Factors associated with viral lower respiratory tract infection in allogeneic hematopoietic cell transplant recipients: hyperglycemia, virus type, multiple transplants and immunodeficiency scoring index

Chikara Ogimi[1,2,3], Hu Xie [3], Alpana Waghmare[1,2,3], Keith R. Jerome[2,3], Wendy M. Leisenring[3], Paul A. Carpenter[1,2,3], Janet A. Englund[1,2], and Michael Boeckh[2,3]

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

Introduction

- Hyperglycemia is associated with poor outcome in patients with SARS-CoV-2.[1, 2]
- Immunodeficiency scoring index (ISI) predicts risk for progression to lower respiratory tract infection (LRTI) in hematopoietic cell transplant (HCT) recipients who present with respiratory syncytial virus (RSV) upper respiratory tract infection (URTI).[3]

Immunodeficiency scoring index (ISI) Criteria*	Assigned weights (score)
Neutrophil counts <500/μL	3
Lymphocyte counts <200/μL	3
Age >= 40 y	2
Myeloablative conditioning	1
GVHD (acute or chronic)	1
Corticosteroid use within 30 days before URTI	1
Allogeneic HCT within 30 days pre-URTI or pre-engraftment	1

*Low risk: 0-2 score, moderate risk 3-6 score, high risk 7-12 score.

Aim

To investigate the impact of hyperglycemia on progression to viral LRTI and the applicability of ISI to other viruses in allogeneic HCT recipients.

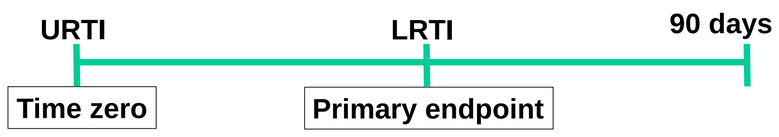
Methods

Study design

- Retrospective cohort study
- Subjects: Children and adults undergoing allogeneic HCT (4/2008-9/2018) at the Fred Hutchinson Cancer Research Center and the Seattle Cancer Care Alliance.
- Inclusion criteria: patients with first respiratory viruses detected from respiratory tract samples by multiplex PCR post-HCT.
- Exclusion criteria: patients presenting with LRTI.

Respiratory virus			
RSV	Respiratory syncytial virus	FLU A/B	Influenza A/B
MPV	Human metapneumovirus	ADV	Adenovirus
PIV 1-4	Parainfluenza 1-4	HRV	Human rhinovirus
COV	Human coronavirus		

Definition of outcomes



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

Analysis

- Cox proportional hazards models.
- Risk factors for progression to LRTI among patients presenting with viral URTI, treating death as a competing risk.
- Glucose and albumin values were recorded within 2 weeks prior to first viral positive test.
- Glucose covariates were evaluated in multivariable models in two ways as follows.

Model 1	most recent glucose >150mg/dl
	any glucose other than most recent >150mg/dl
	any glucose <=150mg/dl or unknown
Model 2	highest glucose >200mg/dl
	highest glucose <=200mg/dl or unknown

- Variables with p values <0.05 were included into multivariable models.

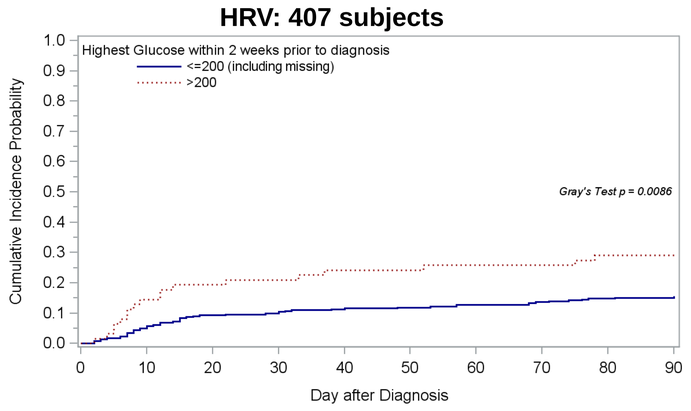
Results

Demographics (patients presenting with URTI)

