Positive Pre-Transplant Respiratory Viral PCR is Associated with Increased Day 100 Transplant-Related Mortality in Pediatric HSCT Recipients.

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October 17, 2024

Abstract

Background: Hematopoietic Stem Cell Transplant (HSCT) is a curative procedure for many life-threatening hematological indications. Respiratory viral infections (RVI) cause substantial morbidity and mortality in pediatric transplant recipients, but the impact of mild/asymptomatic RVI is unclear. Some studies have identified certain viral infections as high-risk for post-transplant complications. To reduce transplant morbidity, a pre-transplant RVI screening program was started at Children's National Hospital which included symptom screening and respiratory viral (RV) PCR testing for each HSCT patient within one week of and on the day of HSCT admission. The objective of this study was to evaluate the impact of RVI on HSCT outcomes. **Methods:** A retrospective review of pre-transplant RV PCR, symptom screening, and clinical outcomes was done for patients receiving allogeneic HSCT from 7/1/2016 to 3/31/2023. Exclusion criteria included missing pre-transplant RV PCR and SCID to prevent bias. **Results:** 161 patients were eligible to be included. Of the 161, 34 tested positive for RVs (26 low-risk, 8 high-risk). Outcomes were initially analyzed separately by low- and high-risk viruses. Within the first 100 days post-transplant, a positive pre-HSCT RVI was significantly associated with increased mortality (odds ratio (OR) = 5.57, p = 0.04 after adjusting for multiple testing) and requirement for ICU transfer (OR = 3.45, p = 0.006). **Conclusions:** Routine pre-transplant viral testing should be performed to increase the safety of HSCTs. Pre-transplant viral testing may allow providers to know when to monitor certain patients more closely post-transplant, and when to potentially delay elective transplant until the patient has cleared their virus.

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Keywords: hematopoietic stem cell transplant, viral infections, pediatric cancer, transplant-related mortality, pediatric intensive care unit

Abbreviations:

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BAL	Bronchoalveolar lavage
GVHD	Graft versus host disease
HMPV	Human metapneumovirus

BAL	Bronchoalveolar lavage
HRV	Human rhinovirus
HSCT	Hematopoietic stem cell transplant
ICU	Intensive care unit
IRB	Institutional review board
LRD	Lower respiratory disease
MUD	Match unrelated donor
PBSC	Peripheral blood stem cells
PCR	Polymerase chain reaction
PEWS	Pediatric early warning score
PICU	Pediatric intensive care unit
PP	Positive pressure
RSV	Respiratory syncytial virus
RV	Respiratory viral
RVI	Respiratory viral infection
SAA	Severe aplastic anemia
SCID	Severe combined immunodeficiency
SOP	Standard operating procedure
TA-TMA	Transplant-associated thrombotic microangiopathy
TRM	Transplant-related mortality

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Running title: RVI pre-HSCT increases post-transplant mortality

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Word counts:

Abstract: 253

Main Text: 2,752

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1 | Introduction :

Hematopoietic Stem Cell Transplant (HSCT) is a curative procedure for many pediatric patients with life-threatening hematological conditions. These patients are at a high risk for post-transplant complications, including secondary infections, respiratory collapse, and even death.[1] This risk is heightened when the transplant is performed in the setting of a respiratory viral infection (RVI), especially in patients who have received myelosuppression, lymphopenia, T-cell therapy, and immunosuppressive regimens.[2-7]When presented with positive RVI testing before an HSCT, multiple factors must be considered in the decision to proceed or delay the transplant. These factors include the condition of the patient, the indication for transplant, associated symptoms, and the specific virus or viruses at hand. The underlying condition necessitating transplant might be aggressive and malignant, in which case delay of transplant despite the presence of an RVI can be seen as more deleterious. Some RVIs have a higher likelihood of causing post-transplant complications, including adenovirus, human metapneumovirus (HMPV), influenza, parainfluenza, and respiratory syncytial virus (RSV).[4, 13, 14] Based on past studies, current clinical guidelines recommend delaying transplant if a patient tests positive for one of these viruses. There is no official stance on the decision to proceed with or delay transplant in the case of lower-risk viruses, coronaviruses, and human rhinoviruses (HRV).[22, 23] Additionally, the availability of the donor and product must be considered in decision-making.

