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Upper and/or lower respiratory tract infection caused by human metapneumovirus after allogeneic hematopoietic stem cell transplantation

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Corresponding Author:	Jose Luis Piñana, MD Hospital Universitario y politécnico La Fe Valencia, SPAIN
First Author:	Jose Luis Piñana, MD
Order of Authors:	Jose Luis Piñana, MD
	Gloria Tridello
	Aliénor Xhaard
	Lotus Wendel
	Juan Montoro
	Lourdes Vazquez
	Inmaculada Heras
	Per Ljungman
	Malgorzata Mikulska
	Urpu Salmenniemi
	Ariadna Perez
	Nicolaus Kröger
	J.J. Cornelissen
	Elisa Sala
	Rodrigo Martino
	Claire Geurten
	Jenny Byrne
	Johan Maertens
	Tessa Kerre
	Murray Martin
	Maria Jesús Pascual
	Moshe Yeshurun
	Jürgen Finke
	Andreas H. Groll
	Peter J. Shaw
	Nicole Blijlevens

	William Arcese
	Arnold Ganser
	Maria Suarez-Lledo
	Mohsen Alzahrani
	Goda Choi
	Edouard Forcade
	Annalisa Paviglianiti
	Carlos Solano
	Jacek Wachowiak
	Tsila Zuckerman
	Peter Bader
	Johannes Clausen
	Jiri Mayer
	Wilfried Schroyens
	Elisabetta Metafuni
	Nina Knelange
	Dina Averbuch
	Rafael de la Camara
Abstract:	Background: Human metapneumovirus (hMPV) epidemiology, clinical characteristics and risk factors for poor outcome after allogeneic stem cell transplantation (allo-HSCT) remain a poorly investigated area. Patients and methods: We report the outcome of a retrospective multicentre cohort study including all consecutive allo-HSCT recipients (adults and children) who developed upper respiratory tract disease (URTD) and/or Lower (LRTD) caused by hMPV diagnosed by multiplex PCR panels between January 2012 and January 2019. Results: We included 428 allo-HSCT recipients who developed 438 hMPV respiratory infections episodes [URTD (n= 264, 60%), LRTD (n= 174, 40%)]. Most recipients were adults (n= 400, 93%). hMPV episodes were diagnosed at a median of 373 days (min-max: -7 to 4766 days) after allo-HSCT. Recipients who developed hMPV LRTD get the infection early during the course of transplant and had a significantly higher proportion of lymphopenia (<1 x109/L), neutropenia (<0.5 x109/L), corticosteroids use and ribavirin therapy (p≤ 0.05 for all comparisons). Multivariate analysis identified lymphopenia [≤0.2 × 109/L: Odds Ratio (OR) 5, 95% confidence interval (C.I.). 2.08-12; >0.2 to 0.5 × 109/L: OR 1.94, 95% C.I. 1.11-3.38; p= 0.0003] and corticosteroids >30 mg/d (OR 4.06, 95% C.I. (2.08-7.91), p< 0.0001) as independent risk factors for LRTD occurrence. Day 30 overall mortality after hMPV detection was 2% vs. 12% vs. 21% for URTD, possible and proven LRTD, respectively (p< 0.0001). Multivariate analysis for day 30 LRTD overall mortality identified lymphopenia (≤0.2 × 109/L OR 4.45, 95% C.I. 1.83-10.87, p = 0.001) as the only independent risk factor. Conclusions: hMPV after allo-HSCT involved LRTD in many instances (40%). LRTD and its severity were mainly driven by lymphopenia and corticosteroids use, and lymphopenia was independently associated with higher mortality in those with possible and particularly proven LRTD.
Suggested Reviewers:	

Valencia, October 21, 2022

Editor in-chief

Dear sir,

We are sending you our manuscript entitled **"Upper and/or lower respiratory tract infection caused by human metapneumovirus after allogeneic hematopoietic stem cell transplantation"**, which we would like you to consider for its publication as a full-length article in *Journal of Infection*.

The current study is original research, has not been previously published and has not been submitted for publication elsewhere. All authors have seen and approved the manuscript and contributed significantly to the work. We conducted a retrospective international multicenter study across 38 transplant centers from 13 countries around the world on behalf of Infectious Diseases Working Party of the European Society for Blood and Marrow Transplantation and the Spanish hematopoietic transplant and cell therapy group. This study reports on epidemiological characteristics, clinical consequences and conditions associated with severe course of human metapneumovirus (hMPV) infection in a highly oncohematological immunossuppressed cohort of patients such as recipients of allogeneic stem cell transplantation (allo-HSCT) where very few data is available to date.

The relatively lower incidence and prevalence of hMPV compare to other common seasonal respiratory viruses has delayed the analyses of large series of hMPV infections after allo-HSCT. Our research shows that the seasonality of hMPV in allo-HSCT recipients mirrors that of the community despite usual counseling in transmission preventive measures applied worldwide. We also observed that hMPV infection severity was mainly associated with lymphopenia and the use of corticosteroids. Overall mortality was high, especially in recipients with proven LRTD, indicating that these

infections can have moderate to severe direct and indirect consequences in a significant proportion of cases. We also were able to analyze the role of co-infections in the severity and found that co-infections were associated with higher rate of oxygen requirement. Finally, we analyze the effect of ribavirin through a propensity score analysis and found no benefit in terms of reduction of mortality.

Looking forward to hearing from you,

Sincerely,

Correspondence:
Jose Luis Piñana MD
Division of Clinical Hematology
Hospital Universitario La Fe
Avinguda Fernando Abril Martorell, 106
CP 46026 Valencia, Spain
Tlf1: +34 96 1244000.
Fax: +34 96 1246201

SUPPLEMENTARY TABLES

Table S1. Syndromic multiplex PCR platforms according to the community acquired respiratory viruses' type performance.

PCR platform
Allplex™ Respiratory Panel 1-2-3 / Anyplex™ RV16
Argene® Respiratory
BioFire® FilmArray® Respiratory
FTD® respiratory pathogens 33
Luminex xTAG RVP Fast v1 assay (Luminex Molecular Diagnostics, Toronto, ON, Canada)
Multiplex RT-nested PCR assay*
NxTAG® Respiratory Pathogen Panel
Pneumovir®
RespiFinder®
xTAG® Respiratory Viral Panel

*In-house platform: M.T. Coiras, J.C. Aguilar, M.L. Garcia, et al. (2004) Simultaneous detection of fourteen respiratory viruses in clinical specimens by two multiplex reverse transcription nested PCR assays. J. Med. Virol. 72(3): 484-495. doi: 10.1002/jmv.20008

‡Total of 32 participating transplant centers: some transplant centers reported use of different PCR panels over the course of the study.

Table S2. Univariate analysis of risk factors for hMPV LRTD and overall mortality of hMPV LRTD.

Variables	**Log. Regr. LRTD (n=438)**		**NRM at 30 days in recipients with LRTD CARV COX. Regr. (n= 174)**	
	Univariate analysis		Univariate analysis	
	OR (95% C.I.)	**P**	HR (95% C.I.)	**P**
Type of donor				
HLA-identical sibling donor	1.00		1.00	
Alternative donor	0.97 (0.65-1.46)	0.9	1.89 (0.71-5.07)	0.2
Recipient age				
<16 years old	1.00		1.00	
≥16 years old	1.12 (0.50-2.51)	0.8	0.68 (0.17-2.74)	0.6
HLA mismatch	0.92 (0.58-1.43)	0.7	1.26 (0.47-3.33)	0.6
ATG as a part of conditioning	0.74 (0.45-1.22)	0.2	1.96 (0.78-4.97)	0.2
GVHD prophylaxis				
Sir-Tac	1.00	0.04		
CsA + MTX	1.98 (0.87-4.55)		1.00	0.04
Post-Cy	2.18 (0.91-5.22)		1.98 (0.44-8.90)	
CsA + PDN and Others	3.00 (1.30-6.91)		3.96 (1.32-11.90)	
CARV LRTD	NT			
On IS	1.52 (1.01-2.29)	0.046	2.15 (0.74-6.26)	0.16
ANC < 0.5 × 109/L	3.66 (1.62-8.25)	0.002	2.10 (0.81-5.46)	0.13
ALC < 0.5 × 109/L	4.63 (2.88-7.46)	<0.0001	3.15 (1.29-7.72)	0.01
ALC< 0.2 × 109/L*	4.84 (2.35-9.97)	<0.0001	4.19 (1.83-9.62)	0.0007

ALC< 1 × 109/L	3.49 (2.30-5.29)	<0.0001	3.95 (1.18-13.29)	0.03
ALC				
• **> 1 × 109/L**	1.00	<0.0001	1.00	0.003
• **≥0.5 to 1 × 109/L**	1.76 (1.03-2.98)		2.21 (0.49-9.89)	
• **>0.2 to 0.49× 109/L**	4.35 (2.36-8.04)		1.79 (0.37-8.73)	
• **≤0.2 × 109/L**	7.63 (3.78-15.43)		7.54 (2.15-26.51)	
Age ≥ 40 years*	1.39 (0.91-2.13)	0.12	0.86 (0.37-2.02)	0.7
Active GvHD at the time RVI*	1.41 (0.95-2.09)	0.09	0.87 (0.39-1.95)	0.7
Periengraftment*	3.61 (1.85-7.06)	0.0002	3.15 (1.41-7.03)	0.005
Allo-HSCT ≤ 6 months	1.52 (1.01-2.29)	0.046	2.01 (0.91-4.47)	0.09
Allo-HSCT ≤ 12 months	1.60 (1.08-2.35)	0.02	1.33 (0.58-3.05)	0.5
Allo-HSCT ≤ 24 months	1.49 (0.96-2.31)	0.08	1.51 (0.51-4.48)	0.5
Allo-HSCT ≤ 100 days	1.81 (1.13-2.89)	0.01	2.97 (1.35-6.57)	0.007
Myeloablative*	0.83 (0.56-1.22)	0.3	1.15 (0.49-2.69)	0.7
Corticosteroids* vs No	2.00 (1.35-2.97)	0.0006	1.98 (0.85-4.60)	0.11
• **No**	1.00	0.0008	1.00	0.6
• **Corticosteroids < 30mg/d**	1.49 (0.93-2.36)		1.41 (0.49-4.07)	
• **Corticosteroids ≥ 30mg/d**	3.63 (1.90-6.96)		1.75 (0.59-5.18)	
• **Corticosteroids < 30mg/d vs ≥ 30mg/d**	0.31 (0.17-0.59)	0.0003	0.65 (0.24-1.76)	0.4
Corticosteroids ≥ 30mg/d vs < 30mg/d	3.19 (1.69-6.02)	0.0003	1.53 (0.57-4.12)	0.4
LRTD				
• **Possible**			1	
• **Proven**			1.66 (0.72-3.87)	0.2
Prior BOS (Y/N)	1.15 (0.60-2.22)	0.7	0.81 (0.18-3.60)	0.8
ICU admission	NT			
Oxygen support	NT			
Co-infection (Y/N)	NT		1.48 (0.66-3.30)	0.3
Ribavirin therapy	NT		2.29 (0.96-5.46)	0.06
Season				
• **summer**	1.00	0.4	1.00	0.8
• **winter**	0.72 (0.32-1.60)		2.07 (0.29-14.90)	
• **spring**	0.85 (0.38-1.89)		1.81 (0.25-13.04)	
• **autumn**	0.51 (0.20-1.33)		3.00 (0.34-26.37)	
ISI				
Low risk (0-2)	1.00	0.002	1.00	0.01
Moderate risk (3-6)	1.11 (0.72-1.69)		1.11 (0.40-3.13)	
High risk (7-12)	5.81 (2.25-15.00)		3.76 (1.44-9.84)	

