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ORIGINAL ARTICLE

Immunodeficiency risk score for prediction of mortality by parainfluenza virus infection in patients with hematologic malignancy

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Abstract

Parainfluenza virus (PIV) infection is a significant cause of morbidity and mortality, especially in hematologic malignancy patients including hematopoietic stem cell transplantation (HCT) recipients. However, limited information is available for risk stratification in PIV-infected patients with hematologic malignancy with or without HCT. Patients with hematologic malignancy diagnosed with PIV from January 2009 to December 2018 were retrospectively included in a tertiary care hospital in Seoul, South Korea. Upper respiratory tract infection (URTI) was defined as the detection of PIV in a nasopharyngeal sample with URTI symptoms without new pulmonary infiltrates. Lower respiratory tract infection (LRTI) was defined as detection of PIV in either upper or lower respiratory tract samples with new pulmonary infiltrates, with or without hypoxia. PIV-associated mortality was defined as death with respiratory failure and persistent LRTI within 90 days after diagnosis. The study included 143 adult patients. Of these, 55 (38%) progressed to or initially presented with LRTI. Among these, 22 (40%) died from PIV-associated mortality. An immunodeficiency risk score was developed from associated risk factors using a multivariable Cox regression model. Patients were stratified into low (0–2), moderate (3–5), and high risk (6–8) groups with PIV-associated mortalities of 0%, 9%, and 67%, respectively ($p < 0.005$, Harrell's C-index = 0.84). PIV infection can result in substantial mortality in patients with hematologic malignancy if it progresses to LRTI. The immunodeficiency risk score presented here may be useful for distinguishing moderate and high risk groups that might benefit from antiviral therapy.

Keywords Parainfluenza virus · Hematologic malignancy · Immunodeficiency · Prediction model

Introduction

Parainfluenza virus (PIV) infection is one of the most common respiratory virus infections and is a significant cause of morbidity and mortality, especially in patients with hematologic malignancy including recipients of hematopoietic stem cell transplantation (HCT) [1–6]. Previous studies have identified various risk factors for the progression of PIV infection to pneumonia and attributable mortality in recipients of HCT [7–10]. In addition, the efficacy of ribavirin (aerosolized, intravenous, or oral) in previous studies showed mixed results [9, 11–14].

PIV infection in hematologic malignancy also results in significant mortality and morbidity in patients without HCT [5, 12]. It is therefore of clinical importance to identify groups at high risk of progression to lower respiratory tract infection and death, among patients with hematologic malignancy with or without HCT. Furthermore, since the heterogeneity of an individual patient's risk might contribute to the mixed results of the efficacy of ribavirin, stratification of such patients by risk could reveal subgroups of patients who might benefit the most from antiviral therapy. However, limited data and tools are available for risk stratification of such patients. Therefore, in this study, we aimed to develop a risk prediction model and analyze the efficacy of ribavirin in each risk group.

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Methods

Study population

A retrospective cohort study was conducted for adult (age ≥ 18) patients with hematologic malignancy who were diagnosed with PIV infection at a 2700-bed, tertiary care hospital in Seoul, South Korea, from January 2009 to December 2018. All patient records were previously de-identified and were reviewed through the electronic medical records database system Asan BiomedicaL Research Environment (ABLE). In cases of patients with recurrent PIV infections, only the first episode was analyzed. Comorbidity status of each patient was assessed using McCabe score and Charlson comorbidity index. This study was approved by the institutional review board in our hospital.

Definitions

Upper respiratory tract infection (URTI) was defined as the detection of PIV in a nasopharyngeal sample with URTI symptoms without new infiltrates in the lungs [7–9, 12, 13]. Lower respiratory tract infection (LRTI) was defined as the detection of PIV in either upper or lower respiratory tract samples with new pulmonary infiltrates, with or without hypoxia [12, 13]. PIV-associated mortality was defined as death with respiratory failure and persistent LRTI within 90 days after the diagnosis of PIV [5, 15]. Nosocomial infection was defined as infection occurring 7 or more days after admission [7, 11]. Coinfection was defined as significant pathogens identified on a nasopharyngeal swab/aspirate, sputum culture, bronchoalveolar lavage, or blood culture within 3 days before or after the first identification of PIV [13]. Steroid use was defined as intravenous or oral use of steroids within 2 weeks before or at the time of PIV diagnosis [9, 10].

