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Refinement of estimates of mortality risk using the Radiologic Severity Index in hematologic malignancy patients with respiratory syncytial virus infection

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Abstract

Background: Immunocompromised hematologic malignancy (HM) patients experience high mortality after respiratory syncytial virus (RSV) lower respiratory tract infection (LRTI). We measured radiologic severity to determine whether it could improve the performance of 60-day mortality models based only upon immunodeficiency severity.

Methods: We studied 155 HM patients, including 84 hematopoietic cell transplant recipients, who developed RSV LRTI from 2001–2013. We measured immunodeficiency using lymphopenia (lymphocyte count <200 cells/mm³), Immunodeficiency Severity Index (ISI), and Severe Immunodeficiency (SID) criteria. Radiologic severity was measured by the Radiologic Severity Index (RSI, range 0–72) at time of LRTI (baseline-RSI) and peak severity (peak-RSI). Delta-RSI was defined as the difference between baseline-RSI and peak-RSI. We used logistic regression models to measure the association of immunodeficiency and RSI with 60-day all-cause mortality, and measured model discrimination using areas under the receiver-operating characteristics curves, calibration using Brier scores, and explained variance using pseudo-R² values.

Results: Forty-one patients died within 60 days of RSV LRTI. Severe immunodeficiency was associated with higher mortality. Peak-RSI (odds ratio [OR] 1.06/point, 95% confidence interval [CI] 1.04–1.08), and delta-RSI (OR 1.07/point, 95% CI 1.05–1.10) were associated with 60-day mortality after RSV LRTI, but not baseline-RSI. Addition of peak-RSI or delta-RSI to baseline

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immunodeficiency improved the discrimination, calibration, and explained variance ($p < 0.001$) of 60-day mortality models.

Conclusions: Although baseline immunodeficiency in HM patients helps predict 60-day mortality after RSV LRTI, mortality risk estimates can be further refined by also measuring LRTI progression using RSI. RSI is well-suited as a marker of LRTI severity in RSV infection.

Introduction

Respiratory syncytial virus (RSV) infection is associated with high morbidity and mortality in immunocompromised hosts, such as those with hematologic malignancies (HM) ¹. Lower respiratory tract infection (LRTI) with RSV is associated with particularly high mortality ²⁻⁹, and treatment with aerosolized ribavirin can be costly and challenging to deliver ¹⁰. A major barrier to the development of new antiviral agents is the difficulty of proving clinical superiority using mortality as a primary endpoint, since mortality may occur due to comorbid conditions or to non-RSV causes ^{11,12}. Additionally, non-mortality endpoints such as viral load are controversial because they do not always correlate with disease severity ¹². Non-mortality endpoints that accurately measure disease severity may reduce barriers to the development of effective anti-RSV treatments.

One solution to improve the chances of showing superiority with new antivirals would be to test these drugs in patients with RSV infection who have high mortality rates due to immunodeficiency. The severe immunodeficiency (SID) criteria stratify hematopoietic cell transplant (HCT) recipients into three groups: moderate (MID), severe (SID), and very severe (vSID) immunodeficiency on the basis of length of time since HCT, leukocyte counts, exposure to leukocyte depletion therapies, presence of acute graft-versus-host disease (GVHD), and exposure to immunosuppressive treatments ^{13,14}. We validated the SID criteria in a cohort of patients who developed RSV infection at our institution and found that these criteria were highly predictive of mortality ¹⁵. Similarly, we developed the Immunodeficiency Score Index (ISI) to quantify immunodeficiency in HCT recipients on the basis of leukocyte counts, age, myeloablative conditioning, GVHD, recent corticosteroid exposure, and time since HCT ^{16,17}. Using these criteria, ISI can successfully stratify HCT recipients into groups at low, moderate, or high risk for progression to LRTI or death after RSV infection ¹⁵.