Abbreviations: C.I., confidence interval; Log. Regr, Logistic regression model; OR, Odds Ratio; IFD, invasive pulmonary fungal disease; ATG, anti-thymocyte globuline; Sir, sirolimus; Tac, tacrolimus; CsA, cyclosporine A; MTX, methotrexate;)Post-Cy, post-transplant cyclophosphamide; PDN, prednisone; CARV LRTD, community-acquired respiratory virus lower respiratory tract disease GvHD, graft-versus-host disease; Allo-HSCT, allogeneic hematopoietic stem cell transplantation; ISI, immunodeficiency score index; ANC, absolute neutrophil count; ALC, absolute lymphocyte count; ns, not significant; NT, not tested.

Table S3. Univariate analysis of risk factors for hMPV oxygen support and hospital admission.

Variables	Log. Regr. Hospital admission (n=434)		Log. Regr. Oxygen support (n= 432)	
	Univariate analysis		Univariate analysis	
	OR (95% C.I.)	P	OR (95% C.I.)	P
Type of donor				
HLA-identical sibling donor	1.00		1.00	
Alternative donor	1.14 (0.73-1.78)	0.6	1.07 (0.64-1.78)	0.8
Recipient age				
<16 years old	1.00		1.00	
≥16 years old	1.23 (0.51-2.98)	0.6	2.05 (0.60-6.98)	0.2
HLA mismatch	0.98 (0.59-1.61)	0.9	1.08 (0.61-1.91)	0.8
ATG as a part of conditioning	0.93 (0.55-1.58)	0.8	0.86 (0.46-1.60)	0.6
GVHD prophylaxis				
Sir-Tac - CsA + MTX	1.00	0.01	1.00	0.0004
Post-Cy	0.56 (0.28-1.13)		1.18 (0.54-2.61)	
CsA + PDN and Others	1.57 (0.99-2.48)		3.11 (1.79-5.39)	
CARV LRTD	NT		1.70 (1.02-2.83)	0.04
On IS	1.24 (0.83-1.84)	0.3	1.79 (1.06-3.03)	0.03
ANC < 0.5 × 109/L	0.51 (0.21-1.24)	0.1	1.97 (0.88-4.41)	0.1
ALC < 0.5 × 109/L, n (%)	1.96 (1.25-3.08)	0.003	4.44 (2.62-7.52)	<0.0001
ALC< 0.2 × 109/L*	0.90 (0.44-1.88)	0.8	3.58 (1.81-7.07)	0.0002
ALC< 1 × 109/L	2.01 (1.15-3.50)	0.01	3.62 (2.11-6.21)	<0.0001
ALC				
> 1 × 109/L	1.00	0.02	1.00	<0.0001
≥0.5 to 1 × 109/L	1.25 (0.72-2.17)		1.85 (0.91-3.75)	
>0.2 to 0.49× 109/L	3.08 (1.63-5.82)		4.64 (2.25-9.56)	
≤0.2 × 109/L	1.31 (0.65-0.63)		6.46 (3.14-13.26)	
Age ≥ 40 years*	1.49 (0.93-2.41)	0.1	2.10 (1.15-3.84)	0.02
Active GvHD at the time RVI*	2.74 (1.78-4.21)	<0.0001	2.67 (1.64-4.36)	<0.0001
Periengraftment*	0.24 (0.09-0.63)	0.004	2.16 (1.10-4.24)	0.03
Allo-HSCT ≤ 6 months	0.73 (0.47-1.13)	0.2	1.55 (0.96-2.50)	0.07
Allo-HSCT ≤ 12 months	1.00 (0.65-1.54)	1	1.42 (0.88-2.27)	0.2
Allo-HSCT ≤ 24 months	0.57 (0.35-0.94)	0.03	1.32 (0.76-2.26)	0.3
Allo-HSCT ≤ 100 days	0.43 (0.24-0.75)	0.003	1.46 (0.86-2.51)	0.2
Myeloablative*	0.74 (0.48-1.14)	0.2	0.65 (0.40-1.08)	0.1
Corticosteroids* vs No	3.22 (2.03-5.10)	<0.0001	3.35 (2.03-5.52)	<0.0001
Corticosteroids ≥ 30mg/d vs < 30mg/d	4.20 (2.10-8.40)	<0.0001	4.95 (2.52-9.73)	<0.0001
Corticosteroids < 30mg/d vs ≥ 30mg/d	0.24 (0.12-0.48)	<0.0001	0.20 (0.10-0.40)	<0.0001
Corticosteroids*				
No	1.00	0.0002	1.00	<0.0001
Corticosteroids < 30mg/d	2.87 (1.73-4.74)		2.46 (1.38-4.39)	
Corticosteroids ≥ 30mg/d	5.84 (2.52-13.56)		6.58 (3.26-13.24)	
LRTD				
• **Possible or Proven**	2.96 (0.42-21.01)	0.2	NA	
Prior BOS (Y/N)	1.95 (1.10-3.47)	0.02	2.30 (1.17-4.50)	0.02

ICU admission	NT			
Oxygen support	NT			
Co-infection (Y/N)	2.13 (1.38-3.27)	0.001	2.38 (1.45-3.88)	0.0006
URTD co-infection	1.54 (0.98-2.41)	0.06	1.72 (1.02-2.89)	0.04
LRTD co-infection	5.44 (2.47-12.01)	<0.0001	6.69 (3.04-14.73)	<0.0001
Ribavirin therapy	2.07 (1.13-3.82)	0.03	4.21 (2.12-8.35)	<0.0001
Season		0.9		
• **summer**	1.00		1.00	0.9
• **winter**	0.81 (0.34-1.93)		0.80 (0.32-2.02)	
• **spring**	0.97 (0.41-2.28)		0.94 (0.37-2.40)	
• **autumn**	0.93 (0.34-2.53)		0.99 (0.33-2.96)	
ISI				0.1
Low risk (0-2)	1.00	0.4	1.00	
Moderate risk (3-6)	1.07 (0.65-1.75)		0.95 (0.54-1.65)	
High risk (7-12)	0.57 (0.21-1.57)		2.82 (1.20-6.64)	

Abbreviations: C.I., confidence interval; Log. Regr, Logistic regression model; OR, Odds Ratio; IFD, invasive pulmonary fungal disease; ATG, anti-thymocyte globuline; Sir, sirolimus; Tac, tacrolimus; CsA, cyclosporine A; MTX, methotrexate;)Post-Cy, post-transplant cyclophosphamide; PDN, prednisone; CARV LRTD, community-acquired respiratory virus lower respiratory tract disease GvHD, graft-versus-host disease; Allo-HSCT, allogeneic hematopoietic stem cell transplantation; ISI, immunodeficiency score index; ANC, absolute neutrophil count; ALC, absolute lymphocyte count; ns, not significant; NT, not tested.

Upper and/or lower respiratory tract infection caused by human metapneumovirus after allogeneic hematopoietic stem cell transplantation

Jose Luis Piñana[1], Gloria Tridello[2], Aliénor Xhaard[3], Lotus Wendel[4], Juan Montoro[5], Lourdes Vazquez[6], Inmaculada Heras[7], Per Ljungman[8], Malgorzata Mikulska[9], Urpu Salmenniemi[10], Ariadna Perez[1], Nicolaus Kröger[11], J.J. Cornelissen[12], Elisa Sala[13], Rodrigo Martino[14], Claire Geurten[15], Jenny Byrne[16], Johan Maertens[17], Tessa Kerre[18], Murray Martin[19], Maria Jesús Pascual[20], Moshe Yeshurun[21], Jürgen Finke[22], Andreas H. Groll[23], Peter J. Shaw[24], Nicole Blijlevens[25], William Arcese[26], Arnold Ganser[27], Maria Suarez-Lledo[28], Mohsen Alzahrani[29], Goda Choi[30], Edouard Forcade[31], Annalisa Paviglianiti[32], Carlos Solano[1,43], Jacek Wachowiak[33], Tsila Zuckerman[34], Peter Bader[35], Johannes Clausen[36], Jiri Mayer[37], Wilfried Schroyens[38], Elisabetta Metafuni[39], Nina Knelange[4], Dina Averbuch[40], Rafael de la Camara[41,42].

On behalf of the Infectious Diseases Working Party of the European Society for Blood and Marrow Transplantation and Infectious Complications Subcommittee of the Spanish Hematopoietic Stem Cell Transplantation and Cell Therapy Group (GETH-TC)

1. Hematology Department, Hospital Clinico Universitario de Valencia, Spain. Fundación INCLIVA, Instituto de Investigación Sanitaria Hospital Clínico Universitario de Valencia, Spain.
2. Azienda Ospedaliera Universitaria Integrata Verona, Verona, Italy.
3. Service d'Hématologie-Greffe, Hôpital Saint-Louis, Université Paris-Diderot, Paris, France.
4. EBMT Leiden Study Unit, Leiden, The Netherlands.
5. Hematology división, Hospital universitario y politécnico La Fe, Valencia, Spain.
6. Hematology Department, Hospital Clinico Universitario de Salamanca, Spain.
7. Hematology Department, Hospital Morales Meseguer, Murcia, Spain.
8. Department of Cellular Therapy and Allogeneic Stem Cell Transplantation, Karolinska Comprehensive Cancer Center, Karolinska University Hospital

Huddinge and Dept. of Medicine Huddinge, Karolinska Institutet, Stockholm, Sweden.