Past experimental studies purport inconsistent data on the effects of pre-transplant RVI of different types on the complications post-transplant. One past study performed in an adult population found that symptomatic patients who tested positive for RVIs pre-HSCT had fewer days alive and out of the hospital at day 100 post-transplant.[14] This trend was seen in all types of RVI, including rhinovirus, the most common RVI seen as incurring the least amount of risk for post-transplant complications. Notably, this increase was not found in asymptomatic patients.[14] In contrast to this finding, a retrospective study performed in Geneva concluded that RVI within a month leading up to allogeneic HSCT was not associated with transplant-related mortality or morbidity.[16]

There are far fewer data and information available concerning pediatric patients alone. One purely pediatric study looking at RVI within 90 days of HSCT found no significant difference in mortality between patients with and without RVI pre-transplant. They did conclude, however, that patients who tested positive for any RVI had notably fewer days alive and out of the hospital as compared to patients who tested negative.[13] More information is needed to determine the cause of prolonged hospitalization but unaffected mortality in pediatric patients going into transplant with RVIs. Another retrospective study of a pediatric population confirmed this pattern, but could not draw the same conclusion of increased hospitalization and viral infections pre-transplant in multivariable models.[17] A pediatric study did find that patients who went into transplant positive for one or more RVIs had decreased survival and increased transplant-related mortality, but that this risk was diminished by the delay of transplant.[18] Overall, more information is needed to conclude the necessity of pre-transplant viral screening, if transplant should be delayed in the case of positive results, and whether the presentation of symptoms informs this decision, especially in a pediatric population.

With knowledge of the possible increased risk for post-transplant complications given RVI, a pre-transplant RVI screening program was started at Children\RL's National Hospital. This program included an RV PCR test and symptom screening for each HSCT patient before and upon admission. This screening program is done on all pre-HSCT patients, despite many institutions not performing RV PCR testing on asymptomatic patients outside of research protocols.

To evaluate the benefit of this pre-transplant testing, we performed a retrospective study on all HSCT pediatric patients at the hospital since the onset of the screening program. The objective of this study was to both assess the impact of RVI on HSCT outcomes, and whether or not the presence of symptoms affected the risk of post-transplant complications.

2 | Methods :

This retrospective review was approved by the Children's National institutional review board (IRB).

2.1 | Patient Composition

A retrospective review of pre-transplant RV PCR, symptom screening, and clinical outcomes was done for all patients receiving allogeneic HSCT from June 1 2016 to March 31 2023 at Children\RL's National Hospital in the District of Columbia (D.C.). All types of allogeneic stem cell sources were included in the study, such as bone marrow (BM), cord blood, peripheral blood stem cells (PBSC), and combinations. Autologous transplants were excluded. Patients missing one or both of their pre-transplant RV PCR tests were excluded from the study. Patients who received more than one HSCT in this time had their second transplant excluded if it was received within 100 days of their first transplant and/or if the second transplant was done within the same hospital admission, as they would not have received appropriate RV PCR testing for the study. Patients with severe combined immunodeficiency (SCID) as an indication for transplant were also excluded due to the higher likelihood of an RV-positive result and poorer post-transplant outcomes. Patients who met all criteria were identified using the bone and marrow transplant department\RL's patient database. If patients were intentionally delayed based on an RV PCR result, the RV PCR results used in this study were the last pre-transplant one before admission. Online medical records were obtained and reviewed to collect relevant information from the time of the first pre-admission RV PCR to 100 days post-transplant.

2.2 | Definitions of respiratory viral infections and transplant outcomes

RVIs were classified into high-risk and low-risk RVIs based on the observed likelihood of risk for complications and type of RVI in prior studies. High-risk RVIs were adenovirus, HMPV, influenza A and B, parainfluenza, and RSV. Low-risk RVIs were coronaviruses and rhinovirus.[13-14, 4] Symptoms of RVI were identified as upper- or lower-respiratory symptoms. Upper-respiratory (UR) symptoms included congestion, sneezing, headaches, sore throat, and mild cough. Lower-respiratory symptoms included phlegm, wheezing, chest pain, serious cough, shortness of breath, and severe cough.