Although immunodeficiency scores can estimate mortality risks based on baseline characteristics, they are not suitable to measure the disease severity of RSV LRTI because they are estimates of the severity of immunodeficiency and not the LRTI itself. We previously developed a semi-quantitative tool of radiologic severity, the Radiologic Severity Index (RSI), which was the strongest predictor of mortality after parainfluenza virus LRTI ¹⁸. Longitudinal measurement of RSI can measure the evolving severity of LRTI. Therefore, RSI may be a suitable non-mortality endpoint in clinical trials that accurately reflects LRTI severity, since progression of radiologic severity would likely be attributable to worsening pneumonia. We previously showed that ISI and SID criteria at the time of RSV infection predicted 60-day mortality after RSV LRTI ¹⁵. We sought to determine whether peak-RSI, or the change from baseline-RSI to peak-RSI (delta-RSI), could improve the discrimination,

calibration, and explained variance in the outcome of 60-day mortality models when added to baseline immunodeficiency scores in HM patients with RSV LRTI.

Materials and Methods

Study Design

We conducted a retrospective review of all adults who were at least 18 years of age at The University of Texas MD Anderson Cancer Center from 01/01 to 08/13 and who had leukemia, lymphoma or multiple myeloma (HM), with or without HCT, and had an RSV infection with chest X-ray (CXR) images available in our electronic health records. This study was approved by our Institutional Review Board (PA12-0483) in accordance with the Helsinki Declaration of the World Medical Association, and waiver of informed consent was granted.

Definitions

We defined RSV LRTI as (1) microbiologic confirmation of RSV in nasal wash or swab or bronchoalveolar lavage fluid, and (2) new infiltrates on CXR consistent with pneumonia within 5 days of microbiologic confirmation. Microbiologic confirmation was performed using shell vial culture or direct immunofluorescent antibody testing per institutional practice at that time. We defined neutropenia as an absolute neutrophil count (ANC) <500 cells/mm³ and lymphopenia as an absolute lymphocyte count (ALC) <200 cells/mm³. We record whether patients had received ribavirin therapy prior to the diagnosis of LRTI (URTI stage) or after the diagnosis of LRTI (LRTI stage). Proven RSV LRTI was defined as detection of RSV in bronchoalveolar lavage fluid.

Grading of immunodeficiency in HCT recipients

All HCT recipients were scored using ISI and SID criteria at the time of RSV LRTI. ISI ranges from 0–12, and ISI scores were calculated as previously described¹⁷. HCT recipients were classified as low-risk (ISI 0–2), moderate risk (ISI 3–6) or high-risk (ISI 7–12). We used SID criteria to classify HCT recipients into three strata: MID, SID, or vSID as previously described^{13,14}. Further details on ISI and SID scoring are available in the Online Supplement.

Measurement of RSI

RSI was calculated for all CXRs by experienced pulmonologists (A.S., E.V., L.B., S.A.F.) at baseline and at peak radiologic severity, estimated qualitatively, within the first 30 days after RSV LRTI. Delta-RSI was calculated by subtracting baseline-RSI from peak-RSI. Table 1 illustrates how RSI is calculated¹⁸. Briefly, chest radiographs were divided into three zones: upper (above carina), middle (below carina, above inferior pulmonary vein), and lower (below inferior pulmonary vein) in both lungs. Pulmonary infiltrates were scored on a three-point scale based on the predominant pattern in that zone - normal attenuation: 1, ground glass opacities (GGOs): 2, consolidation: 3. Consolidation and GGOs were defined per Fleischner Society guidelines¹⁹. We multiplied the pattern score by a factor based on extent of volumetric involvement on planar anteroposterior or posteroanterior views - normal: 0, 1–24%: 1, 25–50%: 2, 51–75%: 3, >75%: 4. Scores from each zone were added to give the

final RSI, which ranges from 0–72. Each CXR had two readers, and we used the mean of the two scores for analysis. RSI readers were blinded to the primary outcome of death and to each other's scoring.

