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Respiratory virus infection after allogeneic hematopoietic stem cell transplant in a tropical center: Predictive value of the immunodeficiency scoring index

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Abstract

Background: Respiratory virus infection (RVI) is a prevalent infection in patients after allogeneic hematopoietic stem cell transplant (allo-HSCT) and can result in significant morbidity and mortality. Ability to assess the potential severity of RVI is important in the management of such patients.

Methods: We reviewed the cases of RVI in allo-HSCT recipients and explored the predictive value of the immunodeficiency scoring index (ISI) established for respiratory syncytial virus (RSV) and its applicability for RVI caused by other respiratory viruses.

Results: RVI occurred year-round in our tropical transplant center, with peaks in the middle and end of the year. Ninety-five of the 195 recipients developed a total of 191 episodes of RVI, giving a cumulative incidence of 28% by 6 months and 52% by 24 months for the first episode of RVI. RSV, influenza, rhinovirus, and parainfluenza were the most common viruses. Pneumonia occurred in 63.64%, 42.31%, and 32.42% of adenovirus, influenza, and RSV RVI episodes, respectively, but was also non-negligible in the more benign viruses, such as coronavirus (31.58%) and rhinovirus (23.68%). Nineteen of the 63 episodes of viral pneumonia required mechanical ventilation and 14 deaths occurred within 6 weeks of the RVI. Receiver operating characteristic analysis showed that an ISI of ≥8 predicted pneumonia with a positive predictive value of >80% for RVI caused by RSV, influenza, adenovirus, and parainfluenza, while it was not predictive for coronavirus and rhinovirus.

Conclusions: The ISI is a useful aid for decision-making during clinic consultation for patients presenting with symptoms suggestive of an RVI.

KEYWORDS

immunodeficiency scoring index, pneumonia, respiratory virus infection

1 | INTRODUCTION

Viral pneumonia caused by respiratory viruses (RV) is a non-negligible cause of morbidity and mortality after allogeneic hematopoietic stem cell transplant (allo-HSCT).[1–8] Among the respiratory viral infections (RVIs), those caused by respiratory syncytial virus (RSV), influenza, and human parainfluenza virus (HPIV) are associated with higher risk of progression to pneumonia and mortality.[9] However, the clinical course of RVI depends not only on the type of virus but also on the immunological status of the host. Several series have identified risk factors such as proximity to transplant, T-cell depletion, cord blood or mismatched transplant, presence of graft-versus-host disease (GVHD),

use of glucocorticoids, and lymphopenia as predictive of poorer outcomes.[1,4,6,10–13] An Immunodeficiency Scoring Index (ISI-RSV) has been developed for allo-HSCT patients with RSV infection, with a high score predicting progression from upper respiratory tract infection (URTI) to pneumonia, need for ventilation, and mortality.[14] Recently, this ISI was shown to be applicable to influenza infection as well, with a significantly higher incidence of pneumonia in the high-score vs low-score group.[15]

In this study, we retrospectively reviewed all allo-HSCT recipients from our center with respiratory symptoms and a positive polymerase chain reaction (PCR) result for RV. The primary aim of the study was to evaluate the applicability of the ISI-RSV in a retrospective cohort of allo-HSCT recipients with RVI, including non-RSV RVI. The secondary aim was to describe the epidemiology of RVI in allo-HSCT recipients at a transplant center in the tropics at which such infections tend to occur year-round,[16] as currently available literature largely originates from centers in temperate climates.

2 | PATIENTS AND METHODS

2.1 | Patient population and data collection

This is a retrospective review of all patients who underwent allo-HSCT in our hospital from December 2010 to March 2015. The electronic medical records for each patient were reviewed for any RV PCR performed. Each episode of PCR-proven RVI was scored using the ISI-RSV: neutrophil <500/μL, lymphocyte <200/μL, score of 3 each; age >40 years, score of 2; ablative conditioning, GVHD, corticosteroid use in prior 30 days and pre-engraftment or within 30 days of HSCT, score of 1 each, for a total score of 0-12.[14] Transplant-related information, treatment, and outcomes were collected and all patients followed up till May 2015 or death, whichever was earlier. This retrospective analysis was approved by the hospital Institutional Review Board.

2.2 | Definitions

We made slight modifications to published definitions for URTI and pneumonia.[12,13,17] A viral URTI was defined as the presence of respiratory symptoms (eg, cough, coryza, sore throat) with a positive RV PCR result from throat/nasopharyngeal swab, without hypoxia or a new infiltrate on chest imaging. Viral pneumonia was defined as a positive RV PCR result from throat/nasopharyngeal swab or bronchoalveolar lavage (BAL) with a new infiltrate on chest imaging (taken 7 days before and up to 7 days after the positive RV PCR). A patient initially presenting with viral URTI and subsequently developing pneumonia was defined as progression to pneumonia, if no other cause could be found for the progression. However, if a bacterial or fungal co-pathogen was isolated from respiratory samples, or if other laboratory or clinical evidence was suggestive of active bacterial or fungal infection (eg, a positive blood culture), then the progression was not attributed to the RVI. When a bronchoscopy is done, BAL fluid is routinely sent for Gram stain, aerobic and anaerobic cultures, fungal smear and culture, acid-fast bacilli smear, and mycobacterial culture, stain for *Pneumocystis jirovecii*, galactomannan, RV PCR panel, cytomegalovirus and herpes simplex virus cultures, *Legionella pneumophilia* culture, and antigen detection by immunofluorescence.