9. Division of Infectious Diseases, University of Genoa (DISSAL) and IRCCS Ospedale Policlinico San Martino, Genova Italy.
10. Hematology Department, HUCH Comprehensive Cancer Center, Helsinki, Finland.
11. Department for Stem Cell Transplantation, University Medical Center Hamburg-Eppendorf/Germany.
12. Hematology Department, Erasmus MC Cancer Institute, Rotterdam, Netherlands.
13. Department of Internal Medicine III, University Hospital of Ulm, Ulm, Germany.
14. Hematology Department, Hospital de la Santa Creu I Sant Pau, Barcelona, Spain.
15. Hematology Department, Birmingham Children`s Hospital, Birmingham, United Kingdom and Centre Hospitalier Universitaire de Liege, Belgique.
16. Hematology Department, Nottingham University, Nottingham, United Kingdom.
17. Hematology Department, University Hospital Gasthuisberg, Leuven, Belgium.
18. Hematology Department, Ghent University Hospital, Gent, Belgium.
19. Hematology Department, Leicester Royal Infirmary, Leicester, United Kingdom.
20. Hematology Department, Hospital Regional de Málaga, Malaga, Spain.
21. Institution of Hematology, Rabin medical Center, Petach-Tikva, Israel and Sackler School of Medicine, Tel-Aviv University, Tel-Aviv, Israel.
22. University of Freiburg, Freiburg, Germany.
23. Infectious Disease Research Program, Department of Pediatric Hemtology and Oncology and Center for Bone Marrow Transplantation, University Children's Hospital, Muenster, Germany.
24. The Children`s Hospital at Westmead, Sydney, Australia.
25. Nijmegen Medical Centre, Nijmegen, Netherlands.
26. Tor Vergata University of Rome, Rome, Italy.
27. Hannover Medical School, Hannover, Germany.
28. Hematology Department, Hospital Clinic, Barcelona, Spain.

29. Department of Oncology, King Abdulaziz Medical City, Ministry of National Guard – Health Affaris, Riyadh, Saudi Arabia.
30. University Medical Center Groningen, University of Groningen, Groningen, the Netherlands.
31. Service d'Hématologie Clinique et Thérapie Cellulaire, CHU Bordeaux, F-33000, Bordeaux, France.
32. Institut Català de Oncología – Hospital Duran i Reynals, Barcelona, Spain.
33. Department of Pediatric Oncology, Hematology and HSCT, University of Medical Sciences, Poznan, Poland.
34. Rambam Medical Center, Haifa, Israel.
35. Division for Stem Cell Transplantation, Immunology and Intensive Care Medicine, Department for Pediatrics and Adolescent Medicine, University Hospital, Goethe University, Frankfurt, Germany.
36. Department of Internal Medicine I, Ordensklinikum Linz - Elisabethinen, Johannes Kepler University, Linz, Austria
37. Masaryk University Hospital Brno, Brno, Czech Rep.
38. Antwerp University Hospital (UZA), Antwerp Edegem, Belgium.
39. Fondazione Policlinico Universitario Agostino Gemelli IRCCS. Dipartimento di Diagnostica per Immagini, Radioterapia Oncologica e EmatologiaGemelli IRCCS, Roma, Italy.
40. Faculty of Medicine, Hebrew University of Jerusalem; Hadassah Medical Center, Jerusalem, Israel.
41. Hematology Department, Hospital de la Princesa, Madrid, Spain.
42. Hematology Department, Hospital Universitario Sanitas La Zarzuela, Madrid, Spain.
43. Department of Medicine. University of Valencia, Spain.

Short Title: hMPV infection after allo-HSCT.

Brief summary: hMPV infection after allo-HSCT frequently involves the lower respiratory tract (40%). Pulmonary involvement was associated with substantial all-cause

mortality rate (14%) at day 30 after hMPV detection, particularly in those with lymphopenia.

Abstract word count: 284

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Key Words: human metapneumovirus, paramyxovirus, community-acquired respiratory virus, human Coronavirus, SARS-CoV-2, allogeneic hematopoietic stem cell transplantation, immunocompromised, upper and lower respiratory tract disease, immunodeficiency score index, multiplex PCR assay.

Financial disclosure statement

The authors report no potential conflicts of interest

Correspondence:

MD. Jose Luis Piñana
Division of Clinical Hematology
Hospital Clínico Universitario de Valencia
Avda Blasco Ibañez, 17, 46010, Valencia, Spain
Phone: +34 963862625 Fax: +34 963987820
E-mail: jlpinana@gmail.com

Abstract

Background: Human metapneumovirus (hMPV) epidemiology, clinical characteristics and risk factors for poor outcome after allogeneic stem cell transplantation (allo-HSCT) remain a poorly investigated area.

Patients and methods: We report the outcome of a retrospective multicentre cohort study including all consecutive allo-HSCT recipients (adults and children) who developed

upper respiratory tract disease (URTD) and/or Lower (LRTD) caused by hMPV diagnosed by multiplex PCR panels between January 2012 and January 2019.

Results: We included 428 allo-HSCT recipients who developed 438 hMPV respiratory infections episodes [URTD (n= 264, 60%), LRTD (n= 174, 40%)]. Most recipients were adults (n= 400, 93%). hMPV episodes were diagnosed at a median of 373 days (min-max: -7 to 4766 days) after allo-HSCT. Recipients who developed hMPV LRTD get the infection early during the course of transplant and had a significantly higher proportion of lymphopenia (<1 $x10^9$/L), neutropenia (<0.5 $x10^9$/L), corticosteroids use and ribavirin therapy ($p \leq 0.05$ for all comparisons). Multivariate analysis identified lymphopenia [$\leq 0.2 \times 10^9$/L: Odds Ratio (OR) 5, 95% confidence interval (C.I.). 2.08-12; >0.2 to 0.5×10^9/L: OR 1.94, 95% C.I. 1.11-3.38; p= 0.0003] and corticosteroids >30 mg/d (OR 4.06, 95% C.I. (2.08-7.91), p< 0.0001) as independent risk factors for LRTD occurrence. Day 30 overall mortality after hMPV detection was 2% vs. 12% vs. 21% for URTD, possible and proven LRTD, respectively (p< 0.0001). Multivariate analysis for day 30 LRTD overall mortality identified lymphopenia ($\leq 0.2 \times 10^9$/L OR 4.45, 95% C.I. 1.83-10.87, p = 0.001) as the only independent risk factor.

Conclusions: hMPV after allo-HSCT involved LRTD in many instances (40%). LRTD and its severity were mainly driven by lymphopenia and corticosteroids use, and lymphopenia was independently associated with higher mortality in those with possible and particularly proven LRTD.

INTRODUCTION

Respiratory virus infection after allogeneic hematopoietic stem cell transplantation (allo-HSCT) is a common infectious complication caused by a wide variety of human respiratory viruses, among which human metapneumovirus (hMPV) was isolated in

2001[1] as a negative-sense RNA paramyxovirus genetically similar to respiratory syncytial virus (RSV)[2]. There are two subgroups, each with two clades (A1, A2, B1 and B2); although all four subtypes typically co-circulate, each season often has one predominant subtype[3]. hMPV infects approximately 5–9% of allo-HSCT recipients[4,5] scoring sixth in incidence/prevalence studies after human rhinovirus (hRhV), RSV, seasonal coronavirus (hCoV), human parainfluenza virus (hPiV) and influenza virus (hIV)[6,7]. This relatively lower incidence and prevalence has hindered the analyses of large series of hMPV infections after allo-HSCT[8-11]. The symptom spectrum is similar to other respiratory viruses and varies from mild to severe[12]. In the allo-HSCT setting, progression from upper (URTD) to lower respiratory tract disease (LRTD) can occur in up to 20% of cases, mainly in recipients with lymphopenia, corticosteroids use or infection occurring early after allo-HSCT[13]. The reported mortality rate after hMPV LRTD in patients with hematological malignancy and/or allo-HSCT recipients ranges from 10% to 40%[4,8,9,14,15]. The mortality rate was higher in allo-HSCT recipients (22% at 30 days) than in the general population (3%)[16]**.** In addition, the mortality rate may exceed 80% in allo-HSCT recipients when the virus is detected in bronchoalveolar samples[17]. However, there is still limited data on risk factors for hospital admission or oxygen requirement, and overall mortality of hMPV infection after allo-HSCT.

Moreover, there are currently no authorized or approved drugs available against hMPV, so infection management is mainly focused on supportive care measures. Although ribavirin has shown certain effect against hMPV in *in vitro* studies and animal models[18,19], to date there is no consistent clinical data showing clear benefit for use of this drug[20,21]. Several small case series suggest that the use of ribavirin with or without intravenous immunoglobulin (IVIG) for hMPV infection could be considered in high-risk patients[22-25]. However, a large study showed no protective effect of ribavirin for hMPV LRTD[8]. As

ma consequence, the European Conference on Leukemia Infection did not recommend ribavirin therapy for hMPV[26].

In this large retrospective international multicenter cohort, we aimed to characterize epidemiological and clinical features and risk factors (RFs) for LRTD and for different outcomes of hMPV infections in the immunocompromised population of allo-HCT recipients.

PATIENTS AND METHODS

Study population and inclusion criteria

This is a retrospective multicenter cohort study of collaboration between the Infectious Diseases Working Party (IDWP) of the European Society for Blood and Marrow Transplantation (EBMT) and the Infectious Complications Subcommittee (GRUCINI) of the Spanish Hematopoietic Stem Cell Transplantation and Cell Therapy Group (GETH-TC). Participating centers were requested to include all consecutive allo-HSCT recipients (children and adults) with multiplex PCR-documented hMPV respiratory infection from January 1 2012 to December 30 2019, occurring from the start of conditioning regimen to last follow-up. During the study period, all allo-HSCT procedures were registered in the EBMT registry by completing an essential medical data form. More detailed data was collected using a second transplant form containing specific information on respiratory symptoms, hMPV-related hospital admission, oxygen requirement and intensive care unit (ICU) admission. Variables such as immunosuppressant drugs, corticosteroids, the presence of signs or symptoms of acute or chronic graft-versus-host disease (GvHD), prior development of bronchiolitis obliterans syndrome (BOS) and variables for immunodeficiency scoring index (ISI) computation[27] (i.e. lymphocyte count, neutrophil count, myeloablative conditioning regimen, age, corticosteroids therapy and graft-versus-

host disease) were requested at the time of community acquired respiratory virus PCR screening. The commercial and in-house PCR used by participating centers for hMPV detection are summarized in supplementary Table S1.

