	1.00	
Yes	11 (79)	3 (21)	0.33 [0.09-1.24]	.102	—	—	0.6 [0.08-4.61]	.623
Pulmonary copathogen before hMPV diagnosis								
None	90 (60)	60 (40)	1.00				1.00	
Pulmonary	13 (42)	18 (58)	2.08 [0.95-4.55]	.068	1.69 [0.64-4.44]	.289	0.22 [0.02-2.57]	.226

Abbreviations: CI, confidence internal; HCT, hematopoietic cell transplant; HM, hematologic malignancy; hMPV, human metapneumovirus; IVIG, intravenous immunoglobulin; LRI, lower respiratory tract infection; OR, odds ratio; URI, upper respiratory tract infections.

[a] Complete information on all variables included in the model was available for 178 patients.

[b] Age was categorized into 10-year intervals.