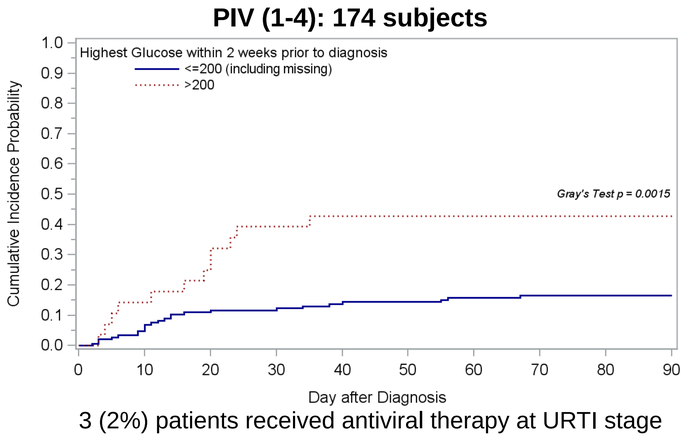
Variables	Categories	N=1027 (%)
Sex	Male	591 (58%)
Age at URTI	<18	216 (21%)
Transplant number	First	870 (85%)
Days to URTI post-HCT	<=30 days	200 (19%)
Immunodeficiency scoring index	Low (0-2)	208 (20%)
	Moderate (3-6)	682 (66%)
	High (7-12)	137 (13%)
Steroid use before diagnosis	None	489 (48%)
	<1 mg/kg	424 (41%)
	>=1 mg/kg	114 (11%)
Glucose values (mg/dl) model 1	Most recent glucose >150	184 (18%)
	Any glucose other than most recent >150	220 (21%)
	Any glucose <=150 or unknown	623 (61%
Glucose values (mg/dl) model 2	Highest glucose >200	177 (17%)
	Highest glucose <=200 or unknown	850 (83%)

Cumulative incidence plot of time to LRTI by highest glucose values

HRV: 407 subjects

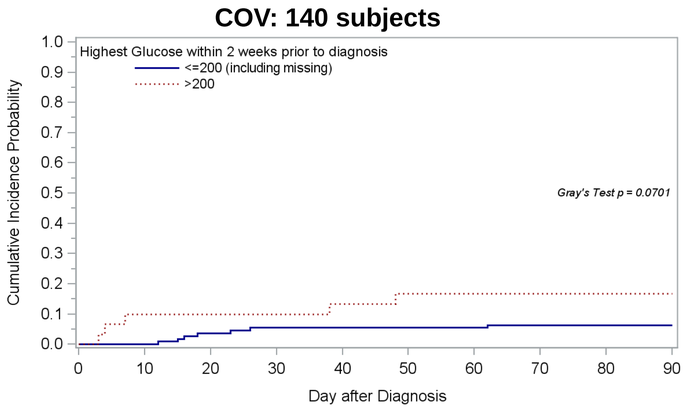


PIV (1-4): 174 subjects

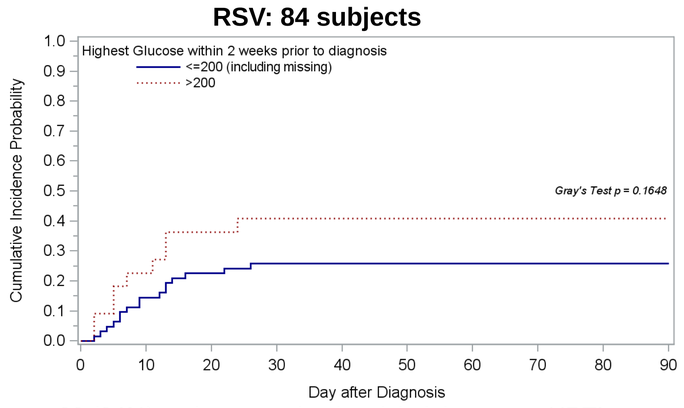


3 (2%) patients received antiviral therapy at URTI stage

COV: 140 subjects

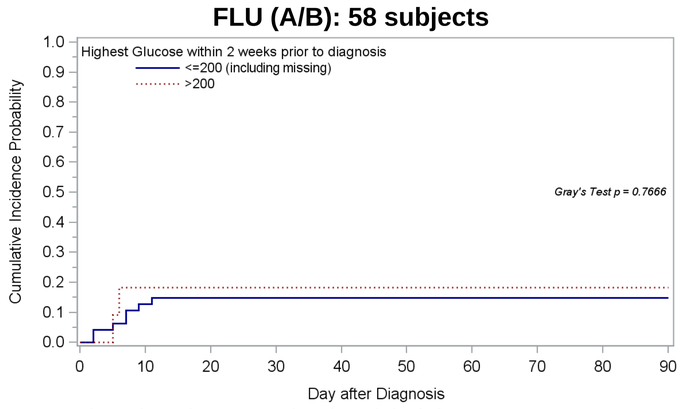


RSV: 84 subjects



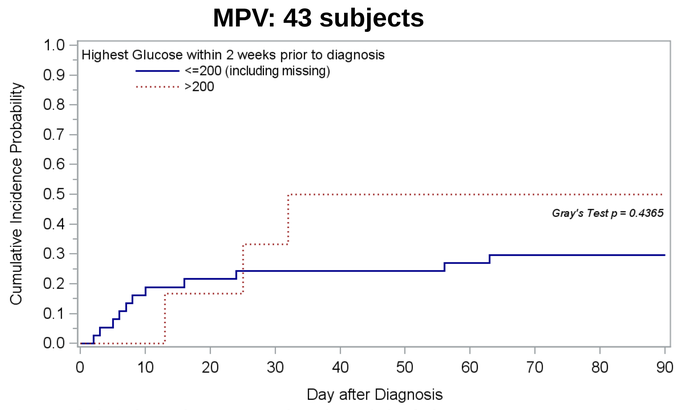
20 (24%) patients received antiviral therapy at URTI stage