Definitions

hMPV URTD was defined as the combination of upper respiratory symptoms (rhinorrhea, sinusitis, otitis, or pharyngitis), hMPV detected by PCR assay and the absence of LRTD symptoms and/or any pulmonary infiltrates on chest X-ray or computed tomography (CT) lung scan. hMPV LRTD was defined as the combination of lower respiratory symptoms and/or any pulmonary infiltrates on chest X-ray or computed tomography (CT) lung scan We classified LRTD as possible, probable or confirmed, as previously described[28]. In brief, possible LRTD required detection of hMPV in the upper respiratory tract in recipients with pulmonary infiltrates during the episode (but without confirmation of its presence in the LRT). Confirmed LRTD was defined when lower respiratory symptoms were accompanied by new pulmonary infiltrates and isolation of the virus in tracheal aspirates or in bronchoalveolar lavage (BAL). Probable LRTD refers to cases with hMPV detection in BAL without radiological proof of pulmonary involvement. However, in the current series there were no probable episodes because bronchoscopies were not performed in patients without radiological proof of pulmonary involvement. Episodes were defined as URTD or LRTD according to ECIL-4 recommendations[26]**.** Acute and chronic graft-vs-host disease (GvHD), including BOS were diagnosed according to standard criteria[29]. We considered active GvHD for both acute and chronic GvHD when signs and/or symptoms were present at the time of respiratory virus screening. Co-infection was defined as a significant co-pathogen detected in concurrent nasopharyngeal or bronchoalveolar lavage during hMPV infection and until its clinical and/or

microbiological resolution. Ribavirin therapy was given according at physician discretion and/or routines at the individual center.

Endpoints and statistical analysis

The primary objective of the study was to describe epidemiological and clinical characteristics of U/LRTD in allo-HSCT recipients with hMPV infection. We also analyzed risk factors for hMPV-related hospital admission, oxygen requirement, LRTD involvement, and all-cause mortality by day 30 after hMPV detection, the latter in recipients with LRTD.

The main patient characteristics were reported by descriptive statistics on the total of available information; median minimum and maximum were used for continuous variables, while absolute and percentage frequencies were used for categorical variables. Between-group differences were tested by linear or logistic regression models, using generalized estimating equation methods, nested by patient, to account for the dependence of observations. Variables with a p-value < 0.1 in the univariate model were included in the multivariate analysis. In recipients with LRTD, the survival analysis was performed by using the Cox regression model. A p-value <0.05 was considered statistically significant. All p-values were two-sided. All analyses were performed using the statistical software SAS vs. 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Patient characteristics

Overall, we included 428 allo-HSCT recipients (93% adults) with a median age of 46 years (min–max 0.3 – 73.8) who developed 438 U/LRTD episodes of hMPV between January 2012 and January 2019 reported from 35 EBMT transplant centers in 13

countries. Clinical and transplant characteristics of the series are detailed in Table 1. The study population comprised a high-risk cohort, since 66% of recipients were allografted from alternative donors (unrelated adult donor, cord blood units (CBU) or haplo-identical family donors). There were 419 allo-HSCT recipients with one hMPV episode whereas nine recipients (2.1%) had two or more hMPV episodes occurring during different seasons.

Epidemiology and characteristics of hMPV infections according to U/LRTD involvement

Figure 1 shows the epidemiology of hMPV infections in allo-HSCT recipients by month. The incidence peak was observed between March and April, with 173 out of 438 episodes (39%). Most cases developed only URTD (n= 264, 60%) whereas 174 (40%) had LRTD (131 possible and 43 proven). Table 2 summarizes clinical and laboratory differences according to URTD or LRTD involvement. As expected, recipients with LRTD had higher rates of immunosuppression markers such as lymphopenia, neutropenia, active GvHD, corticosteroids therapy, and higher ISI score. They also had high rates of fever, co-infection, ribavirin therapy, hospital admission, oxygen requirement, ICU admission and mortality at days 30 and 90 after hMPV detection ($p \leqslant 0.05$ for all comparisons).

Risk factors for LRTD, hospital admission and oxygen requirement.

Univariate analyses of risk factors for LRTD, overall mortality, hospital admission and oxygen requirement are provided in Supplementary Tables S2 and S3. Logistic regression and Cox regression multivariate analyses of conditions associated with hMPV LRTD, hospital admission and oxygen requirements are shown in Table 3.

We identified three conditions associated with hospital admission at the time of hMPV detection; active GvHD [Odds ratio (OR) 2.65], absolute lymphocyte count (ALC) <0.5 $x10^9$/L (OR 1.83), and corticosteroids use >30 mg/d (OR 2.37). For oxygen requirement, four independent RFs were identified: ALC <0.5 $x10^9$/L (OR 4.52), age ≥40 years old (OR 3.19), active GvHD (OR 3.51) and co-infection (OR 2.42). We identified three conditions associated with risk of LRTD: ALC <0.2 $\times10^9$/L (OR 5), ALC between 0.2 and 0.5 $\times10^9$/L (OR 1.94) and corticosteroids >30 mg/d (OR 4.06). No significant differences in outcomes were found between pediatric (< 16 years) and adult patients.

Overall mortality and risk factors

The all-cause mortality rate at 30 days after hMPV detection was 6.6% (n= 29) for the entire group. Mortality in recipients with hMPV limited to URTD was 2% (n= 4), compared with 14% in recipients with LRTD (12% (n= 16) and 21% (n= 9) in those with possible and proven LRTD, respectively) (p <0.0001). Overall survival at day 90 after hMPV detection was 96.2% for those with URTD, whereas it was 80.8% and 62.8% for possible and proven LRTD, respectively (p <0.0001) [Figure 2].

Causes of death in recipients who died by day 30 after hMPV detection were relapse (n=4), GvHD (n=3), infectious respiratory failure (n=16), and other complications (n=6; multiple organ failure, systemic infection). The additional 22 deaths occurring by day 90 were due to disease relapse (n=10), GvHD (n=3), infectious respiratory failure (n=4), and other causes (n=5; systemic infection, multiple organ failure).

Finally, the only condition associated with increased mortality at day 30 after developing hMPV LRTD in multivariate analysis was ALC < 0.5 × 10^9/L [hazard ratio (HR) 4.45] (Table 3).

Co-infection characteristics

As expected, co-infections were more frequent in proven (26/42, 62%) than in possible LRTD (33/131, 25%) or in URTD [60/264, 22%] ($p< 0.001$). Table 4 summarizes the characteristics of co-infectious episodes among all episodes and according to U/LRTD. Most co-infections were of respiratory virus, followed by fungal and bacterial origin. Among respiratory virus co-infection, enterovirus/rhinovirus followed by influenza and respiratory syncytial virus (RSV) were the predominant co-infective agents, whereas A*spergillus spp* was the most common among fungal co-infections. Lastly, *Pseudomonas spp* was the commonest bacterial co-infective agent. Co-infection was only associated in multivariate analyses with oxygen requirement (see Table 3), without any significant effect on mortality. To further evaluate the effect of co-infection on mortality, we compared outcomes in five groups, focusing only on those with possible or proven LRTD, finding no significant differences in overall survival [virus mono-infection (n=144, 19 deaths at 30 days, 30 deaths at 90 days); virus/virus co-infection (n=5, 0 deaths at 30 days, 2 deaths at 90 days); viral/bacterial co-infection (n=5, 1 death at 30 days, 2 deaths at 90 days); virus/fungal co-infection (n=14, 3 deaths at 30 days, 4 deaths at 90 days); mixed co-infections virus/virus +/- bacterial +/- fungal co-infection (n=6, 2 deaths at 30 days, 3 deaths at 90 days)].

Ribavirin therapy characteristics

Ribavirin therapy was administered in 36 (8%) hMPV episodes. Table 5 summarizes clinical and laboratory characteristics of the infection according to treatment or not with ribavirin. Recipients treated with ribavirin had hMPV infection earlier during the course of allo-HSCT, and were more likely to have LRTD (in particular proven LRTD), oxygen requirement, hospital and ICU admission, RSV co-infection, immunosuppressive drugs and lymphopenia compared to those not treated. Overall mortality at day 90 in patients treated with ribavirin was 33% compared to 9.7% in the non-treated group ($p< 0.001$). To

evaluate the effect of ribavirin therapy we performed a propensity score analysis and found no benefit in terms of mortality at day 30 and 90 after hMPV detection according to ALC <0.5 x10^9/L, high-risk ISI, timing of hMPV infection (<180 days after stem cell infusion), oxygen requirement, or hospital and/or ICU admission (Table 6).

DISCUSSION

This study provides clinical insights into hMPV infection after allo-HSCT in a large and multicenter series from the IDWP of the EBMT and the GETH-TC groups. Incidence of hMPV in allo-HSCT recipients reached a peak between March and April. LRTD was frequent, occurring in 40% of all cases. Overall mortality was as high as 37% in recipients with developed proven hMPV LRTD. Co-infections were frequent (27%), but no effect was observed on any outcome except oxygen requirement. Corticosteroids therapy and lymphopenia were the main RFs for LRTD, hospital admission, oxygen requirement and overall mortality. These conditions could serve as the basis for prospective clinical trials design.

The epidemiology of hMPV infections in our allo-HSCT series mirrored that of the general population, with seasonal peak incidence from February to April[30]. Despite repeated guidance from transplant teams on transmission prevention measures (hand washing, social distancing, mask wearing, etc.) provided to allo-HSCT recipients and caregivers, we still observed equivalent epidemiological curves, not only in hMPV but also with other human respiratory viruses such as influenza virus, seasonal human coronavirus and recently with SARS-CoV-2[31-33]. This indicates that even if immunosuppressed patients strictly adhere to preventive measures, if community incidence rises these viruses will eventually reach patients through their environment, visitors, friends, family members, etc. However, when application of global respiratory

preventive transmission measures involves the whole community, as occurred during the COVID-19 pandemic, a dramatic reduction in respiratory virus infections, including hMPV, was observed in recipients of allo-HSCT[34]. This fact supports extending preventive measures to any individual in potential close contact with allo-HSCT recipients, particularly in the health care system where nosocomial outbreak of hMPV infections in immunocompromised patients could be life-threatening[35].

