Seasonal Human Coronavirus Infections Following Allogeneic Hematopoietic Cell Transplantation: Factors Associated With Lower Respiratory Tract Infection

Chikara Ogimi[1,2,3], Hu Xie[3], Alpana Waghmare[1,2,3], Masumi Ueda[2,3], Kanwaldeep K. Mallhi[1,2,3], Chris Davis[3], Ashley Akramoff[1], Anthony Mallory[1], Keith R. Jerome[2,3], Wendy M Leisenring[3], Janet A Englund[1,2] and Michael Boeckh[2,3]

[1]Seattle Children's Hospital, [2]University of Washington, [3]Fred Hutchinson Cancer Research Center

Evidence before this study
- Risk factors for HCoV LRTI in allogeneic HCT recipients are little appreciated.

Added value of this study
- Factors associated with occurrence of HCoV LRTI were male gender, hypoalbuminemia, hyperglycemia, presence of respiratory copathogen and higher immunodeficiency scoring index.
- Steroid induced hyperglycemia appears an important risk factor for progression to HCoV LRTI.

BACKGROUND

Proven/probable lower respiratory tract infection (LRTI) caused by seasonal human coronaviruses (HCoVs) is associated with mortality after hematopoietic cell transplantation (HCT).[1] However, risk factors for LRTI and the significance of virologic documentation of lower respiratory tract involvement by bronchoalveolar lavage (BAL) on outcome are not well characterized.

OBJECTIVE

To identify risk factors for HCoV LRTI in allogeneic HCT recipients and investigate whether outcomes differ among patients with LRTI according to virologic documentation of lower respiratory tract involvement by BAL.

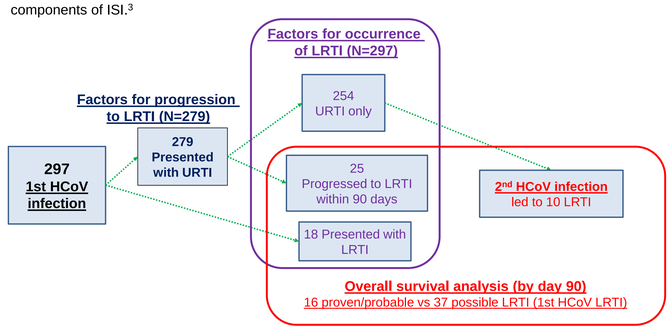
METHODS

- Retrospective cohort study.
- Subjects: Patients undergoing allogeneic HCT at the Fred Hutch from 4/2008 to 9/2018.
- Inclusion criteria: HCoV infection during pretransplant conditioning or after transplantation.[2]

Definition of LRTI outcome[4]

	Virus detection	New pulmonary infiltrate
Proven/Probable LRTI	Lower respiratory tract	+/-
Possible LRTI	Upper respiratory tract	+

Models
- Logistic regression: to evaluate cross-sectional association between each risk factor and occurrence of LRTI among all patients with first HCoV infection (including patients who presented with LRTI).
- Cox regression: to assess factors for progression to LRTI among patients who presented with first HCoV URTI.
- Log-rank/Gray's test: to compare univariable hazards of time-to-event outcomes between categories.
- All covariates with P values <.1 in the univariable analyses were candidates for inclusion in the multivariable models.
- Immunodeficiency scoring index (ISI) was treated as a continuous variable in multivariable models given limited number of outcome events, and steroid and cell counts were not included as these are components of ISI.[3]



