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Improvement of Mortality Prognostication in Patients With Epidermal Necrolysis

The Role of Novel Inflammatory Markers and Proposed Revision of SCORTEN (Re-SCORTEN)

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IMPORTANCE Epidermal necrolysis is a severe cutaneous adverse reaction in which severe systemic inflammation results in extensive epithelial keratinocyte necrosis. The most commonly used prognostic score in epidermal necrolysis, the Severity-of-Illness Score for Toxic Epidermal Necrolysis (SCORTEN), was recently found to overestimate mortality in contemporary cohorts. Identification of independent prognostic markers may help to stratify risk more accurately.

OBJECTIVE This study evaluates the association between novel inflammatory markers and in-hospital mortality in patients with epidermal necrolysis to study the incremental prognostic value of these markers in combination with SCORTEN.

DESIGN, SETTING, AND PARTICIPANTS A retrospective cohort study was conducted over a 17-year period from 2003 to 2019. Patients were enrolled from Singapore General Hospital, the national referral center for epidermal necrolysis. A total of 196 patients with epidermal necrolysis were recruited, 4 (2%) of whom were excluded owing to incomplete data.

MAIN OUTCOMES AND MEASURES The main outcome assessed was the in-hospital mortality rate. Discrimination and calibration of risk scores were assessed using the area under the receiver operating characteristic curve (AUC) and calibration plot, respectively. Evaluation of the incremental prognostic value of these markers was done by comparing the AUC between the old and new risk score, and the use of net reclassification improvement (NRI) and integrated discrimination improvement (IDI).

RESULTS Among 192 total patients (median [IQR] age 56 [42-70] years; 114 [59.4%] women), there were 43 (22.4%) who did not survive to discharge. Of the novel inflammatory markers, only red cell distribution width to hemoglobin ratio was significant in predicting in-hospital mortality (odds ratio [OR] 3.55; 95% CI, 1.76-7.16; $P < .001$) after adjusting for SCORTEN. The RDW/Hb as applied in 4 risk groups showed similar discrimination to SCORTEN (AUC [95% CI]: RDW/Hb in 4 groups, 0.76 [0.69-0.84], vs SCORTEN, 0.78 [0.70-0.85], $P = .89$). When RDW/Hb was added to SCORTEN, the composite score Re-SCORTEN showed significantly better discrimination than SCORTEN alone (AUC [95% CI]: Re-SCORTEN, 0.83 [0.77-0.89], vs SCORTEN, 0.78 [0.70-0.85], $P = .02$). The overall NRI was 0.94 (95% CI, 0.68-1.20), $P < .001$. The IDI was 0.06 (95% CI 0.03-0.08), $P < .001$. Re-SCORTEN showed good calibration based on the calibration plot.

CONCLUSIONS AND RELEVANCE In this cohort of patients, RDW/Hb, an inexpensive and readily available marker, showed similar predictive accuracy with SCORTEN. Furthermore, when used in combination with SCORTEN, it also helped augment prognostic ability.

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Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare severe cutaneous adverse reactions typically induced by medications.[1] They are characterized by extensive epithelial keratinocyte apoptosis and necrosis, a process induced by drug-specific cytotoxic T cells and natural killer cells.[2] Various cytotoxic proteins and cytokines have been implicated as mediators of keratinocyte apoptosis.[3,4]

These adverse reactions are associated with significant mortality, ranging from 10% for SJS to up to 50% for TEN.[5] Risk stratification in SJS/TEN, therefore, constitutes a crucial part of patient evaluation and management. The Severity-of-Illness Score for Toxic Epidermal Necrolysis (SCORTEN), a severity-of-illness score widely used to prognosticate mortality in SJS/TEN, was developed and validated with patient data from 1979 to 1998.[6] It consists of 7 clinical and biochemical parameters with predicted probability of mortality ranging from 3.2% to 90.0%. Apart from its primary role in mortality prognostication, it functions secondarily as an internal control in therapeutic studies for immunomodulatory agents[7] and as a quality of care benchmark across different centers worldwide.[8] Nevertheless, increasing evidence suggests that SCORTEN overestimates mortality in the contemporary population.[9,10] A novel risk prediction model (ABCD-10) derived from 5 variables (age, body surface area, serum bicarbonate below 20 mmol/L, active cancer, and dialysis before admission) has been proposed for contemporary cohorts. However, a recent assessment and comparison of performance of ABCD-10 and SCORTEN showed that ABCD-10 was not superior to SCORTEN.[10] The identification of novel independent prognostic factors may help to stratify risk more accurately in patients with SJS/TEN.