Statistical analysis

Descriptive statistics were calculated for demographic, clinical, and therapeutic data. Categorical variables were compared using chi-square or Fisher's exact test and continuous variables were compared using one-way analysis of variance. We constructed univariate logistic regression models to identify the association of measures of immunodeficiency and RSI with 60-day all-cause mortality. We chose 60 days as our primary endpoint in order to have at least 30 days of follow-up for patients who may have developed peak radiologic severity around day 30 after RSV LRTI. Because ISI and SID are specific to HCT recipients, we used ALC as measure of immunodeficiency in the complete cohort, and included only HCT recipients in models with ISI and SID. All patients were followed for the entire 60 days, and outcomes were right-censored after 60-days. Importantly, models with peak-and delta-RSI cannot be considered predictive models, since this information is measured after study entry. We identified optimal cutoff points for peak-RSI and delta-RSI using the maximum efficiency method, which maximizes sensitivity and specificity. We then constructed bivariate logistic regression models combining measures of immunodeficiency with peak-RSI and delta-RSI. We measured the discriminatory ability of models using area under the receiver-operating characteristics curve (AUC), and we measured the calibration of models using Brier scores²⁰ We considered AUC values of >0.9 to represent excellent discrimination, 0.8–0.9 to represent good discrimination, 0.6–0.8 to represent fair discrimination, and <0.6 to represent poor discrimination²¹. Brier scores are a measure of disagreement between observed and predicted outcomes and range from 0.25 to 0, with lower numbers indicating superior calibration²⁰. We used McFadden's pseudo-R² values to estimate how much each model explained the variance of 60-day mortality, and compared the explained variance in different models using a chi-square test of log-likelihood ratios. Kaplan-Meier survival curves and log-rank tests were performed to compare the probability of survival between patients with varying degrees of immunodeficiency. We then compared the survival of patients with RSI values greater or less than the optimal cutoff point within each strata of immunodeficiency severity. We calculated intra-class correlations (ICC) to estimate reliability between readers for RSI scoring. All statistical analyses were performed using STATA version 14.2 (StataCorp, College Station, Texas) and SAS Enterprise version 5.1 (SAS Institute, Cary, North Carolina). All tests were two-sided with a significance level of 0.05.

Results

Characteristics of the study cohort

We identified 155 patients who met our inclusion and exclusion criteria, of whom 35% (55/155) had proven RSV LRTI. Table 2 describes the characteristics of survivors and non-survivors at 60 days after RSV LRTI. Briefly, non-survivors were more likely to be neutropenic (49% vs. 26%, $p=0.008$) or lymphopenic (54% vs. 29%, $p=0.005$), more likely to have been exposed to corticosteroids within 30 days of LRTI (63% vs. 45%, $p=0.04$), and

more likely to have proven RSV LRTI (29% vs. 11%, $p=0.008$). Further discussion on the impact of proven RSV LRTI on 60-day mortality is included in the online supplement and Supplemental Table 1.

Risk of 60-day mortality by degree of immunodeficiency

We measured the association of lymphopenia with 60-day mortality. We chose lymphopenia and not neutropenia, since our prior analysis suggested the two variables were collinear, and ALC was a common criterion for scoring both ISI and SID. We also calculated ISI grade and SID criteria for 84 HCT recipients and measured association with 60-day mortality after RSV LRTI. Supplemental Table 2 shows univariate logistic regression models using ALC, ISI and SID. In all patients, lymphopenia was associated with increased 60-day mortality (odds ratio [OR] 2.8, 95% confidence interval [CI] 1.4–5.9, $p=0.005$). In HCT recipients, ISI high-risk immunodeficiency (OR 8.3, 95% CI 1.8–37.9, $p=0.007$), SID (OR 6.4, 95% CI 1.428.9, $p=0.02$) and vSID (OR 10.3, 95% CI 2.6–41.1, $p=0.005$) were associated with increased 60-day mortality. Figure 1 shows time to mortality during the first 60 days after RSV LRTI by severity of immunodeficiency. Lymphopenia (Figure 1A, log-rank $p=0.02$), higher-grade ISI (Figure 1B, $p=0.001$) and higher-grade SID (Figure 1C, $p=0.003$) were associated with impaired survival.