As a patient may have >1 episode of RVI and as prolonged viral shedding is common,[17,18] each RVI episode caused by a virus was scored only once for the ISI-RSV. A new episode of RVI was defined as a positive PCR for a different virus, or a positive PCR for the same virus at least 6 weeks after documented clearance. For swabs that were positive for two viruses, those that involved either RSV or influenza were scored under RSV or influenza infection, respectively, while non-RSV, non-influenza viruses were individually scored. Nosocomial infection was defined as a positive swab taken for symptoms that developed >48 hours after admission, or within 72 hours after discharge from hospital. Mortality that occurred within 1 month of viral pneumonia was analyzed for the cause of death, where direct causality was implicated only for patients in whom the RVI was the primary event, without co-pathogens and other incidental causes.[13] For the analysis of outcome in patients treated with specific antiviral drugs such as oseltamivir or ribavirin, treatment was considered "delayed" if initiated 3 days or more after diagnosis.

2.3 | Detection of RV by PCR

From December 2010 to October 10, 2012, the RV multiplex PCR was performed using the Seeplex RV12 ACE Detection kit (Seegene, South Korea), following manufacturer's instructions. This kit detected 12 RV: human adenovirus (AdV), human metapneumovirus, human coronavirus (HCoV) 229E/NL63, HCoV OC43, HPIV1, 2, and 3, influenza A and B viruses, RSV A and B, and human rhinovirus (HRhV) A/B. From October 11, 2012 to August 28, 2013, the Seegene Anyplex II RV16 v1.0 (Seegene, South Korea) was used, and from August 29, 2013 to March 2015, the Seegene Anyplex II RV16 v1.1 (Seegene, South Korea) was used. The latter two kits detect 16 respiratory viruses, including the same viruses detected by the Seeplex RV12 kit and 4 additional viruses (HPIV 4, HRhV C, enterovirus, and human bocavirus [HboV]).

2.4 | Statistical analysis

Overall survival was estimated using the Kaplan-Meier approach. Cumulative incidence of first RVI episode was plotted with death as a competing risk. Fisher's exact test was used to investigate association of ISI-RSV risk groups (low, moderate, high) with each of these outcome measurements including incidence of pneumonia, subsequent progression to pneumonia, need for ventilation, and mortality for each RVI episode involving RSV, influenza, HRhV, HPIV, HCoV, and AdV. Receiver operating characteristic (ROC) analysis, in conjunction with logistic regression, was used to assess ISI-RSV as a predictor of pneumonia for infections caused by the above-named viruses.

3 | RESULTS

3.1 | Demographics

A total of 195 patients underwent allo-HSCT during the study period. Most were adults but 11 patients were 12-17 years of age. Among these 195 patients, 164 had manifestations of an RVI and underwent RV PCR testing, with 95 having at least one positive PCR result. Thirty-one allo-HSCT recipients never had any RVI manifestation and did not undergo RV PCR testing. Table 1 shows the transplant-related characteristics of these three groups of patients.

3.2 | Epidemiology

RVI occurred sporadically throughout the year, with peaks in June-July and December-January. See Figure 1 for the distribution of the types of RVI across the months over 3 years from 2012 to 2014.

TABLE 1 Characteristics of patients

Characteristics	Patients with PCR-proven RVI (n=95)[a]	Patients with negative PCR (n=69)	Patients who never had RVI (n=31)	% Proven RVI within each subgroup (%)
Year of transplant, n (%)				
Dec 2010	1 (1.01)	1 (1.45)	—	50
2011	27 (27.27)	14 (20.29)	11 (35.48)	51.92
2012	31 (31.31)	14 (20.29)	7 (22.58)	59.62
2013	30 (30.30)	14 (20.29)	2 (6.45)	65.22
2014	9 (9.09)	22 (31.88)	8 (25.81)	23.08
Jan-Mar 2015	1 (1.01)	4 (5.80)	3 (9.68)	12.50
Age range at transplant (median)	12-68 (45)	17-67 (46)	19-68 (50)	—
Gender, n (%)				
Male	52 (54.73)	34 (49.27)	19 (61.29)	49.52
Female	43 (45.26)	35 (50.72)	12 (38.71)	47.78
Diagnosis, n (%)				
AML	34 (35.79)	34 (49.28)	12 (38.71)	42.50
ALL	21 (22.11)	10 (14.49)	7 (22.58)	55.26
ABL	6 (6.32)	1 (1.45)	—	85.71
NHL	10 (10.53)	6 (8.70)	3 (9.68)	52.63
HD	3 (3.16)	—	—	100.00
CLL	1 (1.05)	—	—	100.00
CML	5 (5.26)	5 (7.25)	1 (3.23)	45.45
MDS	10 (10.53)	9 (13.04)	5 (16.13)	41.67
MF	2 (2.11)	2 (2.90)		50.00
SAA	3 (3.16)	2 (2.90)	1 (3.23)	50.00
MM	—	—	2 (6.45)	0
Donor type, n (%)				
Matched sib	50 (52.63)	36 (52.17)	20 (64.52)	47.17
Unrelated	34 (35.79)	17 (24.64)	10 (32.26)	55.74
Cord	7 (7.37)	15 (21.74)	1 (3.22)	30.43
Haploidentical	4 (4.21)	1 (1.45)	—	80.00
Conditioning, n (%)				
Myeloablative	63 (64.95)	44 (63.77)	16 (51.61)	51.22
Reduced intensity	25 (25.77)	19 (27.54)	13 (41.94)	43.86
Non-myeloablative	9 (9.28)	6 (8.70)	2 (6.45)	52.94

[a]A total of 99 transplants were done for 95 patients, as 4 patients had 2 transplants.