Transplant-related complications were recorded in order to evaluate the outcome of RVIs on these. These transplant-related complications were the incidence of graft versus host disease (GVHD) and its grade, transfer to the intensive care unit (ICU), need for positive pressure (PP), intubation, bronchoalveolar lavage (BAL), transplant-associated thrombotic microangiopathy (TA-TMA), adenoviremia, and mortality at day 100 post-transplant.

2.3 | Laboratory Testing

Pre-transplant multiplex RV PCR testing was performed twice–once up to 10 days leading up to admission and once upon admission. Multiplex RV PCR is the current clinical recommendation to detect symptomatic respiratory viruses pre-HSCT.[24] Samples were considered positive if one or more virus was detected. At Children\RL's National Hospital, this RV PCR is a BioFire FilmArray (*bioMérieux)* which includes adenovirus, coronavirus, SARS CoV19, human metapneumovirus (HMPV), rhinovirus/enterovirus, influenzae A and B, parainfluenzae 1-4, and RSV A and B. These tests were performed within a week of and on the day of admission for the HSCT procedure. The result of the RV PCR and the presentation of symptoms were factored into the decision to proceed with transplantation.

2.4 | Statistical Analysis

This study was a retrospective comparison of two main groups of patients: those who tested positive or negative for an RVI pre-admission and/or upon admission. Patients who tested positive were further categorized as having a high- or low-risk infection and as to whether the patient presented with LR and/or UR symptoms.

We reported demographic and other characteristics as well as outcomes overall and by RVI group: RVI negative; RVI positive, low-risk, asymptomatic; RVI positive, low-risk, symptomatic; RVI positive, high-risk, asymptomatic; and RVI positive, high-risk, symptomatic. We also presented results collapsing all RVI positive

groups to a single group. Summary statistics include the frequency of each categorical characteristic and five number summaries (mean, standard deviation, median, interquartile range, minimum, and maximum) for each continuous or ordinal characteristic.

We used contingency tables and logistic regression models to evaluate differences in the primary outcomes among the RVI groups. Categorical data were presented with their counts and frequencies and depending on cell counts were statistically tested using either the Chi-Square Test or the Fisher's Exact Test. We used similar methods to evaluate all secondary outcomes. The overall model was first evaluated, with the overall model p-value adjusted for multiple tests using the Holm procedure. Further comparison of RVI groups was only conducted if the overall model test was significant.

3 | Results :

Table 1-4 present detailed data for all patients. Figures 1-3 present findings based on data and statistical analyses.

3.1 | Patient demographics

Since the onset of the pre-transplant RVI screening program at our institution, 161 patients received allogeneic HSCT who were eligible to be included in the study based on viral PCR testing. Patients age ranged from 0.3 to 28.6 years, with the average being 9.7 years. 66 patients were female and 95 patients were male. Table 1 outlines indications for transplant, use of T cell depletion, conditioning intensity, use of serotherapy, stem cell source, HLA mismatch, and CMV concordance.

3.2 | Patterns of RVI and post-transplant outcomes

Of the 161, 34 tested positive for RVs (26 low-risk, 8high-risk). Outcomes were initially analyzed separately by low-risk and high-risk viruses, but given the small number of high-risk patients, statistical analysis was also performed by looking at all positive RVIs as one group. There were too few patients with RV symptoms to analyze independently from those without symptoms. Table 1 displays the number of patients with each characteristic as described previously by RVI negative and RVI positive groups, compared to the overall number of subjects in the study.

