Original Article

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

Firas El Chaer, MD[1,2]; Dimpy P. Shah, MD, PhD[1]; Joumana Kmeid, MD[1]; Ella J. Ariza-Heredia, MD[1]; Chitra M. Hosing, MD[3]; Victor E. Mulanovich, MD[1]; and Roy F. Chemaly, MD, MPH, FACP, FIDSA[1]

BACKGROUND: Human metapneumovirus (hMPV) causes upper and lower respiratory tract infections (URIs and LRIs, 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 the authors' institution between April 2012 and May 2015, clinical characteristics, risk factors for progression to an LRI, treatment, and outcomes in patients with cancer were determined. **RESULTS:** In total, 181 hMPV infections were identified in 90 patients (50%) with hematologic malignancies (HMs), in 57 (31%) hematopoietic cell transplantation (HCT) recipients, and in 34 patients (19%) with solid tumors. Most patients (92%) had a community-acquired infection and presented with URIs (67%), and 43% developed LRIs (59 presented with LRIs and 19 progressed from a URI to an LRI). On multivariable analysis, an underlying HM (adjusted odds ratio [aOR], 3.11; 95% confidence interval [CI], 1.12-8.64; $P = .029$), nosocomial infection (aOR, 26.9; 95% CI, 2.79-259.75; $P = .004$), and hypoxia (oxygen saturation [SpO2], $\leq 92\%$) at presentation (aOR, 9.61; 95% CI, 1.98-46.57; $P = .005$) were identified as independent factors associated with LRI. All-cause mortality at 30 days from hMPV diagnosis was low (4%), and patients with LRIs had a 10% mortality rate at day 30 from diagnosis; whereas patients with URIs had a 0% mortality rate. **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. ***Cancer* 2017;123:2329-37.** © *2017 American Cancer Society.*

KEYWORDS: cancer, death, human metapneumovirus (hMPV), leukemia, pneumonia, respiratory virus, stem cell transplantation.

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 (URIs) and lower respiratory tract infections (LRIs); however, severe disease has been described in young children[5] and older adults.[6] The diagnosis of hMPV from respiratory specimens depends on molecular assays (ie, reverse transcriptase-polymerase chain reaction), which are more sensitive than older methods like direct fluorescent antibody, viral cultures, and serology.[7] In 2012, we adopted a new molecular assay (FilmArray Respiratory Panel; BioFire Diagnostics, LLC, Salt Lake City, Utah), 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

Corresponding author: Roy F. Chemaly, MD, MPH, FACP, FIDSA, Department of Infectious Diseases, Infection Control, and Employee Health, Unit 402, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX 77030-4009; Fax: (713) 745-6839; rfchemaly@mdanderson.org

[1]Department of Infectious Diseases, Infection Control, and Employee Health, The University of Texas MD Anderson Cancer Center, Houston, Texas; [2]Department of Medicine, Baylor College of Medicine, Houston, Texas; [3]Department of Stem Cell Transplantation and Cellular Therapy, The University of Texas MD Anderson Cancer Center, Houston, Texas.

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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, our objective was 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 developing hMPV-associated LRIs, hMPV-associated mortality, and all-cause mortality to identify patients with specific underlying malignancies who are at higher risk for these outcomes and may be suitable targets for antiviral therapy.

MATERIALS AND METHODS

This study was conducted at the University of Texas MD Anderson Cancer Center (Houston, Tex). The Infection Control database was searched to identify all patients who had 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 a waiver for informed consent was granted.

Data Collection

We reviewed patient medical records and collected the following data: demographics, including age, sex, 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 transplantation (matched-related donor, matched-unrelated donor, haploidentical, mismatched, and autologous), the source (bone marrow, cord, or peripheral), date of HCT, receipt of myeloablative versus nonmyeloablative conditioning regimens and type of immunosuppressive therapy used, time of engraftment, history and type of graft-versus-host-disease (acute or chronic), grade and organ involvement, and cytomegalovirus serostatus. For hMPV infection episodes, we included coinfections within 30 days before and after the hMPV episode, if any; date of symptom onset; type of infection at the time of presentation (community-acquired vs nosocomial acquisition); infection site at presentation (URI vs LRI); absolute neutrophil count (ANC); absolute lymphocyte count (ALC); and γ-globulin level (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, receipt of ribavirin (oral vs 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 a 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 developed >5 days after hospitalization were 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 who had a positive hMPV test result in a nasal wash. LRI was defined when new or worsening pulmonary infiltrates were observed 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 an ANC <500/mL, and lymphopenia was defined as an 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 a 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 chi-square test or the Fisher exact test, and continuous variables were compared using the Student *t* test or the Wilcoxon rank-sum test. Multivariable logistic regression was used to identify the risk factors associated with LRI, and the results are reported as adjusted odds ratios (aORs) and 95% confidence intervals (CIs). 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 .05 was considered statistically significant. All statistical analyses were performed sing Stata software (version 13; StataCorp, College Station, Tex).