RVI, respiratory virus infection; PCR, polymerase chain reaction; AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; ABL, acute biphenotypic leukemia; NHL, Non-Hodgkin's lymphoma; HD, Hodgkin's disease; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; MDS, myelodysplastic syndrome; MF, myelofibrosis; SAA, severe aplastic anemia; MM, multiple myeloma.

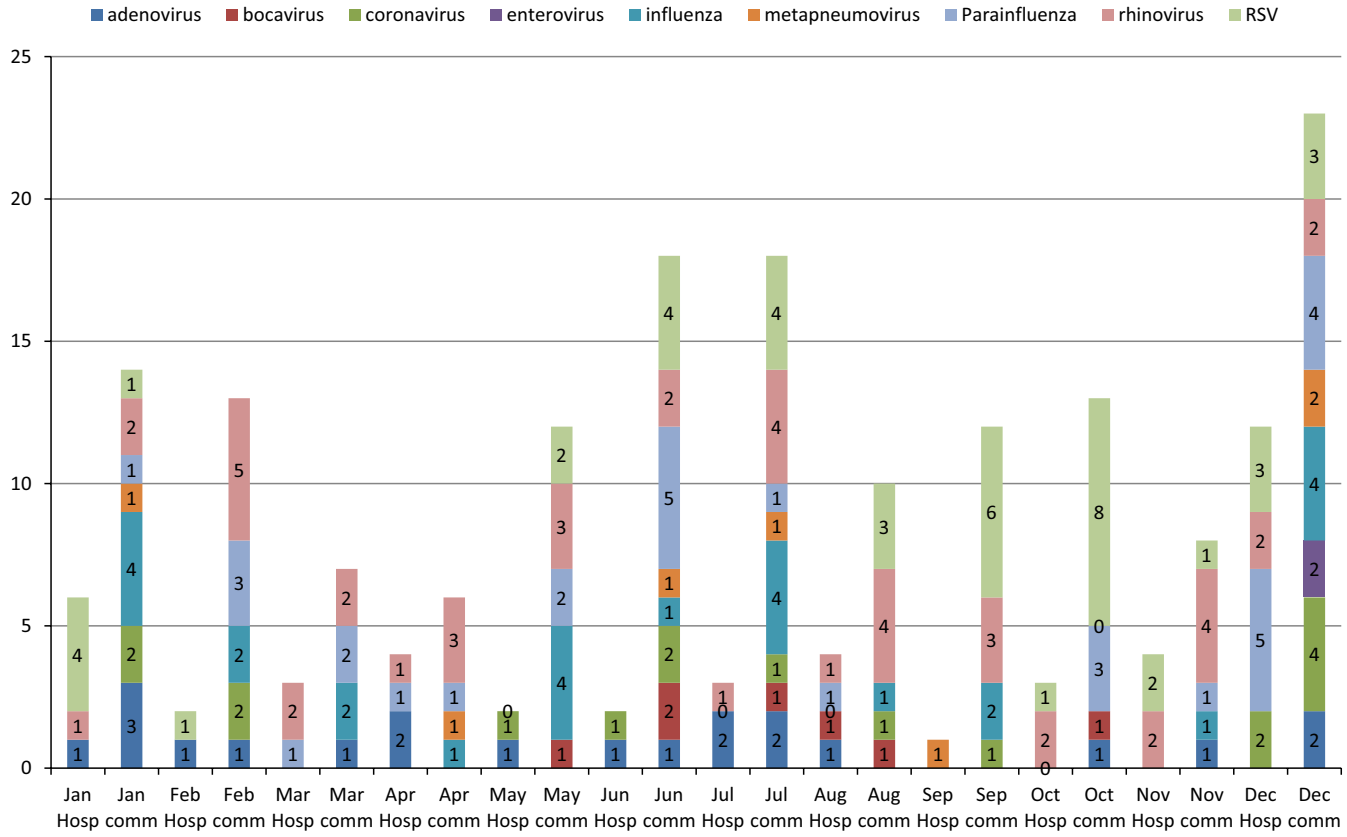

FIGURE 1 Type and distribution of respiratory virus infection (RVI) by months, over a 3-year period from 2012-2014. RSV, respiratory syncytial virus; Hosp, hospital; comm, community

TABLE 2 Frequency and clinical course of respiratory virus infection for each type of virus