Within the first 100 days post-transplant, a positive pre-HSCT RVI was significantly associated with increased mortality (odds ratio (OR) = 6.56, p = 0.04 after adjusting for multiple testing) (Fig. 1) and requirement for ICU transfer (OR = 3.75, p = 0.005). All other outcomes did not differ significantly based on pre-HSCT RV PCR positivity. In a sensitivity analysis, the statistical significance of the two associations did not change when potential confounding covariates were included in analyses. (Table 2)

3.3 | Patterns of ICU transfer

A total of 44 patients were transferred to the ICU within 100 days after transplant. Of these 44 patients, 34 exhibited elevated pediatric early warning signs (PEWS). These signs refer to clinical changes in a patient's respiratory, cardiovascular, and/or neurological state indicative of the potential for rapid deterioration.[25]In this study, the following symptoms were classified as elevating a patient's PEWS score: tachypnea, tachycardia, blood pressure instability (hypotension or hypertension), increased work of breathing, desaturations, hypoxia, apnea, and altered mental status. Of these 34 patients, 19 patients exhibited an elevated PEWS score for respiratory symptoms (tachypnea, increased work of breathing, desaturations, and apnea) alone. The most common causes of ICU transfer were tachypnea, tachycardia, blood pressure instability, fluid overload, and altered mental status. Indications for ICU transfer with a statistically significant increase between RVI+ and RVI- groups included fluid overload (p=0.025) and blood pressure instability (p=0.034). (Table 3)

Overall, increased requirement for ICU transfer was found to be statistically associated with positive pre-transplant RVI PCR results. While in the first 25 days post-transplant ICU transfer remained comparable between the RVI- and RVI+ groups, afterward the disparity between the two greatly increased up to 100 days after HSCT. (Fig. 2)

3.4 | Patterns of post-transplant mortality

There were 7 instances of transplant-related mortality (TRM) within 100 days post-transplant. Four of these were caused by multi-organ failure. The other three were caused by bradycardia, pulmonary hemorrhage, and progressive refractory leukemia. Although there was an overall increase in TRM in the RVI+ group (p=0.0047), no singular cause of mortality was found to have a strong statistical association with RV+ PCR results. (Table 4)

Mortality rates appeared similar until about day 50, but after that, the RVI+ group consistently had increased numbers of mortality through the 100-day post-transplant period. (Fig. 3)

4 | Discussion

Given the inconsistent status of the relationship between pre-transplant RVI and post-transplant outcomes, this study aimed to elucidate the importance of pre-transplant RV PCR screening to avoid post-transplant morbidity and mortality. This study included a cohort of 170 pediatric HSCT patients. We found that pre-transplant RVI was positively correlated with post-transplant mortality and requirement for ICU transfer in the first 100 days post-transplant. These associations remained after multivariate analysis.

The relationship between pre-transplant RVI and transplant-related mortality (TRM) has been examined in prior past studies. Some retrospective analyses of adult allogeneic HSCT patients did not find an association between pre-transplant RV detection and increased mortality.[16, 20] This apparent lack of association between pre-transplant RVI and transplant-related complications and mortality was not found in upper respiratory, lower-risk infections such as coronaviruses and rhinovirus. However, an association between increased mortality and hospitalization and testing positive pre-transplant for the higher-risk RVIs, especially those causing lower-respiratory disease (LRD). The presence of LRD of any type of virus, including HRV alone, was confirmed to be associated with increased mortality, but only in conjunction with pre-transplant myelosuppression.[15] In a pediatric retrospective survey of the same subject, Kim et al (2017) found an association between pre-transplant RVI and hospitalization but not with transplant-related mortality. One explanation for this difference in findings is that they included RVI PCR test results up to 90 days before HSCT,[13] whereas our study had a narrower range of days from which we collected PCR results. Like our study, Ottaviano et al found a significant increase in post-transplant mortality when pediatric patients underwent HSCT in the setting of a respiratory virus. Furthermore, they found that this increased risk for mortality was alleviated in patients who had a delay of HSCT after detecting RV in pre-transplant screening.[21] Multiple retrospective studies focusing on more adult HSCT patients found associations between pre-transplant RVI and increased mortality and hospitalization, especially with increased risk for post-transplant complications such as myeloablative conditioning and symptomatic case.[14, 15]