RESULTS

Patient Characteristics

Between April 2012 and May 2015, 181 laboratory-confirmed hMPV infections were identified in patients with cancer; 34 patients (19%) had solid tumors, 57 (31%) were HCT recipients (in remission), and 90 (50%) 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 (n = 111; 61%) and had never smoked (n = 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 (Fig. 1) and had occurred with URI (67%). The overall LRI rate was 43%, and patients with HM had the highest rate of LRI (54%). The all-cause mortality rate 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 those with URI to have HM (aOR, 3.11; 95% CI, 1.12-8.64; $P = .029$), nosocomially acquired hMPV(aOR, 26.9; 95% CI, 2.79-259.75; $P = .004$), and hypoxia (oxygen saturation [SpO2], $\leq 92\%$) at presentation (aOR, 9.61; 95% CI, 1.98-46.57; $P = .005$). When the logistic model was restricted only to 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; $P = .028$), as did having nosocomially acquired infections (aOR, 500.41; 95% CI, 15.79-15,854.59; $P < .001$). The Kaplan-Meier failure curve indicated a significantly higher incidence of LRI in the HM group versus the solid tumor or HCT groups ($P = .016$) (Fig. 2). Age, sex, smoking status, immunodeficiency status based on ANC and ALC values, steroid use, and the presence of pulmonary copathogens before hMPV diagnosis did not significantly affect progression to LRI in this cohort.

Among the 78 patients who had LRI, 33 (42%) underwent BAL, and hMPV was detected in 23 (70%). *Escherichia 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 who were positive for LRI and hMPV and included cytomegalovirus (n = 1), *E. coli* (n = 1), methicillin-resistant *Staphylococcus aureus* (n = 1), methicillin-sensitive *S. aureus* (n = 1), parainfluenza virus (PIV) 3 (n = 1), respiratory syncytial virus (RSV) (n = 1), coronavirus 229E (n = 1), and *Arthrographis* (n = 1).

All-Cause and hMPV-Associated Mortality

Twelve patients died within a median of 15 days (range, 1-45 days) after their hMPV diagnosis, and mortality rates were similar for all 3 cancer groups. Of these, 4 patients had probable hMPV-attributed deaths (3 with relapsed or refractory HM and 1 matched-unrelated donor and 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 (n = 4) and other causes (n = 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; whereas 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 recipients) 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 postinfection, was observed in 8 patients (36%), including 4 who underwent matched-related donor HCT, 3 who underwent matched-unrelated donor HCT, and 1 who underwent 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.

TABLE 1. Characteristics and Outcomes of 181 Patients With Cancer and Human Metapneumovirus Infections

Characteristic	No. of Patients (%)			
	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)
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)

TABLE 1. *Continued*

Characteristic	No. of Patients (%)			
	Solid Tumors	HCT, Remission	HM	Total
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				
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.

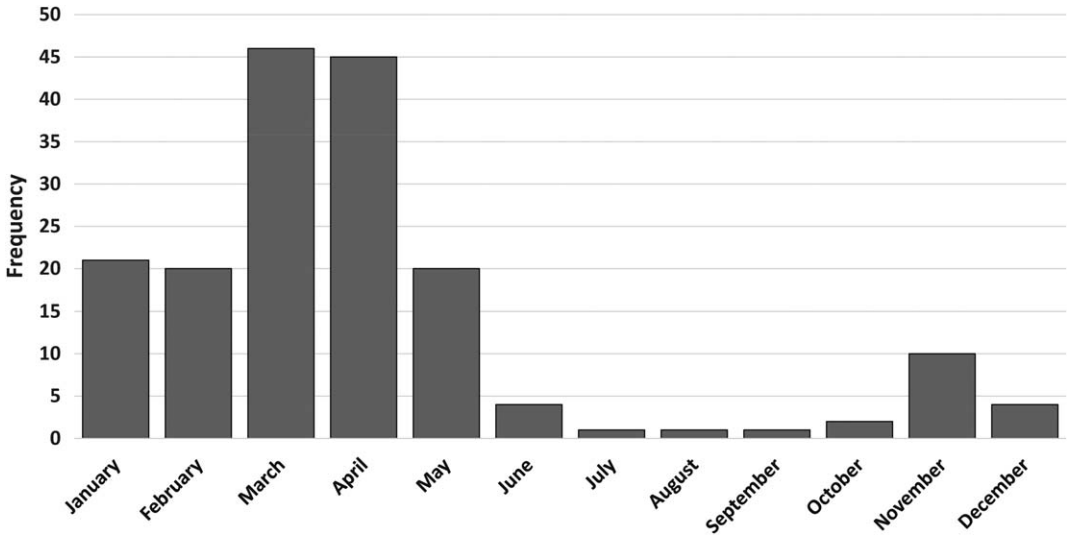

Figure 1. The seasonal distribution of human metapneumovirus infections between April 2012 and May 2015 is illustrated (n = 181).

γ-Globulin Levels

In a subgroup of 39 HCT recipients who had γ-globulin levels checked at the time of presentation, significantly higher levels of γ-globulin were observed in patients with URI (1032 ± 561 mg/dL) versus those with LRI (566 ± 197 mg/dL; $P = .01$).