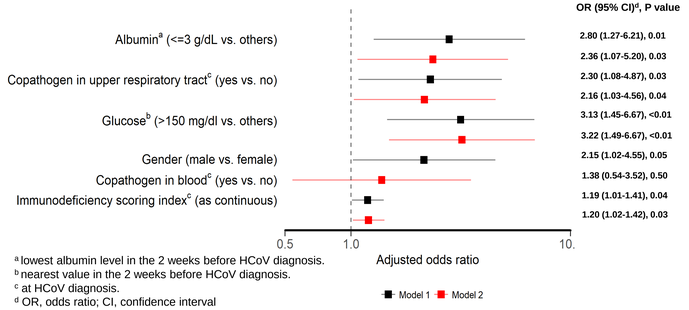
RESULTS

Table 1. characteristics of allogeneic HCT recipients with first HCoV

Characteristics	Categories	URTI[a] (N=254)	LRTI[a] (N=43)
Age at HCoV diagnosis	Median (IQR)	44 (23-60	48 (34-62)
Gender	Male	140 (55%)	30 (70%)
Race	White	206 (81%)	33 (77%)
Year of transplant	2008-2013	123 (48%)	18 (42%)
Transplant number	Multiple	48 (19%)	11 (25%)
Stem cell source	Bone marrow	46 (18%)	6 (14%)
	PBSC	177 (70%)	29 (67%)
	Cord blood	31 (12%)	8 (19%)
Human leukocyte antigen	Mismatch/Unrelated	141 (56%)	19 (44%)
	Haplo/Related	16 (6%)	7 (16%)
	Matched/Related	66 (26%)	9 (21%)
	Cord/Unrelated	31 (12%)	8 (19%)
Recipient blood type[b]	O+ or O-	113 (44%)	24 (56%)
	A+ or A-	94 (37%)	15 (35%)
	B+ or B-	34 (13%)	3 (7%)
	AB+ or AB-	10 (4%)	0 (0%)
Donor blood type[b]	O+ or O-	105 (42%)	18 (42%)
	A+ or A-	93 (37%)	12 (28%)
	B+ or B-	28 (11%)	4 (9%)
	AB+ or AB-	8 (3%)	2 (5%)
Conditioning regimen	Myeloablative	163 (64%)	29 (67%)
Body mass index	Obese	63 (25%)	11 (26%)
Recipient CMV status	+	167 (66%)	30 (70%)
Donor CMV status	+	111 (44%)	15 (35%)
Days between HCT and HCoV infection	<=30	37 (15%)	6 (14%)
	31-365	133 (52%)	25 (58%)
	>365	84 (33%)	12 (28%)
Acute GVHD	Grade 2	158 (62%)	21 (49%)
	Grade 3-4	27 (11%)	8 (19%)
Chronic GVHD	Yes	246 (97%)	40 (93%)
HCoV Species[b]	OC43	2 (1%)	4 (9%)
	NL63	4 (2%)	0 (0%)
	HKU1	2 (1%)	2 (5%)
	229E	2 (1%)	1 (2%)
HCoV Ct values[b]	Median (IQR)	26 (23-31)	28 (26-30)
Copathogen in upper respiratory tract[c]	Yes	52 (20%)	15 (35%)
Copathogen in blood[d]	Yes	28 (11%)	9 (21%)
Immunodeficiency scoring index[c]	Low (0-2)	65 (26%)	1 (2%)
	Moderate (3-6)	172 (68%)	36 (84%)
	High (7-11)	17 (7%)	6 (14%)
Neutrophil count[e]	<=500 (x10^6 cells/L)	18 (7%)	6 (14%)
Lymphocyte count[e]	<=200 (x10^6 cells/L)	25 (10%)	5 (12%)
Monocyte count[e]	<=100 (x10^6 cells/L)	22 (9%)	10 (23%)
Albumin[f]	<=3 (g/dl)	35 (14%)	16 (37%)
Glucose[b, e]	0-100 (mg/dl)	60 (24%)	13 (31%)
	101-150 (mg/dl)	118 (46%)	9 (21%)
	>150 (mg/dl)	34 (13%)	15 (36%)
Steroid dose[g]	None	122 (48%)	12 (28%)
	<1 mg/kg	111 (44%)	25 (58%)
	>=1mg/kg	21 (8%)	6 (14%)

[a] values are in n (%) unless otherwise specified.
[b] missing values exist.
[c] at HCoV diagnosis.
[d] defined as a pathogen (bacteria, fungi, virus) detected in a blood within 2 days of HCoV diagnosis.
[e] using nearest value within 14 days before HCoV diagnosis.
[f] lowest albumin value in the 2 weeks before HCoV diagnosis.
[g] highest daily steroid dose in the 2 weeks before HCoV diagnosis.
Abbreviations: URTI = upper respiratory tract infection, LRTI = lower respiratory tract infection, IQR = interquartile range, PBSC = peripheral blood stem cell, CMV = cytomegalovirus, HCT = hematopoietic cell transplantation, GVHD = graft-versus-host disease, Ct = cycle threshold.