The severity of hMPV infection after allo-HSCT seems similar in terms of LRTD rates to other *Paramyxoviridae* respiratory viruses (RSV and HPiV)[36]. In this large series we observed a 10% rate of proven LRTD, rising to 40% when possible LRTD were included. The ability of hMPV to reach the LRT in the allo-HSCT setting has been estimated at 15%–60% of cases in shorter series[4,8,13]. These facts support that hMPV frequently involves the LRT in these highly immunocompromised patients. In our series, RFs associated with LRTD were corticosteroids use (>30mg/d) and low lymphocyte count ($<0.5 \times 10^9$/L), in line with a prior report[8]. These two LRTD RFs are repeatedly identified in several other CARV infections in the allo-HSCT setting[8,31,37], emphasizing the pivotal role of T-cell immune response in controlling and clearing respiratory viruses which warrants further efforts to improve T-cell function and numbers as early as possible following allo-HSCT.

The large number of recipients included in the current series enabled us to identify RFs for other outcomes of interest such as hospital admission and oxygen requirement that had not previously been analyzed. Hospital admission was required in 29% of cases in the overall cohort and in 56% of those with possible or proven hMPV LRTD. Again, lymphocyte count ($<0.5 \times 10^9$/L) and corticosteroids use were identified as RFs, while presence of active GvHD also increased the risk of hospitalization. Additionally, we observed that age (≥40 years) and co-infections along with lymphopenia, corticosteroids

as GvHD prophylaxis, and active GvHD at the time of hMPV infection increased the risk for oxygen support. These findings are not surprising given that corticosteroids, lymphopenia, moderate to severe GVHD, age and co-infections are known to increase the severity of respiratory virus infections in immunocompromised patients[27,38,39]. These variables could be useful for accurate assessment of individual risk in daily clinical practice.

Very few studies have analyzed mortality after hMPV infection in allo-HSCT. In our series we analyzed the all-cause mortality rate at day 30 and day 90 after hMPV detection to evaluate the direct (day 30) and indirect (day 90) effects of hMPV infection. Overall mortality at day 30 and 90 was 2% and 4% in URTD, 12% and 19% in possible LRTD and 21% and 37% in those with proven LRTD ($p< 0.001$), respectively. These data indicate that all-cause mortality increases with the probability of true hMPV pulmonary involvement. These numbers are similar to those of other Paramyxoviridae viruses[4,40] and crucially, are remarkably similar to those recently reported with SARS-CoV-2 in the allo-HSCT setting[41], although the later in the context of an extremely high community circulation. Altogether, mortality in allo-HSCT appears to be similar across all respiratory virus types, suggesting that the immunosuppression status of these patients is may be more important than the virus virulence by itself. This assumption could be justified in part by the identification of profound lymphopenia (<0.2 x10^9/L) as the only RF for overall mortality in the current and in most published series irrespective of the infection timing with regard to the stem cell infusion. T-cell lymphocytes contribute to clearance of hMPV infection in mice while depletion of T cells leads to prolonged viral replication[3]. Again, seemingly efforts to limit the severity of hMPV infection should include strategies that enhance T-cell immune reconstitution early after allo-HSCT without increasing the risk of GvHD. In this regard, adoptive T-cell transfer from third party donors to prevent

and/or treat respiratory virus infections in immunocompromised patients looks appealing[42].

Treatment of hMPV infection currently consists of supportive care as there are no licensed antivirals against hMPV. Two potential treatments that have been investigated are ribavirin and immunoglobulin. Ribavirin, a nucleoside with activity against RNA viruses, exhibits *in vitro* activity against hMPV[18] and showed efficacy in mice[19]. Few studies report successful treatment of hMPV infections with ribavirin, either with or without intravenous polyclonal immunoglobulins[22,23,43-45]; however, the data are limited to small case series or case reports, with no randomized controlled trials available. Other studies have shown no benefit with ribavirin[12,46]. In our series, recipients treated with ribavirin showed high-risk features such as early infection after transplant, higher rates of hospitalization, ICU admission, LRTD and oxygen requirement. They also showed higher rates of co-infection with RSV, lymphopenia and/or immunosuppressant administration. As a consequence, ribavirin-treated episodes showed a higher mortality rate (see Table 5). All these figures suggest that ribavirin was used in the context of more severe and urgent cases. However, after adjustment for these confounding factors and although mortality differences were reduced among groups, the propensity score analysis did not show any benefit of ribavirin therapy in terms of overall mortality. Thus infection control measures are particularly important for mitigating hMPV incidence, and thus hMPV associated mortality, as there are no effective treatments or vaccines.

Lastly, we conducted an in-depth analysis on the occurrence and effect of significant co-infections during hMPV infections. After respiratory virus co-infections, the most common co-infection was invasive fungal infections (IFI). The risk of IFI may increase particularly in recipients with LRTD respiratory virus infection developing the infection during the first year after transplant, receiving corticosteroids or ATG-based GvHD

prophylaxis[48]. IFI was common and since our identified risk factors for hMPV LRTD also have been identified as risk factors for fungal infections, antifungal prophylaxis should be strongly considered. Otherwise, in multivariate analysis, co-infection only showed a significant effect on the need for oxygen support, without any effect on other events of interest, including overall mortality, likely due to the low number of patients available for comparative purpose.

Although the current study represents the largest series of hMPV infection after allo-HSCT reported to date, some limitations merit attention, such as the retrospective nature of the analyses, the low proportion of bronchoalveolar lavage performed, the absence of lung tissue analyses to establish the exact role of hMPV, and the use of different PCR methods varying in analytical performance for detection and identification of hMPV subtypes.

In conclusion, we provide insights into seasonal hMPV infections after allo-HSCT in terms of epidemiology and clinical outcome. hMPV infection severity was mainly associated with lymphopenia and the use of corticosteroids. Overall mortality was high in recipients with proven LRTD, indicating that these infections can have moderate to severe direct and indirect consequences in a significant proportion of cases. Vaccine and drug developments are urgently needed to limit the dismal prognosis observed in high-risk patients.

CONFLICT OF INTERESTS

The authors declare no conflict of interests.

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628

629 **TABLES AND FIGURES**

630 **Table 1.** Patient and transplant characteristics (n= 428).

Characteristics	**Whole cohort (n=428)**	**Not treated* (n=393)**	**Treated with ribavirin* (n=35)**	**P Value***
Age at allo-HCT (years), median (range)				
• < 16 years, n (%)	27 (6.3)	24 (6.1)	3 (8.6)	0.5
• ≥16-year, n (%)	400 (93.5)	368 (93.6)	32 (91.4)	
• Missing	1 (0.2)	1 (0.3)	0 (0.0)	
Male, n (%)	247 (57.7)	227 (57.8)	20 (57.1)	0.9
Baseline disease, n (%)				
• AL/MDS/MPN	284 (66.4)	259 (65.9)	25 (71.4)	1
• Chronic myeloid leukemia	20 (4.7)	19 (4.8)	1 (2.9)	
• Lymphoid disorders	73 (17.1)	68 (17.3)	5 (14.3)	
• Plasma cell disorders	23 (5.4)	21 (5.3)	2 (5.7)	
• Others	28 (6.5)	26 (6.6)	2 (5.7)	
Disease status at transplant, n (%)				
• CR	248 (57.9)	229 (58.3)	19 (54.3)	0.9
• PR	36 (8.4)	33 (8.4)	3 (8.6)	
• Active disease at transplant	103 (24.1)	94 (23.9)	9 (25.7)	
• Missing	41 (9.6)	37 (9.4)	4 (11.4)	
Prior Autologous-HSCT, n (%)				
• Yes	62 (14.4)	60 (15.2)	2 (5.7)	0.2
• Missing	11 (11.3)	8 (8.9)	3 (42.9)	
Period of transplant, n (%)				
• 2019	18 (4.2)	16 (4.1)	2 (5.7)	0.4
• 2017-2018	106 (24.8)	94 (23.9)	12 (34.3)	
• 2015- 2016	101 (23.6)	94 (23.9)	7 (20.0)	
• 2013-2014	54 (12.6)	48 (12.2)	6 (17.1)	
• Before 2013	148 (34.6)	140 (35.6)	8 (22.9)	
• Missing	1 (0.2)	1 (0.3)	0 (0.0)	
Conditioning regimen, n (%)				
• RIC	221 (51.6)	204 (51.9)	17 (48.6)	0.9
• MAC	190 (44.4)	176 (44.8)	14 (40.0)	
• Missing data	17 (4.0)	13 (3.3)	4 (11.4)	
Type of donor, n (%)				
• HLA-identical sibling	144 (33.6)	134 (34.1)	10 (28.6)	0.9
• Unrelated	188 (43.9)	170 (43.3)	18 (51.4)	
• Unrelated umbilical cord blood	23 (5.4)	21 (5.3)	2 (5.7)	
• Haploidentical family	27 (6.3)	26 (6.6)	1 (2.9)	
• Other	43 (10.0)	40 (10.2)	3 (8.6)	
• Missing	3 (0.7)	2 (0.5)	1 (2.9)	
PB stem cell source, n (%)				
• PB	336 (78.5)	311 (79.1)	25 (71.4)	0.2

• missing	4 (0.9)	4 (1.0)	0 (0.0)	
HLA fully-matched, n (%)	262 (61.2)	248 (63.1)	14 (40.0)	0.7
• missing	56 (13.1)	40 (10.2)	16 (45.7)	
ATG as a part of conditioning regimen, n (%)				
• Yes	86 (20.1)	75 (19.1)	11 (31.4)	0.06
• Missing	9 (2.1)	7 (1.8)	2 (5.7)	
GvHD prophylaxis, n (%)				
• Tacrolimus and sirolimus	33 (7.7)	32 (8.1)	1 (2.9)	0.4
• Tacrolimus or CsA+MTX	166 (38.8)	155 (39.4)	11 (31.4)	
• Post-Cy	67 (15.7)	62 (15.8)	5 (14.3)	
• CsA+PDN and Others	144 (33.6)	129 (32.8)	15 (42.9)	
• Missing	18 (4.2)	15 (3.8)	3 (8.6)	
Number hMPV episodes, n (%)				
• 1	419 (97.9)	384 (97.7)	35 (100.0)	1
• >1	9 (2.1)	9 (2.3)	0	
Median time from allo-HCT to 1st hMPV episode, days (range)	373.5, (-7 – 4766)	382, (- 7 – 4766)	183, (9 – 1798)	0.01
Time from allo-HCT to 1st hMPV episode (category)				
• until day +180	141 (32.9)	124 (31.6)	17 (48.6)	0.1
• 181 – 1 year	70 (16.4)	64 (16.3)	6 (17.1)	
• 1 – 2 years	99 (23.1)	92 (23.4)	7 (20.0)	
• after 2 years	118 (27.6)	113 (28.8)	5 (14.3)	
Death, n (%)	145 (33.9)	128 (32.6)	17 (48.6)	
Median time from hMPV to death, days (range)	231, (0 – 2883)	254, (0 – 2883)	32, (2 – 454)	
Median F/U after last episode of hMPV, years (95% CI)	3.53, (3.22 – 3.96)	3.69, (3.17 – 4.1)	3.32 (2.78 – 3.78)	

Abbreviations: allo-HSCT, allogeneic hematopoietic stem cell transplantation; AL, acute leukemia; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasm; CR, complete remission; PR, partial remission; HSCT, hematopoietic stem cell transplantation; RIC, reduced intensity conditioning; MAC, myeloablative conditioning; PB, peripheral blood; HLA, human leucocyte antigen system; ATG, anti-thymocyte globulin; GvHD, graft versus host disease; Sir, sirolimus; Tac, tacrolimus; CsA, cyclosporine A; MTX, methotrexate; Post-Cy, post-transplant cyclophosphamide; PDN, prednisone; hMPV, human metapneumovirus; SCT, stem cell transplantation; F/U, follow-up; CI, confidence interval.