FLU (A/B): 58 subjects



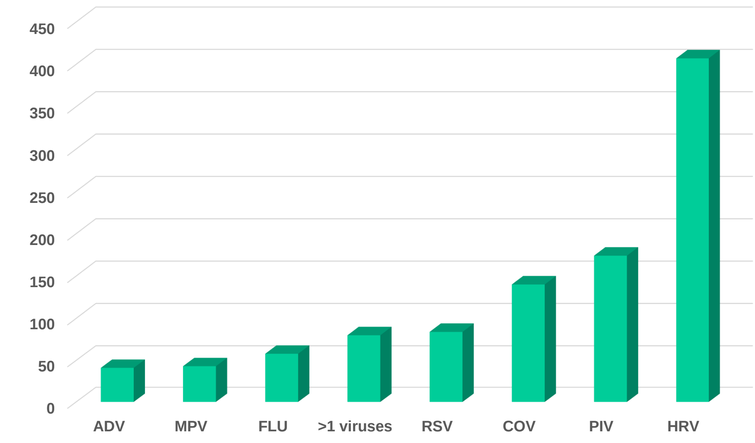
52 (90%) patients received antiviral therapy at URTI stage

MPV: 43 subjects

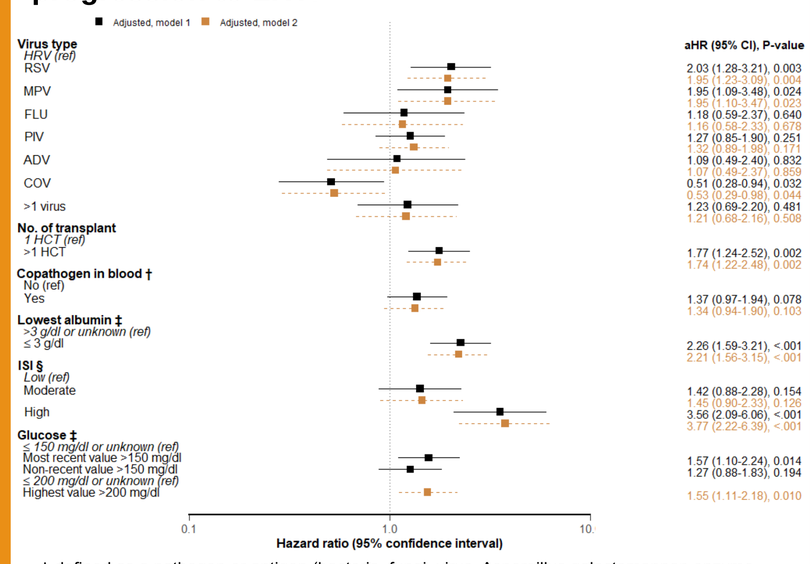


2 (5%) patients received antiviral therapy at URTI stage

Patients presenting with URTI



Multivariable Cox proportional hazards models for progression to LRTI



† defined as a pathogen or antigen (bacteria, fungi, virus, Aspergillus galactomannan enzyme-linked immunosorbent assay) detected in a blood within 2 days of first viral positive test.
‡ using values within 2 weeks before first viral positive test.
§ at viral onset.

- A history of more than 1 transplant, albumin <3g/dl, hyperglycemia (most recent glucose >150mg/dl and highest glucose >200mg/dl), and high ISI (7-12) were associated with an increased risk of progression to LRTI.
- Compared to HRV, RSV and MPV were associated with an increased risk of progression to LRTI.
- COV was associated with a lower risk of progression.

Limitations

- Small number of subjects with certain viruses.
- Challenges to account for the impact of antiviral therapy on LRTI outcomes across different viruses.
- Unavailable or unrecognized confounders.

Conclusions

- We identified novel risk factors for progression to LRTI, including hyperglycemia, virus type and history of multiple transplants in allogeneic HCT recipients.
- ISI appears to predict patients at risk for progression to LRTI across several viruses.
- These data significantly enhance our ability to risk stratify this vulnerable population with respiratory viral infections in the current molecular diagnostic era, and suggest a potential intervention opportunity to reduce the risk of LRTI with glycemic control.

References

1. Cai Y, et al. Diabetes Res Clin Pract. 2020.
2. Singh AK,et al. Diabetes Res Clin Pract. 2020.
3. Shah, D. P., et al. (2014). Blood 123(21): 3263-3268.

Acknowledgements

Grant support: NIH K23 and Clinical Research Scholars Program Award (Seattle Children's Research Institute)

21st ICHS Symposium on Infections in the Immunocompromised Host