Risk of 60-day mortality after RSV LRTI by baseline, peak-, and delta-RSI

Baseline-RSI measurements were not associated with 60-day mortality after RSV LRTI in all patients (OR 1.00 for each 1-point increase in RSI, 95% CI 0.98–1.04, $p=0.54$) or in the subgroup of HCT recipients (OR 1.00 per RSI-point, 95% CI 0.96–1.05, $p=0.84$) (Table 3). Peak-RSI was associated with 60-day mortality in all patients (OR 1.06 per RSI-point, 95% CI 1.04–1.08, $p<0.001$) and in HCT recipients (OR 1.06 per RSI-point, 95% CI 1.03–1.09, $p<0.001$). Similarly, delta-RSI was associated with 60-day mortality in all patients (OR 1.07 per RSI-point, 95% CI 1.05–1.10, $p<0.001$) and in HCT recipients (OR 1.08 per RSI-point, 95% CI 1.04–1.12, $p<0.001$). The ICC for all readers was 0.89 for RSI scoring. 60-day non-survivors had more frequent thoracic imaging than 60-day survivors (median CXRs within 30 days of LRTI: 7 vs. 2). The optimal peak-RSI cutoff value of 42.5 had a sensitivity of 54% and a specificity of 91% for association with 60-day mortality (positive predictive value: 69%, negative predictive value: 85%). Similarly, the optimal delta-RSI cutoff value of 18.5 had a sensitivity of 59% and specificity of 91% for association with 60-day mortality (positive predictive value: 71%, negative predictive value: 86%).

Refinement of 60-day mortality risk models using both immunodeficiency indices and RSI

In order to determine whether RSI improved the explanatory ability of 60-day mortality risk models using immunodeficiency indices as the primary variable, we constructed univariate models of RSI and immunodeficiency indices, and then combined RSI and individual immunodeficiency indices into bivariate logistic regression models. We used lymphopenia to measure immunodeficiency in all patients, and ISI and SID criteria to measure immunodeficiency in HCT recipients. Table 4 lists the discrimination and calibration of the univariate and bivariate models. In all patients, baseline-RSI had poor discrimination for 60-day mortality after RSV LRTI, while lymphopenia, peak-RSI and delta-RSI had fair discrimination. We did not incorporate baseline-RSI into bivariate models because baseline-

RSI was not significantly associated with 60-day mortality (Table 3). In separate bivariate models of lymphopenia with peak-RSI or delta-RSI, discrimination improved modestly in comparison to the lymphopenia univariate model, but only slightly in comparison to the peak-RSI and delta-RSI univariate models. Similarly, in bivariate models of lymphopenia and peak-RSI or delta-RSI, calibration improves modestly with comparison to the lymphopenia univariate model, but only slightly in comparison to the peak-RSI and delta-RSI models. This indicates that much of the improvement in these bivariate regression models is derived from the measurement of peak-RSI and delta-RSI. Addition of peak-RSI or delta-RSI to ALC significantly improved the explained variance in the outcome as measured by pseudo- R^2 ($p<0.001$).

In HCT recipients, baseline ISI and SID assessments of immunodeficiency had fair discrimination for the outcome of 60-day mortality after RSV LRTI. Similarly, peak-RSI and delta-RSI had fair discrimination for 60-day mortality, while baseline RSI had poor discrimination for 60-day mortality. Bivariate models of ISI with peak-RSI or delta-RSI and of SID with peak-RSI or delta-RSI had improved discrimination, with AUC values indicating good discrimination, and had superior calibration as assessed by Brier scores. Both discrimination and calibration improved in bivariate models as compared to univariate models of immunodeficiency or radiologic severity. Addition of peak-RSI or delta-RSI to baseline ISI or SID improved the explained variance in the outcome as measured by pseudo- R^2 ($p<0.001$). This indicates that while baseline immunodeficiency can predict 60-day mortality after RSV LRTI, further refinement of mortality risk estimates can be achieved by measuring progression of radiologic severity using peak-RSI or delta-RSI. Table 5 enumerates adjusted ORs for immunodeficiency variables and RSI in bivariate models. Peak-RSI and delta-RSI remained strongly associated with 60-day mortality after adjustment for lymphopenia, ISI, and SID in separate bivariate models.