Fig 1. Multivariable Logistic Regression on HCoV LRTI (Yes vs. No) - 43 events among 297 patients with first HCoV infection -



[a] lowest albumin level in the 2 weeks before HCoV diagnosis.
[b] nearest value in the 2 weeks before HCoV diagnosis.
[c] at HCoV diagnosis.
[d] OR, odds ratio; CI, confidence interval

Fig 3. Overall Survival by Day 90 according to LRTI classification - among 53 patients with first HCoV LRTI -

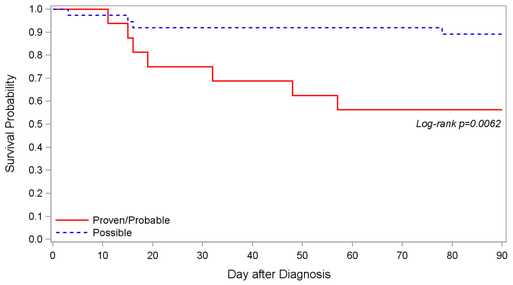
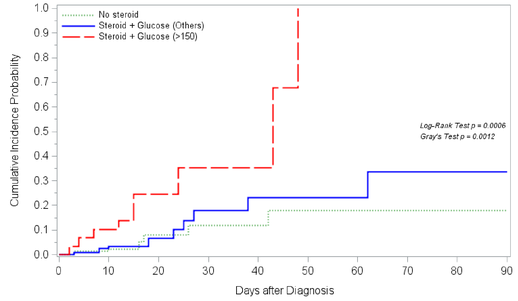


Table 2. Multivariable Cox Regression for progression to HCoV LRTI - 25 events among 279 patients presenting with first HCoV URTI -

	Model 1		Model 2		Model 3	
Covariates	HR 95% CI	P value	HR 95% CI	P value	HR 95% CI	P value
Steroid[a] + glucose[b] (>150) vs. no steroid	4.73 (1.60-14.0)	<.01	4.83 (1.61-14.5)	<.01		
Steroid[a] + glucose[b] (others) vs. no steroid	1.51 (0.58-3.98)	.4	1.44 (0.54-3.84)	.47		
Multiple vs. single (transplant number)	1.56 (0.63-3.90)	.34			2.17 (0.92-5.09)	.08
ISI at diagnosis (continuous)			1.07 (0.89-1.28)	.47	1.14 (0.97-1.34)	.12

[a] highest daily steroid dose in the 2 weeks before HCoV URTI diagnosis.
[b] nearest value in the 2 weeks before HCoV URTI diagnosis.
Abbreviations: HR = hazard ratio, CI = confidence interval, ISI = immunodeficiency scoring index

Fig2. Cumulative incidence of progression to HCoV LRTI by day 90 - among 279 patients presenting with first HCoV URTI -



SUMMARY and LIMITATIONS

- This study demonstrated that male gender, hypoalbuminemia, high glucose, presence of respiratory copathogen and higher ISI were associated with occurrence of HCoV LRTI.
- Hyperglycemia with steroid use was highly associated with progression to HCoV LRTI.
- Mortality rates following proven/probable HCoV LRTI were higher than possible LRTI.
- Our sample size did not allow us to perform full multivariable Cox models to assess the independent effect of hyperglycemia on progression to LRTI from steroid dose and analyze for LRTI outcomes separately (proven/probable LRTI vs. possible LRTI).
- An additional limitation of this study is unmeasured or unknown confounders.

CONCLUSIONS

- Risk factors for HCoV LRTI we identified are uncommonly appreciated for other respiratory viruses in HCT recipients.
- Whether these observations are also applicable to SARS-CoV-2 in HCT recipients requires further studies.
- Assessing the independent effect of hyperglycemia from steroids use and role of glycemic control on progression to LRTI due to HCoV or other respiratory viruses would be warranted.

References:
1. Ogimi C, et al. *Clin Infect Dis.* 2017;64(11):1532-1539. 2. Seo S, et al. *Clin Infect Dis.* 2016;63(2):178-185.
3. Shah DP, et al. *Blood.* 2014;123(21):3263-3268.

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