Therapeutic interventions

Oral ribavirin was given to patients at the discretion of attending hematologists and infectious disease consultants with or without intravenous immunoglobulin (IVIG) at a dose of 500 mg/kg with various durations. Standard and droplet precautions and isolation procedures were applied to all patients.

Virological evaluation

PIV infection was diagnosed by multiplex reverse transcription-PCR (RT-PCR) using Seeplex RV15 ACE Detection (Seegene Inc., Seoul, Republic of Korea) and shell vial culture for parainfluenza virus (Diagnostic Hybrids, Inc., Athens, OH) with specimens obtained by nasopharyngeal swab/aspirate or bronchoalveolar lavage.

Statistical analysis

Statistical analysis was done with Python 3.7.3 (G. van Rossum, The Python Language Reference Manual, Network Theory Ltd., September 2003) using SciPy (Jones E, Oliphant E, Peterson P, et al. SciPy: Open Source Scientific Tools for Python, 2001-, http://www.scipy.org/ [Online; accessed 2019-10-22]) and Lifelines libraries (Davidson-Pilon C et al., doi: https://doi.org/10.5281/zenodo.1252342). Categorical variables were analyzed with a Chi-squared test or Fisher's exact test as appropriate. Continuous variables were analyzed with a Student's *t* test or Mann-Whitney *U* test as appropriate. A significance level of 0.05 was employed for all analyses.

Development of immunodeficiency risk score

Risk factor analysis was performed with a Cox proportional hazards model. All variables subject to analysis in the multivariable model were tested for proportional hazard assumption, and variables that violated the assumption were analyzed as time-dependent variables. Points were assigned according to weighting criteria based on the coefficient of each risk factor in the Cox model. Score was calculated as the sum of all points. The cutoff values of scores for risk groups were defined according to a receiver operating characteristic curve with Youden index. PIV-associated mortality was compared among the risk groups using the Kaplan-Meier failure curves. The performance of this risk prediction model was assessed using the log-rank test and Harrell's C-index.

Results

Clinical and hematologic characteristics of patients

A total of 143 patient records were reviewed and analyzed. Of these, 55 (38%) patients progressed to or initially presented with LRTI. Among these 55 patients, 22 (40%) died with persistent LRTI and respiratory failure within 90 days after diagnosis. The clinical and hematologic characteristics are shown in Table 1. Most characteristics were similar between the URTI and LRTI groups, with the exceptions of place of acquisition ($p = 0.022$), allogeneic hematopoietic stem cell transplantation (44% vs. 67%, $p = 0.017$), coinfection (17% vs. 35%, $p = 0.029$), steroid use (42% vs. 56%, $p = 0.019$), ribavirin use (35% vs. 60%, $p = 0.006$), and IVIG use (8% vs. 38%, $p < 0.001$).

Immunodeficiency risk factors

In a multivariable Cox proportional hazards regression analysis, neutropenia (absolute neutrophil count < 500 μL), age of 40 and above, allogeneic HCT, and