We then constructed Kaplan-Meier survival curves for each stratum of immunodeficiency in HCT recipients, as defined by ISI and SID criteria, and further divided into HCT recipients with peak-RSI (Figure 2) or delta-RSI (Supplemental Figure 1) values above or below the optimal cutoff point identified from receiver-operating characteristics curves of univariate models of peak-RSI and delta-RSI. Importantly, p-values included in these subgroup analyses must be interpreted with caution because the number of subjects and events in each stratum were small. Figure 2 shows that subjects who had peak-RSI values above the optimal cutoff point (42.5) had impaired survival whether they were identified as low- (Figure 2A, $p=0.06$), moderate, (Figure 2B, $p=0.0001$), or high-risk (Figure 2C, $p=0.01$) by ISI. Similarly, subjects who had peak-RSI values above the optimal cutoff point had impaired survival whether they were identified as having MID (Figure 2D, $p=0.0003$), SID (Figure 2E, $p=0.0001$), or vSID (Figure 2F, $p=0.007$). The survival of subjects who had delta-RSI values above the optimal cutoff point was similarly impaired (Online Supplement).

Discussion

In this study, we show that by measuring progression of radiologic severity using RSI, estimates of mortality risk derived from baseline immunodeficiency indices can be

substantially refined. The addition of RSI to immunodeficiency indices using explanatory models of 60-day mortality after RSV LRTI results in improved discrimination, calibration, and explained variance in mortality as compared to univariate models using only baseline assessments of immunodeficiency. Furthermore, within each stratum of immunodeficiency severity, peak-RSI and delta- RSI can further identify patients at higher risk for death. Because progression of radiologic severity is strongly associated with 60-day mortality within each strata of immunodeficiency, progression of radiologic severity would be a logical clinical endpoint in a trial of anti-RSV therapy in HM patients.

Despite the discovery of RSV over 50 years ago, few drugs have been developed to treat RSV infections²². Aerosolized ribavirin has limited efficacy once RSV progresses to LRTI in HCT recipients^{5,23,24}. Oral ribavirin is safer and easier to administer than aerosolized ribavirin²⁵ and may have similar efficacy, though pivotal studies are lacking^{25,26}. Palivizumab, a monoclonal antibody that targets the F protein of human RSV is not useful in established LRTI²⁷, and efficacy in HCT recipients has not been established^{13,28}. Other agents have had limited success in treating RSV infections,^{29,30} and few new agents are being developed to treat RSV infections despite high mortality in HCT recipients¹⁵ and in other high-risk populations³¹.

Identifying high-risk populations using indices of immunodeficiency, such as ISI or SID criteria¹³⁻¹⁷, can help in trials of clinical superiority by enriching event rates in study populations with RSV LRTI. However, defining clinical superiority using mortality as an endpoint is problematic due to the difficulty of attribution to RSV infection, particularly in populations such as HM patients where competing risks are common¹¹. Radiologic severity is an attractive endpoint because it is generally attributable to infection in the absence of hypervolemia or pre-existing interstitial lung disease. We previously showed that in longitudinal models of time-varying radiologic severity, each 1-point increase in RSI was associated with a 13% increase in the hazard for mortality at 30 days after parainfluenza virus LRTI¹⁸. Reliability among readers was excellent, and explanatory models of peak-RSI and delta-RSI showed that increasing RSI was associated with higher rates of mortality and respiratory failure. In the current study, we show that RSI improves the discrimination, calibration, and explained variance of 60-day mortality models when added to models of baseline immunodeficiency. Furthermore, we show that within each stratum of immunodeficiency, values of peak-RSI and delta-RSI above the optimal cutoff points were associated with significantly impaired survival. Reliability among expert pulmonologists was also excellent. In aggregate, we show that measurement of RSI improves the ability of regression models to estimate the mortality risk of any given HM patient, regardless of baseline immunodeficiency.