Table 2. Clinical and biological characteristics of hMPV infection episodes (n= 438) in allo-HCT recipients according to upper or lower respiratory tract involvement.

	Only URTD (n =264)	**Possible LRTD (n =131)**	**Proven LRTD (n=43)**	**P value**
Transplant characteristics				
Age				
• <16 years	17 (6.4)	9 (6.9)	1 (2.3)	0.6
• ≥16 years	247 (93.6)	121 (92.4)	42 (97.7)	
• Missing	0 (0.0)	1 (0.8)	0 (0.0)	
ATG as part of conditioning, n (%)				
• No	203 (76.9)	107 (81.7)	32 (74.4)	0.4
• Yes	57 (21.6)	18 (13.7)	11 (25.6)	
• Missing	4 (1.5)	6 (4.6)	0 (0.0)	
GvHD prophylaxis, n (%)				
• Tacrolimus and sirolimus	27 (10.2)	4 (3.1)	4 (9.3)	0.1

• Tacrolimus or CsA+MTX	105 (39.8)	47 (35.9)	16 (37.2)	
• Post-Cy	43 (16.3)	23 (17.6)	5 (11.6)	
• Others	77 (29.2)	50 (38.2)	18 (41.9)	
• Missing	12 (4.5)	7 (5.3)	0 (0.0)	
HLA mismatch, n (%)				
• Matched	166 (62.9)	75 (57.3)	27 (62.8)	0.6
• Mismatch	73 (27.7)	33 (25.2)	8 (18.6)	
• Missing	25 (9.5)	23 (17.6)	8 (18.6)	
Type of donor, n (%)				
• HLA-identical sibling	87 (33.0)	41 (31.3)	17 (39.5)	0.5
• Unrelated	121 (45.8)	53 (40.5)	18 (41.9)	
• Unrelated umbilical cord blood	11 (4.2)	9 (6.9)	3 (7.0)	
• Haplo-identical family	13 (4.9)	13 (9.9)	1 (2.3)	
• Other	31 (11.7)	13 (9.9)	4 (9.3)	
• Missing	1 (0.4)	2 (1.5)	0 (0.0)	
Immunodeficiency Scoring Index, n (%) ‡				
ANC < 0.5×10^9/L	9 (3.4)	14 (10.7)	6 (14.0)	0.001
• Missing data	15 (5.7)	4 (3.1)	2 (4.7)	
ALC< 0.2×10^9/L	11 (4.2)	21 (16.0)	9 (20.9)	<0.0001
• Missing data	21 (8.0)	8 (6.1)	4 (9.3)	
Age at hMPV (years), median (range)	47.4, 0.7 – 74.0	52.3, 0.7 – 73.9	53.3, 15.8 – 66.5	0.02
Age ≥ 40 years	179 (67.8)	95 (72.5)	35 (81.4)	0.09
• Missing data	1 (0.4)	0 (0.0)	0 (0.0)	
Myeloablative conditioning regimen				
• MAC	122 (46.2)	59 (45.0)	13 (31.0)	0.2
• RIC	132 (50.0)	64 (48.9)	30 (69.8)	
• Missing data	10 (3.8)	8 (6.1)	0 (0.0)	
GvHD (acute or chronic)	98 (37.1)	55 (42.0)	24 (55.8)	0.04
• Missing data				
Corticosteroids	91 (34.5)	68 (51.9)	21 (48.8)	0.001
• Missing data	2 (0.8)	1 (0.8)	0 (0.0)	
Recent or pre-engraftment allo-HSCT	14 (5.3)	20 (15.3)	9 (20.9)	<0.0001
ISI, n (%)				
• Low risk (0-2)	155 (58.7)	70 (53.4)	20 (45.5)	0.003
• Moderate risk (3-6)	84 (31.8)	39 (29.8)	15 (34.9)	
• High risk (7-12)	6 (2.3)	16 (12.2)	4 (9.3)	
• Missing data	19 (7.2)	6 (4.6)	4 (9.3)	
Other characteristics ‡				
On IS, n (%)	162 (61.4)	89 (67.9)	34 (79.1)	0.03
ALC< 0.1×10^9/L, n (%)	6 (2.3)	12 (9.2)	5 (11.6)	0.001
ALC < 0.5×10^9/L, n (%)	33 (12.5)	47 (35.9)	22 (51.2)	<0.0001
ALC < 1×10^9/L, n (%)	81 (30.7)	74 (56.5)	29 (67.4)	<0.0001
Missing	21 (8.0)	8 (6.1)	4 (9.3)	
RVI characteristics and clinical consequences				
Ribavirin therapy, n (%)	8 (3.0)	18 (13.7)	10 (23.3)	<0.0001
Co-infections, n (%)	63 (23.9)	41 (31.3)	28 (65.1)	<0.0001
Hospital admission, n (%)	33 (12.5)	71 (54.2)	26 (60.5)	<0.0001

• Missing data	1 (0.4)	3 (2.3)	0 (0.0)	
ICU admission, n (%)	4 (1.5)	22 (16.8)	10 (23.3)	<0.0001
Fever during hMPV, n (%)	105 (39.8)	89 (67.9)	33 (76.7)	<0.0001
• Missing data	8 (3.0)	5 (3.8)	2 (4.7)	
Prior BOS, n (%)	24 (9.1)	13 (9.9)	5 (11.6)	0.6
• Missing data	1 (0.4)	0 (0.0)	0 (0.0)	
Oxygen support, n (%)	4 (1.5)	57 (43.5)	24 (55.8)	<0.0001
• Missing data	5 (1.9)	0 (0.0)	1 (2.3)	
Median time of dx after HSCT infusion, days (range)	422, (-7 – 4766)	305, (-7 – 4584)	237, (-2 – 2086)	0.03
Day + 30 overall mortality rate, n (%)	4 (2%)	16 (12%)	9 (21%)	<0.0001
Day + 90 overall mortality rate, n (%)	10 (4%)	25 (19%)	16 (37%)	<0.0001
Median time to death, days (95% CI)	385 (0-2483)	151 (3 – 2883)	39 (2 – 982)	
Median time to death, years (95% CI)	1.05 (0.0-6.80)	0.41 (0.008 – 7.89)	0.11 (0.005 – 2.69)	

Abbreviations. URTD, upper respiratory tract disease; LRTD, lower respiratory tract disease; ATG, anti-thymocyte globulin; GvHD, graft-versus-host disease; Sir, sirolimus; Tac, tacrolimus; CsA, cyclosporine A; MTX, methotrexate; Post-Cy, post-transplant cyclophosphamide; HLA, human leukocyte antigen; ; ANC, absolute neutrophil count; ALC, absolute lymphocyte count; hMPV, human metapneumovirus; MAC, myeloablative conditioning, RIC, reduced intensity conditioning; ISI, immunodeficiency scoring index; RVI, respiratory virus infection; IS, immunosuppressants; Allo-HSCT, allogeneic hematopoietic stem cell transplantation; ICU, intensive care unit; BOS, bronchiolitis obliterans syndrome; dx, diagnostic; SC, stem cells.

‡ All variables were captured at the time of hMPV diagnosis.

Table 3. Multivariate analyses for different outcomes.

Outcome	Variables	OR/HR (95% C.I.)	P value
Hospital admission (n=361) Ω **variables used for multivariate analysis:**		**Log. Regr. (OR)**	
GVHD prophylaxis, Age ≥ 40 years, Active GvHD at the time RVI, Co-infection, ALC < 0.5 × 10^9/L ANC < 0.5 × 10^9/L BOS Corticosteroids ≥ 30mg/d	Active GvHD at the time of RVI	2.65 (1.57-4.48)	0.0003
	ALC < 0.5 × 10^9/L	1.83 (1.06-3.18)	0.03
	Corticosteroids ≥ 30mg/d	2.37 (1.16-4.87)	0.02
Oxygen support (n=350) Ω **variables used for multivariate analysis:**		**Log. Regr. (OR)**	
GVHD prophylaxis On IS ANC < 0.5 × 10^9/L ALC < 0.5 × 10^9/L ¥ ALC< 0.2 × 10^9/L ¥ ALC< 1 × 10^9/L ¥ Age ≥ 40 years	ALC < 0.5 × 10^9/L	4.52 (2.38-8.59)	<0.0001
	Age ≥ 40 years	3.19 (1.42-7.16)	0.005
	Active GvHD at the time RVI	3.51 (1.83-6.73)	0.0002

Active GvHD at the time RVI Periengraftment Allo-HSCT ≤ 6 months Corticosteroids vs No Prior BOS Co-infection post-Cy vs tacrolimus	Co-infection Y/N	2.42 (1.29-4.52)	0.01
	CsA+PDN or Others vs tacrolimus	2.30 (1.19-4.44)	0.01
LRTD (n=365) Ω **variables used for multivariate analysis:**		**Log. Regr. (OR)**	
GVHD prophylaxis ALC On IS ANC < 0.5 × 109/L Active GvHD at the time RVI Periengraftment Allo-HSCT ≤ 12 months or Allo-HSCT ≤ 6 months	ALC		0.0003§
	• ≤ 0.2 × 10^9/L, vs ≥0.5	5.00 (2.08-12.00)	0.0003
	• 0.2-0.5 × 10^9/L, vs ≥0.5	1.94 (1.11-3.38)	0.02
	Corticosteroids ≥ 30mg/d	4.06 (2.08-7.91)	<0.0001
LRTD NRM 30-day mortality (n=155) Ω **variables used for multivariate analysis:**		**Cox Regr (HR)**	
GVHD prophylaxis ALC < 0.5 × 10^9/L & ALC< 0.2 × 10^9/L & ALC< 1 × 10^9/L & Periengraftment Allo-HSCT ≤ 6 months or Allo-HSCT ≤ 100 days Corticosteroids* vs No	ALC < 0.2 × 10^9/L	4.45 (1.83-10.87)	0.001

652 **Abbreviations: C.I.,** confidence interval; OR, odds ratio; HR, hazard ratio; Log. Regr, logistic regression
653 model; Cox Regr, cox regression model; GvHD, graft-versus-host disease; IS, immunosuppressants;
654 ANC, absolute neutrophil count; ALC, absolute lymphocyte count; BOS, bronchiolitis obliterans
655 syndrome; RVI, respiratory virus infection; Y, yes; N, no; LRTD, lower respiratory tract disease.