A novel finding of this study is the relationship found between pre-transplant RVI and the requirement for ICU transfer post-HSCT. This correlation helps further the argument for the delay of transplant in lieu of a positive RV PCR result. ICU transfer is associated with substantial expenses, such as for invasive procedures and treatments taking place in the ICU, and the burden of heightened patient load for hospitals. The average overall cost for a stay in the pediatric intensive care unit (PICU) is approximately $15,000.[19] Patients could benefit from the delay of transplant for non-malignant patients. This push for a delay of transplant is more significant given the increase in non-malignant conditions as indication for pediatric BMTs, Sickle Cell Anemia and Beta Thalassemia for example. As these conditions do not face an imminent risk of death, transplants for these patients could benefit from delay to avoid the potentially increased morbidity and mortality from HSCT.

This study corroborates associations between pre-transplant RVI and mortality and morbidity (in the form of requirement for ICU transfer), but limitations should be acknowledged before accepting this correlation. One, this study is retrospective, so delays in transplants were made on a case-by-case basis and not according to a proposed guideline. Due to its subjective nature, the reliability of the benefit of delay of transplant in the situation of a positive RVI PCR test result is limited. As this was a single center study it is possible that thresholds for transfer to ICU may vary which may impact generalizability. Although we sought to evaluate

differences between asymptomatic and symptomatic patients, the too-small number of cases of symptomatic disease forced us to join the two groups in statistical analyses. Despite these shortcomings, the study was systematic and part of a standard operating procedure (SOP).

More research needs to be done to compare how symptomatic and asymptomatic RVI differ in their increased risk for post-transplant mortality and morbidity. While the delay of transplant may be effective at reducing complications in the setting of pre-transplant RV detection, a delay affordable for HSCTS for non-malignant disease, the extent of this benefit needs to be determined. This is important in cases of a malignant indications for transplant in which a delay in transplant may pose a more severe risk than the complications conferred by pre-transplant RVI. Delay of transplant may also necessitate the cryopreservation of donor, which have been associated with worse outcomes in cases such as severe aplastic anemia (SAA), or the loss of a match unrelated donor. Future studies would ideally be multi-center and prospective.

5 | Conflicts of Interest

The authors declare no conflicts of interest.

6 | Acknowledgements

We would like to thank the patients and parents included in the study for their retrospective contribution.

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TABLE 1 Patient disease and transplant characteristics by whether a patient had an RVI

	RVI- (N=127)	RVI+ (N=34)	Ov (N=
Malignant			
Yes	46 (36.2%)	15 (44.1%)	61
No	81 (63.8%)	19 (55.9%)	100
T Cell Depletion			
Yes	14 (11.0%)	4 (11.8%)	18
No	113 (89.0%)	30 (88.2%)	143
Myeloblative Conditioning			
Yes	80 (63.0%)	28 (82.4%)	108
No	47 (37.0%)	6 (17.6%)	53
Serotherapy			
Yes	56 (44.1%)	15 (44.1%)	71
No	71 (55.9%)	19 (55.9%)	90
Stem Cell Source			
BM	67 (52.8%)	26 (76.5%)	93
CORD	14 (11.0%)	3 (8.8%)	17
PBSC	46 (36.2%)	5 (14.7%)	51
Donor Type			
Match	75 (59.1%)	23 (67.6%)	70
Mismatch	52 (40.9%)	11 (32.4%)	91
CMV Concordance			
No	51 (40.2%)	19 (55.9%)	70
Yes	76 (59.8%)	15 (44.1%)	91

TABLE 2 Statistical Association between RV positivity and each post-transplant outcome, comparing RVI- and RVI+ grou

ICU transfer
Day 100 transplant-related mortality
Positive pressure ventilation
Intubation
BAL
TA-TMA
Adenoviremia
Severe GVHD (grade 3/4)

TABLE 3 Statistical Association between RV positivity and each indication for ICU transfer comparing RVI-

and RVI+ groups.