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%) after these infections. Risk factors associated with LRI were underlying HM, nosocomially acquired infection, and hypoxia at

TABLE 2. Patient Characteristics Associated With Human Metapneumovirus Lower Respiratory Tract Infection

Characteristic	No. (%)		Total Cohort, n = 178[a]				Restricted to Patients who Presented With URI, n = 122	
	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	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]	.004	500.41 [15.79-15,854.59]	< .001
Steroids								
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.

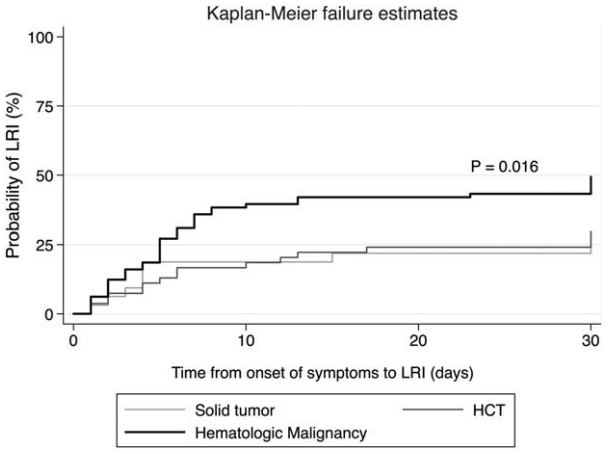

Figure 2. Kaplan-Meier failure curves illustrate the probability of progression to lower respiratory tract infection (LRI) over time (restricted to patients who presented with upper respiratory infection). HCT indicates hematopoietic cell transplantation.

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 an LRI (mortality rate, 10% in patients with LRI vs 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 who had cancer and an hMPV diagnosis.[22] The 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 higher rates of LRI and death in patients with cancer who have RSV, PIV, and influenza.[23] Oxygen use may be a surrogate marker for the extent of lung injury, which may lead to poor outcomes.[24] It is interesting to note that an underlying diagnosis of HM significantly increased the 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 patients with PIV-associated respiratory infections.[25] Patients with HM might have a high level of immunosuppression caused by active chemotherapy at the time of hMPV infection or because of their underlying relapsed or refractory disease with subsequent prolonged cytopenias compared with engrafted HCT recipients who are in remission.[26,27] Nosocomial acquisition of hMPV was associated with a significantly higher risk for hMPV-associated LRI. Substantial numbers of nosocomial hMPV infections also were 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 health care workers. This highlights the importance of infection-control measures, because nosocomial infections were associated with higher morbidity rates in our study 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 in other studies that examined patients with cancer who had hMPV and may be explained by the finding that only a few patients had these risk factors.[8] Similarly, other risk factors for progression to LRI and death (ie, older age, smoking history, and steroid use) reported with other respiratory viruses were not observed in this population with hMPV infection.

Overall mortality rates of 4% at day 30 and 7% at day 90 are consistent with previous smaller case series in patients with cancer.[8,9,11,28,29] Also, the rate of hMPV-associated death was only 2%. When evaluated against other respiratory viral infections in patients with cancer (ie, 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 demonstrated 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 after 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 patients, and particularly in those with LRIs.

In a subgroup analysis of 39 HCT recipients who had γ-globulin levels checked at the time of presentation, we observed significantly higher levels of γ-globulins in patients with URI than in those with LRI. Levels of γ-globulin are much lower in patients with chronic lymphocytic leukemia who have a history of any infection than in those who have chronic lymphocytic leukemia with no history of infection.[36] This suggests that higher γ-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 demonstrated 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, cytomegalovirus serostatus of the donor or recipient, graft-versus-host-disease, time of engraftment, HCT cell source, or HCT recipient exposure to steroids. In a 2015 study, receipt of ≥ 1 mg/kg of steroids within 2 weeks before 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 observed in hMPV studies in populations for which higher viral loads have been associated with increased risk for LRI and hospitalization.[38,39] Several studies have suggested 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 after hMPV infections is lower than that 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 γ-globulin levels and the role of IVIG in preventing hMPV-associated LRI and/or mortality should be determined in future studies, especially among HCT recipients and patients with HM.

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CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

AUTHOR CONTRIBUTIONS

Firas El Chaer: Conceptualized and designed the study, clinical research and data collection, helped with data acquisition, writing–initial draft, writing–revisions and final review, and responsible for overall content as guarantor. **Dimpy P. Shah**: Conceptualized and designed the study, performed statistical analyses, writing–initial draft, writing–revisions and final review, and responsible for overall content as guarantor. **Joumana Kmeid**: Clinical research and data collection and writing–revisions and final review **Ella J. Ariza-Heredia**: Helped with data acquisition and writing–revisions and final review. **Chitra M. Hosing**: Helped with data acquisition and writing–revisions and final review. **Victor E. Mulanovich**: Writing–revisions and final review. **Roy F. Chemaly**: Conceptualized and designed the study, helped with data acquisition, writing–initial draft, writing–revisions and final review, and responsible for overall content as guarantor.

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