656 § overall comparison.

657 Ω number of patients with complete data on all the variables included in the MVA

658 ¥ We only include in the final multivariate analysis ALC <0.5 x 10^9/mL.

659 & We only include in the final multivariate analysis ALC <0.2 x 10^9/mL.

660

661 **Table 4.** Co-infection characteristics according to upper or lower respiratory tract
662 involvement.

Co-infections	**All HMPV cases (n=438)**	**HMPV URTD (n =264)**	**HMPV LRTD (n =174)**
CARV co-infections, n			
• HCoV	21	10	11
• EvRh	36	20	16
• RSV	18	10	8
• HPiV	19	10	9
• ADV	9	6	3
• HiV	25	13	12
• HBoV	3	3	0
Bacterial co-infection, n			

• *Pseudomonas spp*	6	1	5
• *Streptococcus pneumoniae*	2	2	0
• *Haemophilus influenza*	2	0	2
• *E. coli*	3	0	3
• *Stenotrophomonas maltophilia*	1	0	1
• *Staphylococcus aureus*	1	0	1
• *Enterococcus spp*	3	0	3
• Others*	5	0	5
Fungal co-infection, n			
• Probable invasive fungal infection	19	4	15
• Proven invasive fungal infection	6	0	6
• Median time from hMPV to IFI, days (range)	11 (0- 82)	45 (7 - 79)	9 (0 - 82)
• *Aspergillosis spp*	18	0	18
• *Candidemia spp*	2	0	2
• *Pneumocystis jiroveci*	4	0	4
• *Mucormycosis*	1	0	1

Abbreviations, URTD, upper respiratory tract disease; LRTD, lower respiratory tract disease; CARV, cummunity acquired respiratory virus; HCoV, human coronavirus; EvRh, Enterovirus/rhinovirus; RSV, respiratory syncytial virus; HPiV, human parainfluenza virus; ADV, adenovirus; HiV, human influenza virus, HBoV, human bocavirus; IFI, invasive fungal infection.

* Haemophilus parahaemolyticus, 1; Streptococcus alpha haemolytic, 1; Bordetella sp, 1; Coagulase-negative Staphylococcus, 1; Lactobacillus rhamnosus + Enterococcus, 1.

Table 5. Characteristics of hMPV infection episodes according to ribavirin treatment.

	All hMPV cases (N=438)	**Not treated (N=402)**	**Treated with ribavirin (N=36)**	**P value***
Number of Episodes, n (%)				0.8
• 1	428 (97.7)	393 (97.8)	35 (97.2)	
• 2	9 (2.1)	9 (2.2)	0 (0.0)	
• 3	1 (0.2)	0 (0.0)	1 (2.8)	
Only URTD, n (%)				<0.0001
• Yes	264 (60.3)	256 (63.7)	8 (22.2)	
LRTD, n (%)				
• Possible	131 (29.9)	113 (28.1)	18 (50.0)	0.2
• Proven	43 (9.8)	33 (8.2)	10 (27.8)	
Fever, n (%)				0.8
• Yes	227 (51.8)	209 (52.0)	18 (50.0)	
• Missing	15 (3.4)	11 (2.7)	4 (11.1)	
CRP in mg/dL, median (min-max)	20, 0 – 452	18, 0 – 452	44, 1 – 368	0.1
ISI (Low/Mod/High), n (%)				0.09
• Low	245 (55.9)	226 (56.2)	19 (52.8)	
• Moderate	138 (31.5)	130 (32.3)	8 (22.2)	
• High	26 (5.9)	19 (4.7)	7 (19.4)	
• Missing	29 (6.6)	27 (6.7)	2 (5.6)	

Hospitalization, n (%)				0.02
• Yes	130 (29.7)	113 (28.1)	17 (47.2)	
• Missing	4 (0.9)	4 (1.0)	0 (0.0)	
URTD RV co-infection, n (%)	106 (24.2)	93 (23.1)	13 (36.1)	0.09
LRTD co-infection, n (%)				
• Viral-Fungal	14 (3.2)	11 (2.7)	3 (8.3)	
• Viral-Bacterial	5 (1.1)	4 (1.0)	1 (2.8)	
• Viral-viral-bacterial	4 (0.9)	3 (0.7)	1 (2.8)	
• Viral-bacterial-fungal	1 (0.2)	1 (0.2)	0 (0.0)	
• Viral-viral	5 (1.1)	5 (1.1)	0 (0.0)	
• Viral-viral-fungal	1 (0.2)	0 (0.0)	1 (2.8)	
RSV co-infection	18 (4.1)	9 (2.2)	9 (25.0)	<0.0001
HPIV co-infection	19 (4.3)	2 (5.6)	17 (4.2)	0.7
Oxygen support, n (%)				<0.0001
• Yes	85 (19.4)	68 (16.9)	17 (47.2)	
• Missing	6 (1.4)	6 (1.5)	0 (0.0)	
ICU, n (%)	36 (8.2)	27 (6.7)	9 (25.0)	0.0004
On IS, n (%)	285 (65.1)	252 (62.7)	33 (91.7)	0.002
ALC< 0.1 × 109/L, n (%)	23 (5.3)	17 (4.2)	6 (16.7)	0.004
ALC< 0.2 × 109/L, n (%)	41 (9.4)	31 (7.7)	10 (27.8)	0.0003
ALC < 0.5 × 109/L, n (%)	102 (23.3)	84 (20.9)	18 (50.0)	0.0002
ALC < 1 × 109/L, n (%)	184 (42.0)	160 (39.8)	24 (66.7)	0.003
Corticosteroids	180 (41.1)	164 (40.8)	16 (44.4)	0.7
• Missing	3 (0.7)	3 (0.7)	0 (0.0)	
Periengraftment*	43 (9.8)	33 (8.2)	10 (27.8)	0.0005
Allo-HSCT ≤ 100 days	90 (20.5)	79 (19.7)	11 (30.6)	0.1
Allo-HSCT ≤ 6 months	142 (32.4)	125 (31.1)	17 (47.2)	0.03
Allo-HSCT ≤ 12 months	214 (48.9)	191 (47.5)	23 (63.9)	0.05
Allo-HSCT ≤ 24 months	317 (72.4)	286 (71.1)	31 (86.1)	0.06
Day + 30 overall mortality, n (%)	29 (6.6)	21 (5.2)	8 (22.2)	0.0002
Day + 90 overall mortality, n (%)	51 (11.6)	39 (9.7)	12 (33.3)	<0.0001

Abbreviations: URTD, upper respiratory tract disease; LRTD, lower respiratory tract disease; CRP, C-reactive protein; ISI, immunodeficiency score index; RSV, respiratory syncytial virus; HPiV, human parainfluenza virus; IS, immunosuppressants; ALC, absolute lymphocyte count; Allo-HSCT, allogeneic hematopoietic stem cell transplantation.

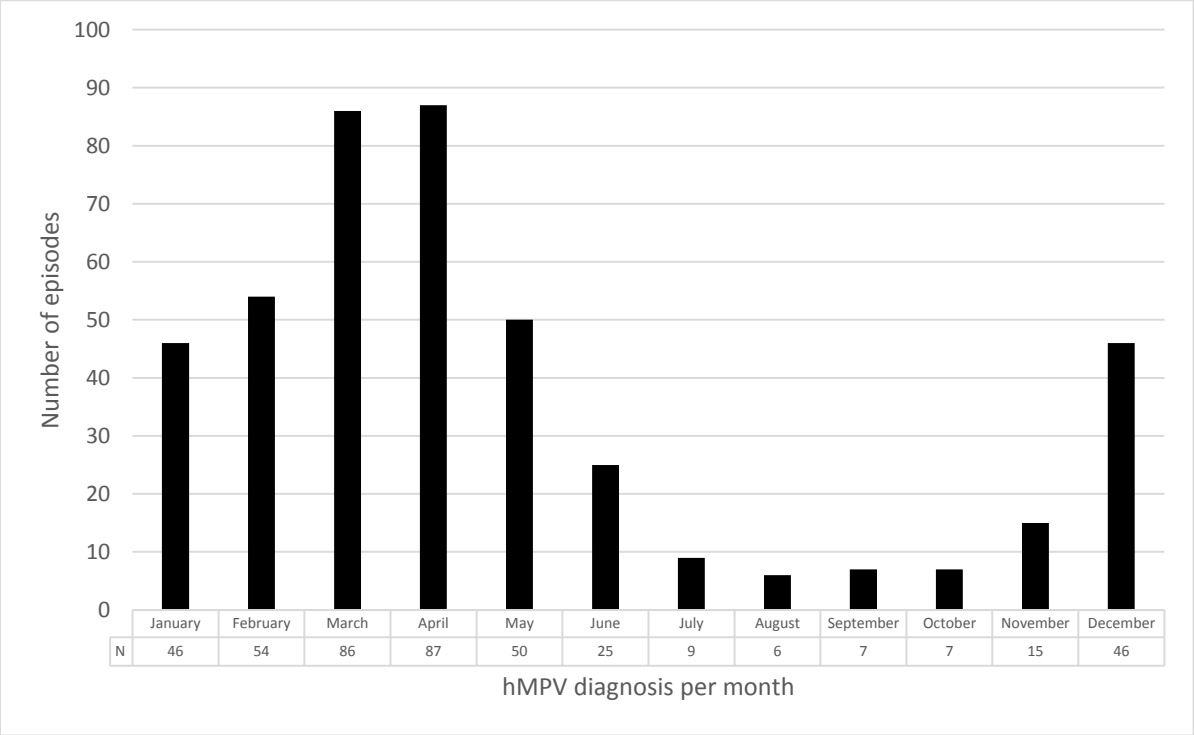
Table 6. Propensity score analysis.