Table 1 Clinical and hematologic characteristics of all patients

Characteristics	Total ($n = 143$)	URTI ($n = 88$)	LRTI ($n = 55$)	p value
Age, median years (IQR)	50 (34–58)	49 (32–57)	51 (38–61)	0.120
Male gender, *n* (%)	67 (47)	44 (50)	23 (42)	0.434
Site of infection at diagnosis, *n* (%)				< 0.001
Upper respiratory tract	103 (72)	88 (100)	15 (27)	
Lower respiratory tract	40 (28)	0 (0)	40 (73)	
Place of acquisition, *n* (%)[a]				0.022
Community	45 (31)	21 (24)	24 (45)	
Nosocomial	98 (69)	67 (76)	31 (55)	
Type of parainfluenza virus, *n* (%)				0.370
PIV 1	17 (12)	10 (11)	7 (13)	
PIV 2	2 (1)	2 (2)	0 (0)	
PIV 3	112 (78)	71 (81)	41 (74)	
PIV 4	12 (8)	5 (6)	7 (13)	
Diagnosis, *n* (%)				0.166
Acute myeloid leukemia	92 (64)	56 (64)	36 (65)	
Acute promyelocytic leukemia	1 (1)	0 (0)	1 (2)	
Acute lymphoblastic leukemia	48 (34)	32 (36)	16 (29)	
Chronic lymphocytic leukemia	1 (1)	0 (0)	1 (2)	
Aggressive NK-cell leukemia	1 (1)	0 (0)	1 (2)	
HCT, *n* (%)	76 (53)	39 (44)	37 (67)	0.017
Type of transplant				0.372
Allogeneic, siblings	18/76 (24)	7/39 (18)	11/37 (30)	
Allogeneic, non-sibling, family member	30/76 (40)	17/39 (44)	13/37 (35)	
Allogeneic, unrelated	28/76 (37)	15/39 (39)	13/37 (35)	
Stem cell source				0.423
Bone marrow	1/76 (1)	0/39 (0)	1/37 (3)	
Peripheral blood	72/76 (95)	38/39(97)	32/37 (92)	
Unknown	3/76 (4)	1/39 (3)	2/37 (5)	
Conditioning regimen, *n* (%)				0.692
Myeloablative with TBI	1 (1)	1/39 (3)	0/37 (0)	
Myeloablative without TBI	64 (84)	34/39 (87)	30/37 (81)	
Reduced intensity	3 (4)	3/39 (8)	6/37 (16)	
Uncertain	0 (0)	1/39 (3)	1/37 (3)	
GVHD, *n* (%)	34/76 (45)	17/39 (44)	17/37 (46)	0.981
Type of GVHD				0.799
Acute	8/76 (11)	3/17 (18)	5/17 (29)	
Chronic	26/76 (34)	14/17 (82)	12/17 (71)	
Hematologic disease status, *n* (%)				0.803
Remission	93 (65)	59 (67)	34 (62)	
Persistent/relapse	48 (33)	28 (32)	20 (36)	
Uncertain	2 (1)	1 (1)	1 (2)	
McCabe score, *n* (%)				0.317
Rapidly fatal	135 (94)	81 (92)	54 (98)	
Ultimately fatal	7 (5)	6 (7)	1 (2)	
Non-fatal	1 (1)	1 (1)	0 (0)	
Charlson comorbidity index score, median (IQR)	3 (2–4)	3 (2–4)	3 (2–4)	0.423
Coinfection, *n* (%)[b]	34 (45)	15 (17)	19 (35)	0.029
Type of coinfection				0.028

Table 1 (continued)

Characteristics	Total ($n = 143$)	URTI ($n = 88$)	LRTI ($n = 55$)	p value
Bacterial[c]	6 (18)	1/15 (7)	5/19 (26)	
Viral[d]	20 (59)	11/15 (73)	9/19 (47)	
Fungal[e]	8 (24)	3/15 (20)	5/19 (26)	
Steroid use, n (%)	68 (48)	37 (42)	31 (56)	0.019
Median dose (mg) per kilogram (IQR)[f]	0.33 (0.19–0.63)	0.36 (0.24–0.50)	0.32 (0.17–0.87)	0.001
Immunosuppressant use [g], n (%)	64 (45)	41 (47)	23 (42)	0.699
Initial total WBC count, median (IQR)	2500 (600–6000)	2250 (600–5400)	3000 (450–7100)	0.459
Initial ANC, median (IQR)	1080 (75–3350)	940 (78–3133)	1360 (70–3865)	0.314
Initial ALC, median (IQR)	570 (154–1308)	559 (191–1302)	570 (100–1309)	0.359
Initial monocyte count, median (IQR)	225 (24–659)	222 (25–662)	230 (27–613)	0.339
Ribavirin use, n (%)	64 (45)	31 (35)	33 (60)	0.006
Median dose (mg) per kilogram (IQR)	16.4 (14.2–21.6)	16.2 (13.6–20.9)	16.5 (14.7–21.5)	0.002
Intravenous immunoglobulin use, n (%)	28 (20)	7 (8)	21 (38)	< 0.001