Types of virus	% of 191 episodes (n)	% community acquired (n)	% with pneumonia (n)	% requiring ventilation (n)	% died within 6 weeks (n)
RSV alone	19.37 (37)	75.68 (28)	32.43 (12)	10.81 (4)	10.81 (4)
Influenza alone	13.61 (26)	96.1525)	42.31 (11)	3.85 (1)	0.00 (0)
Rhinovirus alone	19.90 (38)	63.16 (24)	23.68 (9)	10.53 (4)	5.26 (2)
Parainfluenza alone	14.66 (28)	67.86 (19)	25.00 (7)	7.14 (2)	10.71 (3)
Coronavirus alone	9.95 (19)	78.95 (15)	31.58 (6)	10.53 (2)	0.00 (0)
Adenovirus alone	5.76 (11)	36.36 (4)	63.64 (7)	18.18 (2)	9.09 (1)
Metapneumovirus alone	3.14 (6)	83.33 (5)	33.33 (2)	0.00 (0)	0.00 (0)
Bocavirus alone	2.09 (4)	75.00 (3)	50.00 (2)	25.00 (1)	25.00 (1)
Enterovirus alone	0.52 (1)	100.00 (1)	0.00 (0)	0.00 (0)	0.00 (0)
Mixed virus infection[a]	10.99 (21)	80.95 (17)	38.10 (7)	14.29 (3)	14.29 (3)

[a]Mixed virus infection: including 20 with 2 viruses and 1 with 3 viruses. These include RSV (7), influenza (2), rhinovirus (12), parainfluenza (7), adenovirus (9), bocavirus (3), metapneumovirus (1), enterovirus (1) in various combinations.
RSV, respiratory syncitial virus.

Of the 95 patients who had RVI, 46 had 1 episode, while 49 patients had >1 episode (27 patients had 2 episodes, 10 had 3, 6 had 4, 2 had 5, 3 had 6, and 1 patient had 7 episodes). Therefore, altogether a total of 191 episodes of RVI were detected with various types of viruses, including RSV A and B (RSV), influenza (A and B), HRhV, HPIV (1, 2, 3, and 4), HCoV, AdV, metapenumovirus, HboV, and human enterovirus, with the first 5 being most prevalent, each comprising between 10% and 20% of all RVI episodes. Twenty-one episodes were

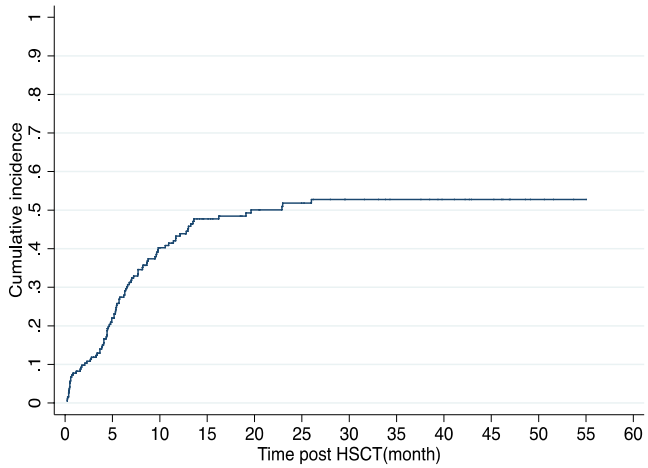

FIGURE 2 Cumulative incidence of first episode of respiratory virus infection. HSCT, hematopoietic stem cell transplantation

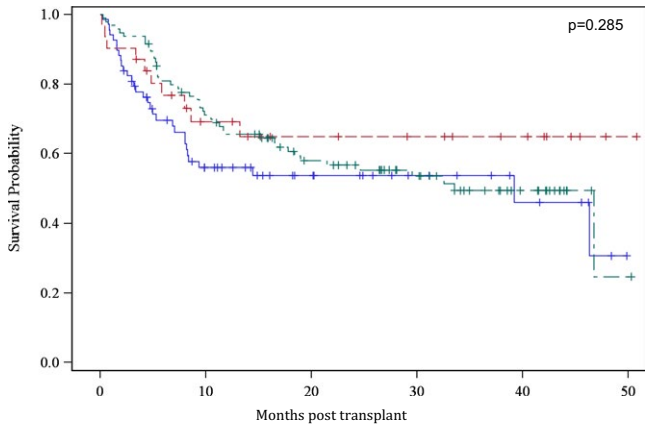

FIGURE 3 Survival curve for the three groups. Green line represents patients who had proven respiratory virus infection (RVI) by polymerase chain reaction (PCR), blue line represents symptomatic patients who had a negative PCR, and red line represents asymptomatic patients who never had any RVI

mixed infections, with two viruses (n=19) and three viruses (n=2) detected in the same sample. Table 2 shows the distribution and clinical association of each virus.

The cumulative incidence for the development of the first episode of RVI from day 0 of transplant was 28% by 6 months, 43% by 12 months, and 52% by 2 years post HSCT (Figure 2).

3.3 | Clinical presentation and treatment outcome

Of the 191 RVI episodes, 49 episodes (25.65%) manifested as pneumonia at presentation. A further 15 of 142 episodes initially manifesting as URTI subsequently progressed to pneumonia, giving a total of 64 episodes (33.51%) of pneumonia. As shown in Table 2, the potentially virulent viruses such as RSV, influenza, and AdV were associated with a high incidence of pneumonia (32.43%, 42.31%, and 63.64% of the episodes, respectively). However, we noted that even seemingly benign viruses such as HCoV and HRhV were also associated with a non-negligible incidence of pneumonia, in 31.58% and 23.68% of the episodes, respectively.

As expected, influenza was the only RVI that was consistently treated. Twenty-six of 28 influenza episodes were treated with oseltamivir. Of the two untreated episodes, one was a patient diagnosed after many days of URTI symptoms in whom treatment was deemed not useful; the other presented acutely with respiratory failure and septic shock caused by a bacterial process, with throat swab returning positive for H3N2 influenza A, posthumously. While 11 episodes of influenza presented as pneumonia at diagnosis, only 1 of the 16 influenza URTI episodes at presentation progressed to pneumonia. Whether oseltamivir prevented progression to pneumonia cannot be analyzed here, as all except 2 episodes were treated and only 1 case progressed to pneumonia after presentation as URTI.