Variables used for propensity score matching	**Propensity score matched**		
Characteristics	**Whole cohort (n=66)**	**Not treated (n=33)**	**Treated with ribavirin (n=33)**
ALC < 0.5 × 109/L, n (%)	31 (47)	15/31 (48)	16/31 (52)
ISI (High), n (%)	13 (20)	7/13 (54)	6/13 (46)
Allo-HSCT ≤ 180 days	33 (50)	17/33 (52)	16/33 (48)
Oxygen support	32 (48)	16/32 (50)	16/32 (50)
Hospitalization, n (%)	31 (47)	16/31 (52)	15/31 (48)
ICU, n (%)	13 (20)	5/13 (38)	8/13 (62)

Survival outcome	Propensity score matched		
	Not treated (n=33)	Treated with ribavirin (n=33)	p value
Day + 30 overall mortality, n (%)	15.2 (5.4-29.5)	21.2 (9.2-36.5)	0.5
Day + 90 overall mortality, n (%)	18.2 (7.2-33.1)	33.3 (17.9-49.6)	0.2

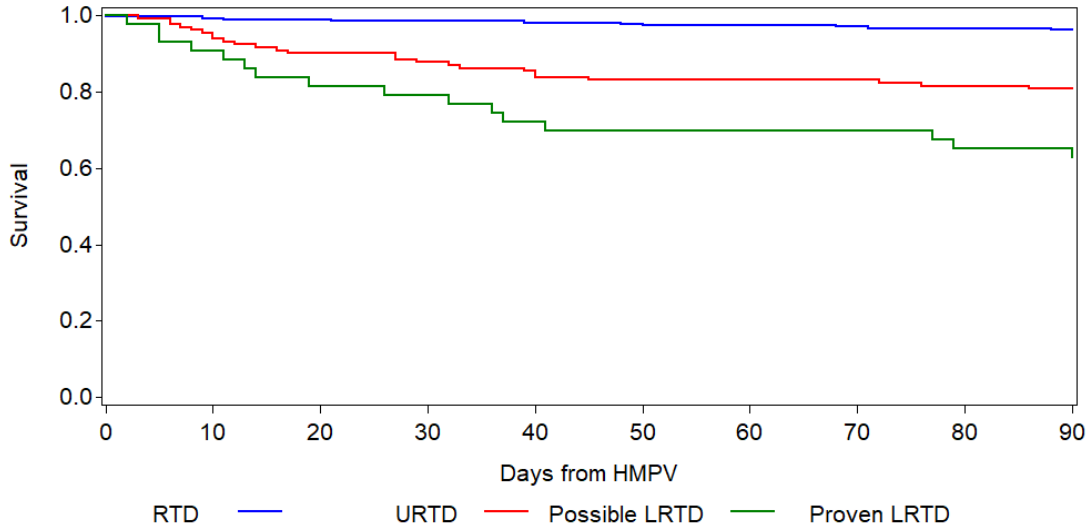
Abbreviations: ALC, absolute lymphocyte count; LRTD, lower respiratory tract disease; ISI, immunodeficiency score index; Allo-HSCT, allogeneic hematopoietic stem cell transplantation; URTD, upper respiratory tract disease; ICU, intensive care unit.

Figure 1. Seasonality of human metapneumovirus infections in recipients of allogeneic hematopoietic stem cell transplant. (From January to December*)



*5 cases (2 in September, 2 October, 1 November) occurred in Australia

Figure 2. 90-day overall survival from hMPV detection according to URTD and possible or proven LRTD.



697

Group	Episodes	Death	90-day OS (95% C.I.)	p
URTD	264	10	96.2 (93.0 – 97.9)	<0.0001
Possible LRTD	131	25	80.8 (72.9 – 86.6)	
Proven LRTD	43	16	62.8 (46.6 – 75.3)	

698

Upper and/or lower respiratory tract infection caused by human metapneumovirus after allogeneic hematopoietic stem cell transplantation

Jose Luis Piñana[1], Gloria Tridello[2], Aliénor Xhaard[3], Lotus Wendel[4], Juan Montoro[5], Lourdes Vazquez[6], Inmaculada Heras[7], Per Ljungman[8], Malgorzata Mikulska[9], Urpu Salmenniemi[10], Ariadna Perez[1], Nicolaus Kröger[11], J.J. Cornelissen[12], Elisa Sala[13], Rodrigo Martino[14], Claire Geurten[15], Jenny Byrne[16], Johan Maertens[17], Tessa Kerre[18], Murray Martin[19], Maria Jesús Pascual[20], Moshe Yeshurun[21], Jürgen Finke[22], Andreas H. Groll[23], Peter J. Shaw[24], Nicole Blijlevens[25], William Arcese[26], Arnold Ganser[27], Maria Suarez-Lledo[28], Mohsen Alzahrani[29], Goda Choi[30], Edouard Forcade[31], Annalisa Paviglianiti[32], Carlos Solano[1,43], Jacek Wachowiak[33], Tsila Zuckerman[34], Peter Bader[35], Johannes Clausen[36], Jiri Mayer[37], Wilfried Schroyens[38], Elisabetta Metafuni[39], Nina Knelange[4], Dina Averbuch[40], Rafael de la Camara[41,42].

On behalf of the Infectious Diseases Working Party of the European Society for Blood and Marrow Transplantation and Infectious Complications Subcommittee of the Spanish Hematopoietic Stem Cell Transplantation and Cell Therapy Group (GETH-TC)

1. Hematology Department, Hospital Clinico Universitario de Valencia, Spain. Fundación INCLIVA, Instituto de Investigación Sanitaria Hospital Clínico Universitario de Valencia, Spain.
2. Azienda Ospedaliera Universitaria Integrata Verona, Verona, Italy.
3. Service d'Hématologie-Greffe, Hôpital Saint-Louis, Université Paris-Diderot, Paris, France.
4. EBMT Leiden Study Unit, Leiden, The Netherlands.
5. Hematology división, Hospital universitario y politécnico La Fe, Valencia, Spain.
6. Hematology Department, Hospital Clinico Universitario de Salamanca, Spain.
7. Hematology Department, Hospital Morales Meseguer, Murcia, Spain.
8. Department of Cellular Therapy and Allogeneic Stem Cell Transplantation, Karolinska Comprehensive Cancer Center, Karolinska University Hospital

Huddinge and Dept. of Medicine Huddinge, Karolinska Institutet, Stockholm, Sweden.

9. Division of Infectious Diseases, University of Genoa (DISSAL) and IRCCS Ospedale Policlinico San Martino, Genova Italy.
10. Hematology Department, HUCH Comprehensive Cancer Center, Helsinki, Finland.
11. Department for Stem Cell Transplantation, University Medical Center Hamburg-Eppendorf/Germany.
12. Hematology Department, Erasmus MC Cancer Institute, Rotterdam, Netherlands.
13. Department of Internal Medicine III, University Hospital of Ulm, Ulm, Germany.
14. Hematology Department, Hospital de la Santa Creu I Sant Pau, Barcelona, Spain.
15. Hematology Department, Birmingham Children`s Hospital, Birmingham, United Kingdom and Centre Hospitalier Universitaire de Liege, Belgique.
16. Hematology Department, Nottingham University, Nottingham, United Kingdom.
17. Hematology Department, University Hospital Gasthuisberg, Leuven, Belgium.
18. Hematology Department, Ghent University Hospital, Gent, Belgium.
19. Hematology Department, Leicester Royal Infirmary, Leicester, United Kingdom.
20. Hematology Department, Hospital Regional de Málaga, Malaga, Spain.
21. Institution of Hematology, Rabin medical Center, Petach-Tikva, Israel and Sackler School of Medicine, Tel-Aviv University, Tel-Aviv, Israel.
22. University of Freiburg, Freiburg, Germany.
23. Infectious Disease Research Program, Department of Pediatric Hemtology and Oncology and Center for Bone Marrow Transplantation, University Children's Hospital, Muenster, Germany.
24. The Children`s Hospital at Westmead, Sydney, Australia.
25. Nijmegen Medical Centre, Nijmegen, Netherlands.
26. Tor Vergata University of Rome, Rome, Italy.
27. Hannover Medical School, Hannover, Germany.
28. Hematology Department, Hospital Clinic, Barcelona, Spain.

29. Department of Oncology, King Abdulaziz Medical City, Ministry of National Guard – Health Affaris, Riyadh, Saudi Arabia.
30. University Medical Center Groningen, University of Groningen, Groningen, the Netherlands.
31. Service d'Hématologie Clinique et Thérapie Cellulaire, CHU Bordeaux, F-33000, Bordeaux, France.
32. Institut Català de Oncología – Hospital Duran i Reynals, Barcelona, Spain.
33. Department of Pediatric Oncology, Hematology and HSCT, University of Medical Sciences, Poznan, Poland.
34. Rambam Medical Center, Haifa, Israel.
35. Division for Stem Cell Transplantation, Immunology and Intensive Care Medicine, Department for Pediatrics and Adolescent Medicine, University Hospital, Goethe University, Frankfurt, Germany.
36. Department of Internal Medicine I, Ordensklinikum Linz - Elisabethinen, Johannes Kepler University, Linz, Austria
37. Masaryk University Hospital Brno, Brno, Czech Rep.
38. Antwerp University Hospital (UZA), Antwerp Edegem, Belgium.
39. Fondazione Policlinico Universitario Agostino Gemelli IRCCS. Dipartimento di Diagnostica per Immagini, Radioterapia Oncologica e EmatologiaGemelli IRCCS, Roma, Italy.
40. Faculty of Medicine, Hebrew University of Jerusalem; Hadassah Medical Center, Jerusalem, Israel.
41. Hematology Department, Hospital de la Princesa, Madrid, Spain.
42. Hematology Department, Hospital Universitario Sanitas La Zarzuela, Madrid, Spain.
43. Department of Medicine. University of Valencia, Spain.

Short Title: hMPV infection after allo-HSCT.

Brief summary: hMPV infection after allo-HSCT frequently involves the lower respiratory tract (40%). Pulmonary involvement was associated with substantial all-cause

mortality rate (14%) at day 30 after hMPV detection, particularly in those with lymphopenia.

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Correspondence:

MD. Jose Luis Piñana
Division of Clinical Hematology
Hospital Clínico Universitario de Valencia
Avda Blasco Ibañez, 17, 46010, Valencia, Spain
Phone: +34 963862625 Fax: +34 963987820
E-mail: jlpinana@gmail.com