Abbreviations: *URTI*, upper respiratory tract infection; *LRTI*, lower respiratory tract infection; *PIV*, Parainfluenza virus; *HCT*, hematopoietic stem cell transplantation; *TBI*, total body irradiation; *GVHD*, graft-versus-host disease; *WBC*, white blood cell; *ANC*, absolute neutrophil count; *ALC*, absolute lymphocyte count; *IQR*, interquartile range

[a] Nosocomial infections were defined as those occurring 7 or more days after admission

[b] Coinfections were defined as significant pathogens identified on a nasopharyngeal swab/aspirate, sputum culture, bronchoalveolar lavage, or blood culture within 3 days before or after the first identification of parainfluenza virus

[c] Includes *Enterococcus faecium* ($n = 1$), *Pseudomonas aeruginosa* ($n = 1$), *Escherichia coli* ($n = 1$), *Streptococcus pneumoniae* ($n = 1$), *Stenotrophomonas maltophilia* ($n = 1$), and *Klebsiella pneumoniae* ($n = 1$)

[d] Includes rhinovirus ($n = 5$), RSV ($n = 3$), metapneumovirus ($n = 3$), adenovirus ($n = 2$), coronavirus ($n = 2$), and bocavirus ($n = 2$). PIV 1 and PIV 3 were found simultaneously on the nasopharyngeal PCR of one patient

[e] Includes aspergillosis ($n = 5$, 4 probable IPA, 1 possible IPA), *Candida tropicalis* ($n = 1$), *Pneumocystis jirovecii* ($n = 1$)

[f] Peak dose of steroid used within 2 weeks before or at PIV diagnosis

[g] Includes cyclosporin, cyclophosphamide, or intensive chemotherapy that renders patients nadir status at PIV diagnosis

LRTI at presentation were found to be significant risk factors independently associated with PIV-associated mortality (Table 2). The cutoff value of 40 years was included in the multivariable analysis because, among the age cutoff values include in a univariable analysis (30-year, 40-year, 50-year, 60-year and 70-year), this was the only value that resulted in a p value less than 0.1 (hazard ratio [HR], 3.38; 95% confidence interval [CI], 1.0–11.47; $p = 0.05$). Rituximab was used within 6 months (median, 3 months; interquartile range [IQR], 2.75–3 months) prior to the diagnosis of PIV infection in 4 patients (3 with acute lymphoblastic leukemia and 1 with acute myeloblastic leukemia), and it was not significantly associated with PIV-associated mortality in univariable analysis (HR, 3.52; 95% CI, 0.82–15.03; $p = 0.09$). Other immunosuppressants such as cyclosporin, cyclophosphamide, or intensive chemotherapy were not significantly associated with PIV-associated mortality in both univariable (HR, 1.01; 95% CI, 0.44–2.34; $p = 0.97$) and multivariable Cox regression analysis (HR, 0.584; 95% CI, 0.23–1.49; $p = 0.261$). Steroid use was not a significant risk factor in both univariable and multivariable analyses.

Development of risk score model

For each risk factor, points were assigned according to the aforementioned calculations. To define score cutoff values for risk groups, sensitivity and specificity were calculated for each score as a cutoff value for a 90-day PIV-associated mortality (Table 3). For all scores, a score of 5 resulted in the maximal Youden index (0.62), and among the scores equal to or less than 5, a score of 2 resulted in the maximal Youden index (0.36) with 100% sensitivity (Fig. 1). According to these results, risk groups were defined as low risk (0–2), moderate risk (3–5), and high risk (6–8).