Oral ribavirin was used to treat 34 of the 44 episodes with RSV. Treatment with ribavirin did not seem to have an impact on progression to pneumonia in the 35 episodes presenting as URTI. Two of the 14 episodes of RSV URTI that were untreated or treated late progressed to pneumonia, while 4 of the 21 episodes of RSV URTI treated early progressed to pneumonia (P=1.0 by Fisher's exact test).

Among the 63 episodes of pneumonia, 19 episodes required mechanical ventilation. A total of 14 deaths occurred within 6 weeks of the viral pneumonia (Table 2), of which 3 were deemed directly attributed to viral pneumonia, including 2 with RSV and 1 with HPIV as the primary cause of death. The other 11 deaths within 6 weeks of a documented RVI occurred n the context of multiple active complications such as GVHD, neutropenic sepsis, co-pathogens, and multi-organ failures. In these instances, the extent to which the RVI contributed toward death was difficult to ascertain. It is therefore not surprising that no difference in survival was observed among the 95 patients with PCR-proven RVI, the 69 patients who were PCR-negative, and the 31 patients who never had RVI (P=.285) (Figure 3).

3.4 | Predictive value of ISI-RSV for different viruses

As the primary objective was to explore the applicability of the ISI-RSV to other RVIs, we analyzed the data of the 95 patients with PCR-proven RVI by applying the ISI-RSV. Based on the ISI-RSV, 37.81% of all episodes were classified as low risk (score 0-2), 46.27% as moderate risk (score 3-6), and 15.92% as high risk (score 7-12). Using Fisher's exact test, the ISI-RSV risk score showed significant association with pneumonia for RVI with RSV, influenza, HCoV, and AdV (Table 3). Such association was not found for HRhV and HPIV.

With the above-observed association, we further explored the prognostic value of the ISI-RSV for all RVI episodes by ROC analysis. For prediction of pneumonia, taking all the viruses together, ROC analysis showed a positive predictive value (PPV) of 86% for ISI-RSV of ≥9 and a negative predictive value (NPV) of 81% for ISI-RSV of ≤2. ISI-RSV of between 3 and 8 were poorly predictive. When analyzed by specific viruses, the PPV was >80% for ISI-RSV of ≥8 and NPV was >80% for ISI-RSV of ≤2 for RSV, influenza, AdV, and HPIV causing pneumonia, with the area under the ROC curve of 0.739, 0.770, 0.825, and 0.770, respectively (Figure 4). The ISI-RSV was not predictive for pneumonia

TABLE 3 Association between risk group and respiratory viral infection (RVI) outcome

Risk groups	Low risk	Moderate risk	High risk	*P*-value
RVI episodes involving RSV (n=44)	17	20	7	
Total pneumonia episodes	4	5	6	**.009**
URTI progressed to pneumonia	1	3	2	.292
Required ventilation	0	3	3	**.018**
Resulted in mortality	0	4	1	.124
RVI episodes involving influenza (n=28)	11	14	3	
Total pneumonia episodes	2	7	3	**.033**
URTI progressed to pneumonia	0	1	0	1
Required ventilation	0	2	0	.593
Resulted in mortality	0	0	0	—
RVI episodes involving rhinovirus[a] (n=47)	17	20	10	
Total pneumonia episodes	3	3	3	.57
URTI progressed to pneumonia	0	2	1	.44
Required ventilation	1	0	3	.056
Resulted in mortality	1	1	1	1
RVI episodes involving parainfluenza[a] (n=33)	13	16	4	
Total pneumonia episodes	1	5	2	.114
URTI progressed to pneumonia	0	2	1	.23
Required ventilation	0	2	0	.606
Resulted in mortality	0	4	0	.152
RVI episodes involving coronavirus[a] (n=18)	9	7	2	
Total pneumonia episodes	3	0	2	**.025**
URTI progressed to pneumonia	1	0	0	1
Required ventilation	0	0	1	.111
Resulted in mortality	0	0	0	—
RVI episodes involving adenovirus[a] (n=18)	4	9	5	
Total pneumonia episodes	1	2	5	**.015**
URTI progressed to pneumonia	0	0	0	—
Required ventilation	0	0	2	.105
Resulted in mortality	0	0	2	.105

Bold *P*-values are significant.
Analysis was not done for metapneumovirus, human bocavirus, and enterovirus as there were <10 cases of each of these viruses.
[a]Excludes episodes with co-infection involving RSV or influenza, which were analyzed under RSV or influenza, respectively.
RSV, respiratory syncytial virus; URTI, upper respiratry tract infection.

for HCoV and HRhV. ROC analysis was not done for prediction of need for mechanical ventilation (n=19) or death (n=14), owing to the small number of these two outcome indicators.

4 | DISCUSSION

In this study, we explored the applicability of ISI-RSV in allo-HSCT patients with RVI caused by a broad range of different viruses. In reviewing the data, we also generated, for the first time, information on RVI in such patients at a tropical center.