Because 1) increases in RSI are generally attributable to worsening disease severity of LRTI, 2) progression of LRTI is more common than mortality and associated with substantial morbidity and cost³² and 3) RSI is an easily measurable and reproducible continuous variable, the use of RSI as an endpoint in clinical trials of antiviral therapies offers more statistical power to show clinical superiority over control arms. In the current study, we show that RSI is a reliable measure that is strongly associated with 60-day mortality in HM patients with RSV infection. Whether RSV infection progresses to LRTI, or paves the way

for a secondary bacterial LRTI³³, the prevention of LRTI progression is an important clinical goal. Therefore, in trials of anti-RSV therapies, radiologic severity would be well-suited for inclusion in a composite outcome of clinical failure alongside all-cause mortality, as recommended by the Food and Drug Administration in 2014³⁴. This could be applied to patients with RSV URTI, where prevention of any LRTI could serve as a primary endpoint, but severity of any LRTI as measured by RSI could be an important secondary endpoint. Alternatively, this could be applied to a population with early proven RSV LRTI, where prevention of further LRTI progression could be measured precisely using LRTI. For example, measurement of RSI at baseline and at day 14 after initiation of an anti-RSV therapy would allow for adjudication of clinical failure on the basis of whether disease severity progressed beyond a pre-defined threshold (e.g., peak-RSI of 40). Finally, because RSV infection predisposes to secondary bacterial pneumonias^{33,35}, and appropriate antiviral treatment may modify this predisposition^{36,37}, RSI could be useful in trials including possible RSV LRTI whether the cause of LRTI is a non-RSV pathogen (e.g. secondary bacterial pneumonia) or because the LRTI was caused by RSV, but considered “possible” because bronchoscopy was not performed. Indeed, with regards to 60-day mortality, we show that the definition of proven vs. possible RSV LRTI is less important than the degree of LRTI progression as measured by RSI. Because RSI is a precise, quantitative estimate of disease severity, it is likely that anti-RSV therapies that effectively reduce the severity of LRTI will be able to show superiority over control arms, particularly in populations facing high mortality rates with the current standards of care³⁸. Furthermore, as we show here and in a prior report¹⁸, reliability as measured by ICC is excellent, suggesting that using RSI measurements from multiple readers in larger multi-center studies would be a feasible and valid approach.

There are some limitations to our findings. Because this is a retrospective study, imaging studies were obtained on a clinical basis, and not systematically. This reduces the precision of our estimates of association between RSI and 60-day mortality because it is possible that we underestimated peak-RSI and delta-RSI in patients who died before chest imaging at peak severity, and because patients who were not symptomatic likely had less frequent chest imaging. Systematic measurement of RSI would help minimize measurement bias. Furthermore, although we performed logistic regression to estimate the discrimination and calibration of mortality models, more precise estimates of the association between RSI and 60-day mortality could be derived using extended Cox models with time-varying RSI measurements, such as in our prior study in HM patients with parainfluenza LRTI¹⁸. However, our estimate of the incremental mortality risk associated with a 1-point increase in RSI is similar in the current and prior studies, and our main goal was to show the additional improvement in the explanatory ability of mortality models of immunodeficiency with RSI. Because peak-RSI and delta-RSI occur after the development of LRTI, models including peak-RSI and delta-RSI must be interpreted as explanatory and not predictive models. We did not include RSI scores from chest computed tomographic images in this analysis due to sparse data and variable timing of imaging. Finally, prospective studies of LRTI using RSI are needed to determine optimal thresholds of peak-RSI and delta-RSI.