Prediction of PIV-associated mortality

In the univariable Cox proportional hazard model, risk group as an ordered factor was significantly associated with PIV-associated mortality (HR, 12.51; 95% CI, 5.37–29.37; $p < 0.005$). The Kaplan-Meier failure curves showed an increasing trend of PIV-associated mortality according to risk group with significant differences

Table 2 Immunodeficiency risk scores for patients with hematologic malignancy infected with parainfluenza virus

		Patients, n = 143	PIV-associated mortality (90-day), n = 22				
Variables		*n* (%)	*n* (%)	Adjusted HR[a] (95% CI)	Coefficient	Weighing criteria	Points
1	ANC < 500/μL	61 (43)	17 (28)	11.13 (3.52–35.16)	2.410	> 2	3
2	Age ≥ 40 yr	96 (67)	19 (20)	4.56 (1.14–18.28)	1.518	1–2	2
3	Allogeneic HCT [b]	53 (37)	11 (21)	3.39 (1.32–8.72)	1.222	1–2	2
4	LRTI at presentation	40 (28)	15 (38)	1.03 (1.004–1.059)	0.031	0–1	1
	Minimum possible score	0					
	Maximum possible score	8					
	Low risk	0–2					
	Moderate risk	3–5					
	High risk	6–8					

Abbreviations: *LRTI*, lower respiratory tract infection; *HR*, hazard ratio; *CI*, confidence interval; *n*, number; *ANC*, absolute neutrophil count; *HCT*, hematopoietic stem cell transplantation

[a] Adjusted for Charlson comorbidity index score and ribavirin use

[b] All patients received allogeneic stem cell transplantation

between the groups: 0% in the low risk group, 9% in the moderate risk group, and 67% in the high risk group. Harrell's C-index for this prediction model was 0.84 (Fig. 2).

When this model was applied to the subgroup of allogeneic HCT recipients, mortality in each risk group showed similar results and tendency: 0% in the low, 9% in the moderate, and 57% in the high risk group with Harrell's C-index 0.81 (Fig. 3).

Efficacy of oral ribavirin according to risk group

Oral ribavirin use had no significant impact on PIV-associated mortality in all risk groups. Although more patients died in the ribavirin group than in the non-ribavirin group in the moderate risk group (5% vs. 14%; HR, 2.50; $p = 0.27$), the result was not statistically significant. Fewer patients died in the ribavirin group in the high risk group, but this was also not statistically significant. When stratified according to ribavirin dose, a

Table 3 Sensitivity and specificity for cutoff values to predict PIV-associated mortality

Score	Sensitivity (%)	Specificity (%)	Positive predictive value	Negative predictive value	Youden index
0	100	3	0.16	1.00	0.03
1	100	5	0.16	1.00	0.05
2	100	34	0.22	1.00	0.34
3	95	46	0.24	0.98	0.41
4	86	60	0.28	0.96	0.46
5	68	94	0.68	0.94	0.62
6	27	96	0.55	0.88	0.23
7	14	100	1.00	0.86	0.14
8	0	100	N/A	0.85	0.00
Score (≤ 5)					
0	100	4	0.06	1.00	0.04
1	100	5	0.06	1.00	0.05
2	100	36	0.09	1.00	0.36
3	86	49	0.09	0.98	0.35
4	57	64	0.09	0.96	0.21
5	0	100	N/A	0.94	0.00