The main thrust of our study was to see if the ISI-RSV, when applied to RSV and non-RSV RVI, had predictive values for adverse outcomes. The findings that PPV and NPV of 80% for ISI-RSV in predicting pneumonia at cutoff values of ≥8 and ≤2, respectively, for RSV, influenza, AdV, and HPIV, have practical relevance. For example, when a patient with URTI symptoms and a high ISI-RSV is seen in the clinic, it will be prudent to have a lower threshold for a chest x-ray

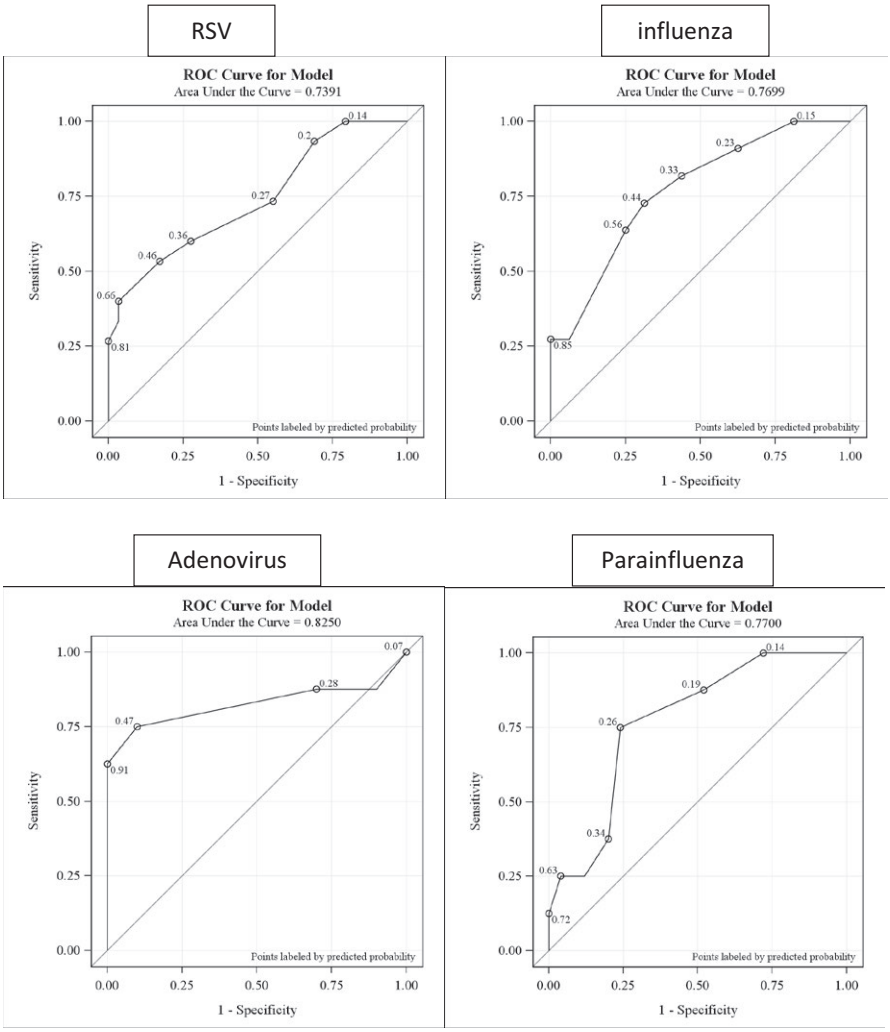

FIGURE 4 Receiver operating characteristic (ROC) curves for four viruses. RSV, respiratory syncytial virus

and perhaps, for admission to hospital for closer observation. For RVIs that have established drug therapy, ISI also gives guidance for early institution of treatment.

Finding that the ISI-RSV had predictive value for non-RSV RVIs is not wholly surprising. The components of the index have been shown, individually, to be risk factors for adverse outcomes in different studies of infections with the different RVIs. Lymphopenia, for example, emerged as a risk factor for adverse outcomes in several studies.[6,13] Steroids were an independent risk factor for progression to pneumonia in a review of HPIV infections in allo-HSCT recipients.[12] The absence of virus-specific factors in the index gives it potential for applicability beyond RSV. Indeed, the group that developed the ISI-RSV has found that it is similarly useful when applied to allo-HSCT patients with influenza.[15] We have now, with our modest number of patients with AdV (n=11) and HPIV (n=28) RVI, observed a similar pattern for these two viruses as well.

Immunodeficiency scoring index-RSV was not found to be predictive of pneumonia for HRhV and HCoV in our series, which could be a result of inadequate number of cases, or a relative lack of opportunistic potential of these two viruses, even in immunocompromised patients. HRhV are the commonest cause of the common cold,[19] as well as the most common virus found in allo-HSCT recipients.[6,7,18] Milano et al.[18] calculated the cumulative incidence of HRhV to be 22% at 100 days after allo-HSCT. In these studies, HRhV infections were only infrequently associated with pneumonia. On the other hand, Ghosh et al.[20] described 22 HSCT recipients who developed HRhV infection in the pre-engraftment period, among whom 7 developed pneumonia and all 7 died. Ison et al.[21] found that HRhV detected in the BAL fluid of HSCT recipients was associated with a high rate of co-infection and mortality. In our series, 9 episodes of HRhV pneumonia and 2 deaths occurred within 6 weeks of the HRhV pneumonia, amid other transplant complications. A similar profile was observed for HCoV, with pneumonia seen in 6 of 19 cases, including 2 episodes that required mechanical ventilation. These observations highlight that even RV of low virulence may be associated with life-threatening complications in the immunocompromised hosts, and remind us that all cases of RVI in such patients have to be taken seriously.[17,18]