In conclusion, in a high-risk population of HM patients with RSV LRTI, we found that progression of radiologic severity as measured by RSI was associated with increased 60-day

mortality. Furthermore, the addition of RSI to baseline estimates of immunodeficiency improved the discrimination and calibration of 60-day mortality models. Thus, although baseline immunodeficiency partially predicts 60-day mortality after RSV LRTI in HM patients, further refinement of the estimates of the risk for mortality can be achieved by measuring RSI. RSI would be well suited for inclusion in a composite endpoint of clinical failure in clinical trials of antiviral agents developed for the treatment of RSV.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

AUC	area under the receiver-operating characteristics curve
ANC	absolute neutrophil count
ALC	absolute lymphocyte count
CI	confidence interval
CXR	chest X-ray
GGOs	ground glass opacities
GVHD	graft-versus-host disease
HCT	hematopoietic cell transplant
HM	hematologic malignancy
ISI	Immunodeficiency Scoring Index
LRTI	lower respiratory tract infection
OR	odds ratio
SID	Severe Immunodeficiency
URTI	upper respiratory tract infection

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Figure 1.

Kaplan-Meier survival curves for patients with and without lymphopenia (Figure 1A, log-rank $p=0.02$), with low-, moderate-, or high-risk immunodeficiency as graded by ISI (Figure 1B, $p=0.001$), and MID, SID, or vSID as graded by SID criteria (Figure 1C, $p=0.003$). Higher-grade immunodeficiency was associated with impaired survival.

Figure 2.

Kaplan-Meier survival curves for patients who had peak-RSI values above (blue line) or below (red line) 42.5, the optimal cutoff point as identified by univariate logistic regression models. Subjects who had peak-RSI values (“peak” in figure legends) above the optimal cutoff point had impaired survival whether they were identified as low-(Figure 2A, $p=0.06$), moderate, (Figure 2B, $p=0.0001$), or high-risk (Figure 2C, $p=0.01$) by ISI or whether they had MID (Figure 2D, $p=0.0003$), SID (Figure 2E, $p=0.0001$), or vSID as defined by SID criteria (Figure 2F, $p=0.007$).

Table 1.

Scoring Algorithm for the Radiologic Severity Index

Predominant Radiologic Pattern in Lung Zone	Pattern Score	Extent of Volumetric Radiologic Involvement	Volumetric Score
Normal lung	1	0% (Normal)	0
Ground glass opacities	2	1–24%	1
Consolidation	3	25–49%	2
		50–74%	3
		75–100%	4

Radiologic Severity Index (RSI) scores are calculated by multiplying the predominant pattern for each lung zone by the extent of volumetric radiologic involvement for that zone. The sum of scores from all six zones gives the final RSI, ranging from 0–72.

Table 2.

Characteristics of survivors and non-survivors at 60 days after RSV LRTI

	Survivors	Non-survivors	p-value
Number	114	41	
Mean age $\pm$ SD (years)	52 $\pm$ 14	55 $\pm$ 14	0.31
Sex, n (%) Female Male	50 (44) 64 (56)	11 (27) 30 (73)	0.06
Malignancy, n (%) Leukemia Lymphoma Myeloma	52 (46) 33 (29) 29 (25)	19 (46) 14 (34) 8 (20)	0.79
Type of HCT No HCT Autologous HCT Allogeneic HCT	54 (47) 23 (20) 37 (33)	17 (42) 5 (12) 19 (46)	0.23
Recent chemotherapy (within 1 month prior to RSV), n (%)	58 (51)	22 (54)	0.76
Corticosteroid (within 1 month prior to RSV diagnosis), n (%)	51 (45)	26 (63)	0.04
Neutropenia at RSV diagnosis (ANC <500 cells/mm ³) n (%)	30 (26)	20 (49)	0.008
Lymphopenia at RSV diagnosis (ALC <200 cells/mm ³), n (%)	33 (29)	22 (54)	0.005
Ribavirin therapy, n (%) None URTI stage LRTI stage	17 (15) 12 (11) 85 (75)	8 (20) 8 (20) 25 (61)	0.22
Proven RSV LRTI	13 (11)	12 (29)	0.008

Abbreviation. RSV: respiratory syncytial virus; LRTI: lower respiratory tract infection; HCT: hematopoietic cell transplant; ANC: absolute neutrophil count; ALC: absolute lymphocyte count; URTI: upper respiratory tract infection

Table 3.