Abbreviations: *N/A*, not applicable

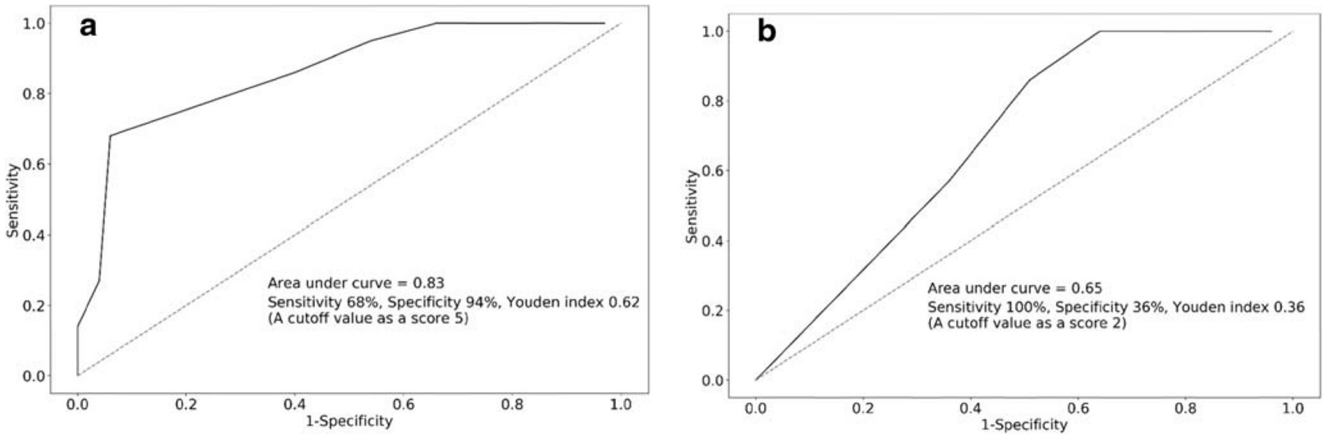

Fig. 1 Receiver operating characteristic curve for all scores (a) and scores equal to or lower than 5 (b)

similar trend was observed, yet the differences were significant in the moderate risk group in both < 15 mg/kg and > 20 mg/kg subgroups (Table 4). The median time from diagnosis to ribavirin use was 2 days (IQR, 1–4 days), with no significant difference ($p = 0.196$) between patients who died with LRTI and respiratory failure (median, 2 days; IQR, 2–4.5 days) and patients who did not (median, 2 days; IQR, 1–4 days).

Discussion

In our cohort, 38% of all patients with PIV infection initially presented with or progressed later to LRTI, and 15% of patients who initially presented with URTI progressed to LRTI. In addition, 40% of patients who initially presented with or progressed to LRTI died due to respiratory illness within 90 days of diagnosis. The progression rate to LRTI and the mortality rate by respiratory failure of LRTI patients were similar to the findings of previous studies, 12–35% and 17–47%, respectively [4–7, 10, 12]. The immunodeficiency risk score developed here using previously known and prevalent risk factors [6–10, 12, 15] distinctly differentiates low, moderate, and high risk groups among patients who have hematologic malignancy with or without HCT and also within the subgroup of HCT recipients. Oral ribavirin showed no effect on the prevention of PIV-associated death in any risk group, even after stratification by dosage.

Shah et al. [15] previously reported a score model for respiratory syncytial virus (RSV) infection among HCT recipients to predict progression to LRTI and RSV-associated mortality combining known risk factors for immunodeficiency. PIV has comparable mortality and morbidity to RSV in immunocompromised patients, yet it differs in that a substantial portion of LRTI patients initially present with LRTI at the time of diagnosis [10]. Moreover, although previous studies have investigated risk factors for progression to LRTI and PIV-associated mortality in HCT recipients [7–10], to our knowledge, this study is the first to develop a score model to predict PIV-associated mortality among patients with hematologic malignancy with or without HCT.