In this series, we also reviewed our data on treatment and outcome for RSV and influenza. Controversy exists on the usefulness of oseltamivir for influenza in immunocompetent persons.[22] However, it is generally accepted that immunocompromised persons should receive oseltamivir.[23] In our series, 11 of the 12 episodes of

influenza pneumonia presented with pneumonia at presentation and only 1 episode with influenza URTI progressed to pneumonia—this skewed presentation prevented us from studying the usefulness of oseltamivir to prevent progression to pneumonia. As for RSV, RSV pneumonia in allo-HSCT recipients is associated with significant mortality,[3–5,24] and a systematic review concluded that ribavirin (aerosolized, oral, or intravenous) was probably beneficial.[25] Our data failed to show that early treatment (within 3 days of a positive PCR result) could prevent progression to pneumonia. However, this could be a result of selection bias, as all the untreated patients were outpatients who were very well and some had had symptoms for many days. The use of oral, as opposed to aerosolized, ribavirin which is unavailable locally, could be the cause of failure to prevent progression.

We made a few other observations in this analysis. The epidemiology of influenza and RSV is known to differ between tropical and temperate areas. In Singapore, influenza and RSV occur year-round, with small peaks in the June-July and the December-January periods, corresponding to the southern and northern hemisphere winters, respectively.[16] Our data are consistent with these trends, and RVI occurred sporadically year-round in our cohort of patients (Figure 1). Nosocomial viral infections are known to occur in HSCT units. The rather large percentages of nosocomial HPIV (32.14%) and AdV cases (63.64%) reflect the outbreaks with these two viruses that we had in 2012 and 2013, respectively. It is gratifying that only one case of influenza (3.85%) was of nosocomial origin, possibly owing to the annual influenza vaccination that all hospital staff receive. Nevertheless, the nosocomial rate might be lower if we had easier access to single rooms for our patients. Because of a shortage of single rooms, we reserve positively pressured single rooms only for patients undergoing transplantation and those who are neutropenic.

We also noted that the incidence of RVI in HSCT as reported in the literature differed greatly among studies. We suspect that this is related largely to diagnostic methods. Martino et al.[26] used culture methods to diagnose RVI (with PCR only for metapneumovirus) and found a rate of 29% over a 2-year period. Furthermore, their report makes no mention of coronaviruses. Wolfromm et al.[6], using a multiplex PCR, reported that 34.65% (131/378) of their HSCT patients developed an RVI. The 3-year cumulative incidence was 40%. Using a PCR kit that detected a range of viruses akin to ours, Ambriosini et al.[7] found an incidence of 47.4% of upper respiratory samples surveyed, a figure almost like ours. Therefore, our incidence of RVI is not unusually high.

Our study has some limitations. In the absence of a prospective protocol, we cannot be confident of complete capture of cases. Nevertheless, two operational factors enabled a high capture rate. As we are geographically small, loss to follow-up is a rarity. Our HSCT patients are advised to return directly to our outpatient clinic should problems arise, and our in-house guidelines are closely followed. This gives us confidence in attributing symptoms to viral infections. We also have a low threshold to test for RV, with a single symptom (eg, coryza) being a trigger. One problem we struggled with was the definition of RVI as a cause of death, mainly because little guidance was available in the literature. We adhered to what had been published, but remain concerned that the published statements lack stringency.[13,27]

In summary, our review of RVIs in allo-HSCT recipients verifies that the ISI-RSV is applicable to patients with RSV, and in addition, influenza, AdV, and HPIV RVI, for predicting the risk for development of pneumonia. This finding is useful beyond clinical management, as it may also be used for stratification in clinical trials of novel antivirals. We document the high association between HRhV and HCoV and pneumonia. The high incidence of pneumonia caused by RVI, the non-negligible incidence of need for mechanical ventilation, and death all testify to the unmet needs for effective antiviral therapy for RVI in this group of immunocompromised hosts.

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AUTHOR CONTRIBUTIONS

B.H.T. and Y.C.L. designed the project; L.W. collected the data; J.A. conducted the statistical analysis; L.W., B.H.T., and Y.C.L. performed the data interpretation and drafting; C.D., Y.T.G., S.G., A.H., W.H., F.L., L.O., and T.T.T. were involved in laboratory and clinical management of patients.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

1. Seo S, Xie H, Campbell AP, et al. Parainfluenza virus lower respiratory tract disease after hematopoietic cell transplant: Viral detection in the lung predicts outcome. *Clin Infect Dis*. 2014;58:1357-1368.
2. Chemaly RF, Hanmod SS, Rathod DB, et al. The characteristics and outcomes of parainfluenza virus infections in 200 patients with leukemia or recipients of hematopoietic stem cell transplantation. *Blood*. 2012;119:2738-2745.
3. Avetisyan G, Mattsson J, Sparrelid E, Ljungman P. Respiratory syncytial virus infection in recipients of allogeneic stem-cell transplantation: A retrospective study of the incidence, clinical features, and outcome. *Transplantation*. 2009;88:1222-1226.
4. Seo S, Campbell AP, Xie H, et al. Outcome of respiratory syncytial virus lower respiratory tract disease in hematopoietic cell transplant recipients receiving aerosolized ribavirin: Significance of stem cell source and oxygen requirement. *Biol Blood Marrow Transplant*. 2013;19:589-596.
5. Champlin RE, Whimbey E. Community respiratory virus infections in bone marrow transplant recipients: The M.D. Anderson Cancer Center experience. *Biol Blood Marrow Transplant*. 2001;7(Suppl):8S-10S.
6. Wolfromm A, Porcher R, Legoff J, et al. Viral respiratory infections diagnosed by multiplex PCR after allogeneic hematopoietic stem cell transplantation: Long-term incidence and outcome. *Biol Blood Marrow Transplant*. 2014;20:1238-1241.
7. Ambrosioni J, Bridevaux PO, Wagner G, Mamin A, Kaiser L. Epidemiology of viral respiratory infections in a tertiary care centre in