	Total, N= 161	RVI-, N= 127	RVI+, N= 34	P value
PEWS elevation	35	22	13	0.128
PEWS elevation w/ respiratory causes	21	13	8	0.275
Fluid overload	5	5	0	0.025
Blood pressure instability	8	7	1	0.034
Altered mental status	5	4	1	0.180
GI bleed	3	0	3	0.083
DI	1	0	1	0.317
Anaphylaxis	1	0	1	0.317
Plasmapheresis	1	0	1	0.317
Acute stroke event	1	1	0	0.317
Preventative	1	0	1	0.317
Pericardial effusion	1	1	0	0.317
Seizures	1	0	1	0.317

TABLE 4 Statistical association between RV positivity and each cause of mortality comparing RVI- and RVI+ groups.

Cause of Mortality	Total	RVI+	RVI-	P-value
Multi-organ failure	4	2	2	1.000
Bradycardia	1	0	1	0.317
Pulmonary hemorrhage	1	1	0	0.317
Progressive refractory leukemia	1	1	0	0.317

FIGURE 1 Incidence of post-transplant mortality among RVI-; RVI+, low risk; and RVI+, high risk groups (1A). Statistical comparison of post-transplant mortality by RVI- and RVI+ groups (1B).

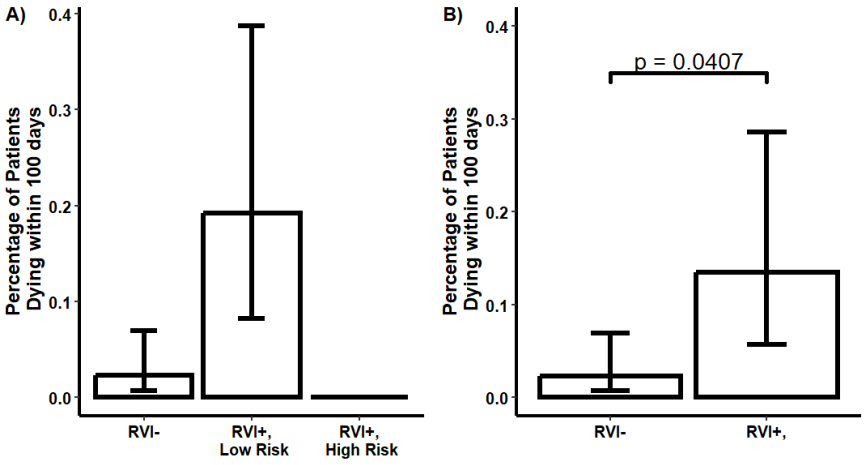

FIGURE 2 Cumulative incidence of transfer to ICU among RVI+ and RVI- negative groups on an 100-day scale.

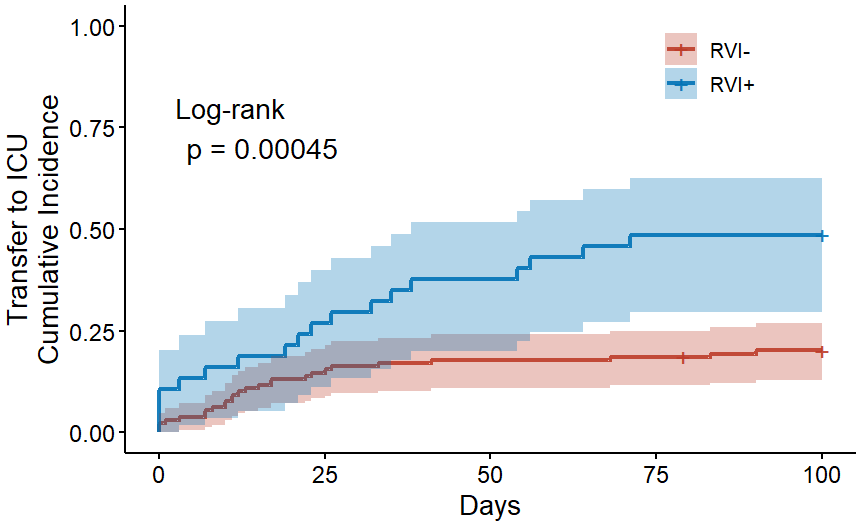

FIGURE 3 Cumulative incidence of transplant-related mortality within 100 days post-transplant comparing RVI- and RVI+ groups.