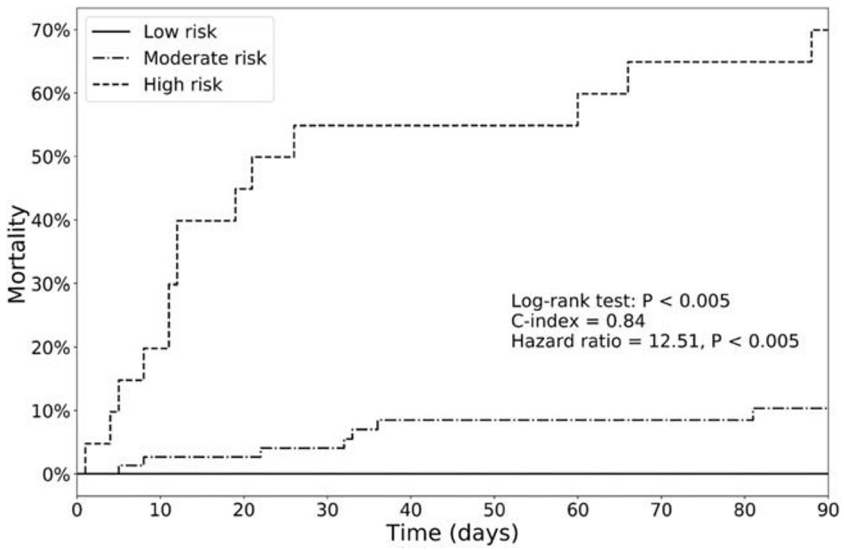

Fig. 2 Kaplan-Meier curves for PIV-associated mortality by risk group

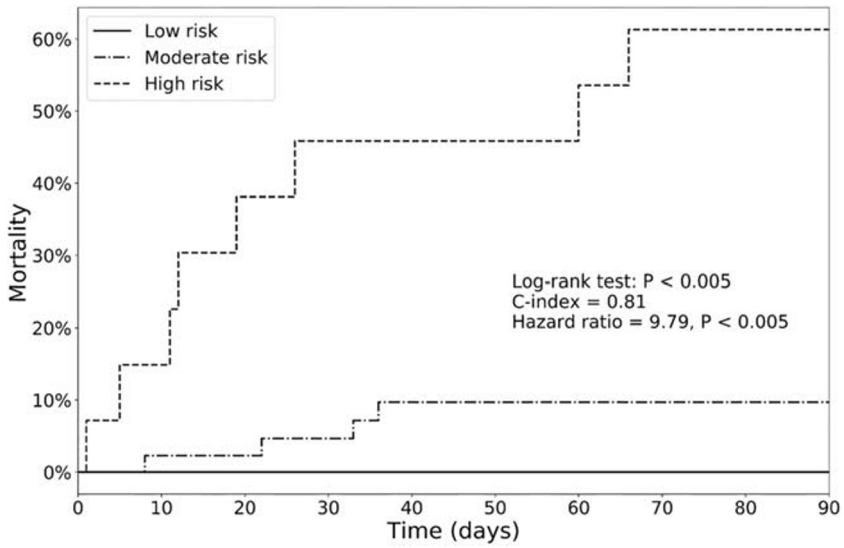

Fig. 3 Kaplan-Meier curves for PIV-associated mortality by risk group for HCT recipients

Steroid use has been consistently suggested as a significant risk factor of progression to LRTI and PIV-associated mortality in many studies in a dose-dependent fashion, especially at a dose of more than 1 mg/kg [7, 9, 10, 13, 15]. However, in the present study, steroid dose was mostly under 1 mg/kg (median, 0.33 mg/kg; IQR, 0.19–0.63 mg/kg), and only those who received steroids before or at PIV diagnosis were deemed to have this factor, which might have led to the result that steroid use was not significant in both univariable and multivariable analyses.

Ribavirin, oral or aerosolized, has been shown to be efficacious for RSV treatment in HCT recipients [16], especially in the high risk group [15]. However, for PIV, except in several small studies [11, 14, 17], retrospective studies have not shown either oral or aerosolized ribavirin to prevent progression to LRTI and

Table 4 PIV-associated mortality according to risk group and ribavirin use

Risk group	*n*	PIV-associated mortality (90-day) *n* (%)	n	PIV-associated mortality (90-day) *n* (%)	HR (95% CI)
Ribavirin use, median (IQR) 16.4 mg/kg (14.2–21.6)					
	No		Yes		
Low	29	0 (0)	12	0 (0)	N/A
Moderate	43	2 (5)	37	5 (14)	2.50 (0.49–12.94)
High	7	5 (71)	15	10 (67)	0.84 (0.29–2.48)
Ribavirin < 15 mg/kg, median (IQR) 12.9 mg/kg (10.6–14.4)					
	No		Yes		
Low	34	0 (0)	7	0 (0)	N/A
Moderate	55	2 (4)	25	5 (20)	5.25 (1.02–27.11)
High	13	10 (77)	9	5 (56)	0.56 (0.19–1.65)
Ribavirin 15–20 mg/kg, median (IQR) 17.0 mg/kg (16.2–17.4)					
	No		Yes		
Low	37	0 (0)	4	0 (0)	N/A
Moderate	65	5 (8)	15	2 (13)	1.64 (0.32–8.41)
High	18	14 (78)	4	1 (25)	0.21 (0.03–1.65)
Ribavirin > 20 mg/kg, median (IQR) 23 mg/kg (23.0–27.5)					
	No		Yes		
Low	38	0 (0)	3	0 (0)	N/A
Moderate	70	4 (6)	10	3 (30)	5.21 (1.16–23.34)
High	17	11 (65)	5	4 (80)	1.25 (0.39–3.97)