the era of molecular diagnosis, Geneva, Switzerland, 2011-2012. *Clin Microbiol Infect*. 2014;20:O578-O584.
8. Ljungman P, Ward KN, Crooks BN, et al. Respiratory virus infections after stem cell transplantation: A prospective study from the Infectious Diseases Working Party of the European Group for Blood and Marrow Transplantation. *Bone Marrow Transplant*. 2001;28:479-484.
9. Hirsch HH, Martino R, Ward KN, et al. Fourth European Conference on Infections in Leukaemia (ECIL-4): Guidelines for diagnosis and treatment of human respiratory syncytial virus, parainfluenza virus, metapneumovirus, rhinovirus, and coronavirus. *Clin Infect Dis*. 2013;56:258-266.
10. Small TN, Casson A, Malak SF, et al. Respiratory syncytial virus infection following hematopoietic stem cell transplantation. *Bone Marrow Transplant*. 2002;29:321-327.
11. Kim YJ, Guthrie KA, Waghmare A, et al. Respiratory syncytial virus in hematopoietic cell transplant recipients: Factors determining progression to lower respiratory tract disease. *J Infect Dis*. 2014;209:1195-1204.
12. Nichols WG, Corey L, Gooley T, Davis C, Boeckh M. Parainfluenza virus infections after hematopoietic stem cell transplantation: Risk factors, response to antiviral therapy, and effect on transplant outcome. *Blood*. 2001;98:573-578.
13. Martino R, Rámila E, Rabella N, et al. Respiratory virus infections in adults with hematologic malignancies: A prospective study. *Clin Infect Dis*. 2003;36:1-8.
14. Shah DP, Ghantoji SS, Ariza-Heredia EJ, et al. Immunodeficiency scoring index to predict poor outcomes in hematopoietic cell transplant recipients with RSV infections. *Blood*. 2014;123:3263-3268.
15. Kmeid J, Vanichanan J, Shah DP, et al. Outcomes of influenza infections in hematopoietic cell transplant recipients: Application of an immunodeficiency scoring index. *Biol Blood Marrow Transplant*. 2016;22:542-548.
16. Chow A, Ma S, Ling AE, Chew SK. Influenza-associated deaths in tropical Singapore. *Emerg Infect Dis*. 2006;12:114-121.
17. Hakki M, Rattray RM, Press RD. The clinical impact of coronavirus infection in patients with hematologic malignancies and hematopoietic stem cell transplant recipients. *J Clin Virol*. 2015;68:1-5.
18. Milano F, Campbell AP, Guthrie KA, et al. Human rhinovirus and coronavirus detection among allogeneic hematopoietic stem cell transplantation recipients. *Blood*. 2010;115:2088-2094.
19. Turner RB. Rhinovirus. In: Mandell GL, Bennett JE, Dolin R, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*, 7th edn. Philadelphia: Churchill Livingstone Elsevier; 2009:2389-2398.
20. Ghosh S, Champlin R, Couch R, et al. Rhinovirus infections in myelosuppressed adult blood and marrow transplant recipients. *Clin Infect Dis*. 1999;29:528-532.
21. Ison MG, Hayden FG, Kaiser L, Corey L, Boeckh M. Rhinovirus infections in hematopoietic stem cell transplant recipients with pneumonia. *Clin Infect Dis*. 2003;36:1139-1143.
22. Jefferson T, Jones M, Doshi P, et al. Oseltamivir for influenza in adults and children: Systematic review of clinical study reports and summary of regulatory comments. *BMJ*. 2014;348:g2545.
23. Manuel O, Estabrook M; AST Infectious Diseases Community of Practice. RNA respiratory viruses in solid organ transplantation. *Am J Transplant*. 2013;13(Suppl 4):212-219.
24. Machado CM, Boas LSV, Mendes AVA, et al. Low mortality rates related to respiratory virus infections after bone marrow transplantation. *Bone Marrow Transplant*. 2003;31:695-700.
25. Shah JN, Chemaly RF. Management of RSV infections in adult recipients of hematopoietic stem cell transplantation. *Blood*. 2011;117:2755-2763.
26. Martino R, Porras RP, Rabella N, et al. Prospective study of the incidence, clinical features, and outcome of symptomatic upper and lower respiratory tract infections by respiratory viruses in adult recipients of hematopoietic stem cell transplants for hematologic malignancies. *Biol Blood Marrow Transplant*. 2005;11:781-796.
27. Hassan IA, Chopra R, Swindell R, Mutton KJ. Respiratory viral infections after bone marrow/peripheral stem-cell transplantation: The Christie Hospital experience. *Bone Marrow Transplant*. 2003;32:73-77.

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