Association of baseline, peak-, and delta-RSI with 60-day mortality after RSV LRTI RSI Score

RSI Score	OR per 1-point increase in RSI (95% CI)	p-value
All patients		
Baseline-RSI	1.00 (0.98–1.04)	0.54
Peak-RSI	1.06 (1.04–1.08)	<0.001
Delta-RSI	1.07 (1.05–1.10)	<0.001
HCT Recipients Only		
Baseline-RSI	1.00 (0.96–1.05)	0.84
Peak-RSI	1.06 (1.03–1.09)	<0.001
Delta-RSI	1.08 (1.04–1.12)	<0.001

Abbreviation. RSI: Radiologic Severity Index; RSV: respiratory syncytial virus; LRTI: lower respiratory tract infection; OR: odds ratio; CI: confidence interval

Table 4.

Discrimination and calibration of univariate and multivariate regression models for 60-day mortality after RSV LRTI

Model	AUC	Brier score	Pseudo-R ²
All patients			
Lymphopenia	0.62	0.18	0.04
Baseline-RSI	0.53	0.19	0.002
Peak-RSI	0.77	0.15	0.20
Delta-RSI	0.76	0.14	0.23
Peak-RSI and lymphopenia	0.78	0.14	0.21
Delta-RSI and lymphopenia	0.78	0.14	0.24
HCT Recipients Only			
ISI	0.69	0.18	0.10
SID Criteria	0.73	0.17	0.15
Baseline-RSI	0.52	0.20	0.004
Peak-RSI	0.74	0.15	0.20
Delta-RSI	0.74	0.14	0.24
Peak-RSI and ISI	0.80	0.14	0.25
Delta-RSI and ISI	0.81	0.13	0.29
Peak-RSI and SID	0.83	0.13	0.30
Delta-RSI and SID	0.85	0.12	0.36

Abbreviation: RSV: respiratory syncytial virus; LRTI: lower respiratory tract infection; AUC: area under the receiver-operating characteristics curve; RSI: Radiologic Severity Index; HCT: hematopoietic cell transplant; ISI: Immunodeficiency Scoring Index; SID: severe immunodeficiency criteria

Table 5.

Association of immunodeficiency and RSI with 60-day mortality after RSV LRTI in multivariate models

Model	Adjusted OR (95% CI)	p-value
All patients		
Lymphopenia and peak-RSI Lymphopenia Peak-RSI	1.9 (0.8–4.3) 1.06 (1.03–1.08)	0.15 <0.001
Lymphopenia and delta-RSI Lymphopenia Delta-RSI	1.9 (0.8–4.4) 1.08 (1.04–1.10)	0.16 <0.001
HCT Recipients Only		
ISI and peak-RSI	1.0	-
ISI-Low	1.7 (0.4–8.0)	0.51
ISI-Moderate	5.3 (1.0–28.8)	0.052
ISI-High Peak-RSI	1.06 (1.02–1.09)	<0.001
ISI and delta-RSI	1.0	-
ISI-Low	1.9 (0.4–10.3)	0.45
ISI-Moderate	6.5 (1.0–40.1)	0.045
ISI-High Delta-RSI	1.08 (1.04–1.12)	<0.001
SID and peak-RSI	1.0	-
MID	7.5 (1.4–40.8)	0.02
SID	8.6 (1.9–40.1)	0.006
vSID Peak-RSI	1.06 (1.03–1.09)	<0.001
SID and delta-RSI	1.0	-
MID	10.0 (1.5–64.1)	0.02
SID	12.0 (2.1–69.2)	0.005
vSID Delta-RSI	1.08 (1.04–1.13)	<0.001

Abbreviation: RSI: Radiologic Severity Index; RSV: respiratory syncytial virus; LRTI: lower respiratory tract infection; OR: odds ratio; CI: confidence interval; HCT: hematopoietic cell transplant; ISI: Immunodeficiency Scoring Index; SID: severe immunodeficiency criteria