Abbreviation: *LRTI*, lower respiratory tract infection; *n*, number; *N/A*, not applicable; *IQR*, interquartile range

death with respiratory failure [7–10, 12, 13]. In the present study, oral ribavirin did not significantly reduce PIV-associated mortality in any risk group regardless of dosage. This finding is consistent with our previous study using propensity score matching to offset selection bias, which revealed that in hematologic malignancy patients with paramyxovirus infection, ribavirin was not associated with better outcomes [13]. Interestingly, more patients died in the ribavirin group in the moderate risk group at doses of under 15 mg/kg and over 20 mg/kg. The reason for these counterintuitive findings is unclear. However, selection bias may play a role. Nevertheless, we cannot rule out the possibility of an adverse effect of oral ribavirin therapy in critically ill patients with PIV infection.

It is noteworthy that Fludase (DAS181, Ansun BioPharma, Inc., San Diego, CA), a sialidase fusion protein, was efficacious against PIV in vitro and in small studies with HCT recipients [18–21]. Currently, phase 3 clinical trials of DAS181 in hospitalized patients with PIV infection are ongoing. This novel antiviral agent needs to be validated in a larger trial, and an immunodeficiency risk score might be helpful in selecting patients who would benefit the most from antiviral therapy.

The present study has several limitations. First, as a relatively small number of events (PIV-associated death) limited the analytic power of the Cox proportional hazards model, a few risk factors that were previously reported as significant might be excluded from the final model, such as low monocyte count, coinfection, and the status of hematologic malignancy [7, 10, 12]. In addition, some may argue that the heterogenous population including both HCT recipients and non-HCT patients with hematologic malignancy could result in missed analysis for the effect on infection severity of other potential factors. However, since both non-HCT recipients with hematologic malignancy and HCT recipients are at risk of PIV with similar mortality risk [12], we believe that our simple and practical prediction model might have clinical value.

Second, the effect size of significant risk factors might be overestimated due to a limited sample size. To offset such a statistical bias, the final model includes previously established risk factors, and points were assigned using risk factor coefficients, not hazard ratios. Finally, although the prediction model in the present study showed good performance, the possibility of overfitting cannot be ruled out since it was not validated using an external cohort. To ensure the generalizability of the model, external validation using a larger cohort is required.

Conclusions

PIV infection results in substantial mortality if it progresses to LRTI in patients who have hematologic malignancy with or without HCT, especially in moderate to high risk groups. The immunodeficiency risk score developed here may be employed as a useful tool to distinguish moderate and high risk groups who might benefit from antiviral therapy, not only among patients with hematologic malignancy but also HCT recipients. Oral ribavirin was not efficacious in preventing PIV-associated death in any risk group.

Author contributions Sung-Han Kim as the corresponding author, designed, initiated the study, conducted manuscript writing/review, and has the final responsibility for the decision to submit for publication; Jeongsoo Lee collected and analyzed patients' data, carried out the statistical analysis, manuscript writing, and built the final score model. Jiwon Jung, Min-Jae Kim, Yong Pil Chong, Sang-Oh Lee, Sang-Ho Choi, Yang Soo Kim, Jun Hee Woo, Eun-Ji Choi, Han-Seung Park, Jung-Hee Lee, Je-Hwan Lee, and Kyoo-Hyung Lee were involved in the study design, interpretation of results, and manuscript writing. All the authors participated in the review of the manuscript.

Compliance with ethical standards

Conflict of interest There are no potential conflicts of interest for any authors.

Ethics approval and consent to participate The protocols of this study were approved by the institutional review board of Asan Medical Center. All procedures followed were in accordance with institutional and national ethical standards and with the Helsinki Declaration of 1975, as revised in 2008. Informed consent was waived in view of the retrospective nature of the study. Confidentiality and anonymity of patient data was maintained throughout.

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