Attention has recently focused on novel inflammatory markers such as red cell distribution width to hemoglobin ratio (RDW/Hb),[11] neutrophil to lymphocyte ratio (NLR),[12] platelet to lymphocyte ratio (PLR),[13] lymphocyte to monocyte ratio (LMR),[14] and mean platelet volume to platelet ratio (MPV/Plt).[15] These hematological indices are easily abstracted from the complete blood cell count, which is routinely collected in clinical practice. These biomarkers, which are closely tied to systemic inflammation, have been found to be significant prognostic markers in various malignant conditions and sepsis.

Severe systemic inflammation and disregulation is one of the hallmarks of SJS/TEN and the role of such biomarkers in prognostication in SJS/TEN remains unclear. The present study, therefore, aims to evaluate the association between the novel inflammatory markers and in-hospital mortality in a contemporary Asian cohort of SJS/TEN patients. The secondary aim was to examine the incremental prognostic value of these markers in combination with SCORTEN.

Key Points

Question Are novel inflammatory markers such as red cell distribution width to hemoglobin ratio (RDW/Hb) useful in prognostication of mortality in patients with epidermal necrolysis?

Findings In this cohort study of 192 patients in an Asian reference center, RDW/Hb was found to be strongly predictive of in-hospital mortality and bacteremia. Overall, RDW/Hb had similar discrimination to SCORTEN, and, when added to SCORTEN, improved the predictive accuracy of the composite score (Re-SCORTEN).

Meaning Measurement of RDW/Hb is a useful addition to SCORTEN in improving the mortality prognostication of epidermal necrolysis.

Methods

Patients and Data Collection

This was a retrospective cohort study conducted over a 17-year period from 2003 to 2019 at Singapore General Hospital, the national referral center for SJS/TEN. Diagnosis and classification of SJS/TEN was based on established consensus criteria with supportive histological evidence.[16] Patients with limited skin involvement (body surface area involved <10%) are nursed in the general ward while patients with more severe disease (body surface area involved >10%) are managed in the burns unit under the care of dermatologists, with onsite intensive care facilities. In combination with supportive care, immunomodulatory treatment prescribed during the study period includes intravenous immunoglobulin[17] and cyclosporine.[18] Patients in the earlier decade (2003-2010) were treated with intravenous immunoglobulin while patients in the later decade (2011-2019) were treated with cyclosporine. This study was approved by the Singhealth Institutional Review Board (CIRB Ref 2014/2011).

Patient demographics, comorbidities, SCORTEN, and parameters relevant to the calculation of the novel inflammatory markers were collected on admission. Each patient's RDW/Hb was computed by dividing the red cell distribution width by the hemoglobin. Similarly, NLR was calculated for each patient by dividing the total absolute neutrophil counts by the total absolute lymphocyte counts. The same applies for MPV/Plt, LMR, and PLR using the mean platelet volume, total absolute platelet counts, total absolute monocyte counts, and total absolute lymphocyte counts. In-hospital mortality was the outcome of interest in this examination.

Data Presentation and Statistical Analysis

Data were presented as medians for continuous data and percentages for categorical data. For univariate analysis, continuous data were analyzed using the Mann-Whitney *U* test. Multivariate analysis was performed adjusting for SCORTEN, a confounder in mortality prognostication in SJS/TEN. Malignancy, which is associated with the biomarkers, is a component of SCORTEN, and hence is implicitly adjusted for. Novel inflammatory markers which were found to be significantly associated with in-hospital mortality were converted from continuous data into categorical data for further examination. The optimum cutoff of the significant novel inflammatory markers were obtained via receiver operating characteristic (ROC) curve analysis.

Table 1. Baseline Characteristics of Patients With SJS/TEN

Parameters	Value, No. (%)
No.	192
Age, median (IQR), y	56 (42-70)
Gender	
Female	114 (59.4)
Male	78 (40.6)
Ethnicity	
Chinese	131 (68.2)
Malay	43 (22.4)
Others	18 (9.4)
Disease classification	
SJS	65 (33.9)
SJS/TEN overlap	61 (31.8)
TEN	66 (34.4)
SCORTEN, median (IQR)	2 (1-3)
Hypertension	88 (45.8)
Hyperlipidemia	46 (24.0)
Diabetes	47 (24.5)
Cardiovascular disease	39 (20.3)
Renal disease	28 (14.6)
Liver disease	8 (4.2)
Autoimmune disease	21 (10.9)
Malignant neoplasm	35 (18.2)
AIDS	5 (2.6)

Abbreviations: AIDS, acquired immune deficiency syndrome; SCORTEN, Severity-of-Illness Score for Toxic Epidermal Necrolysis; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.

Internal validation was performed by using the bootstrap technique with 200 resamples. The bias-corrected area under the curve (AUC) and bias-corrected calibration curve were generated to assess discrimination and calibration, respectively. The maximum absolute error was also reported to measure the predictive accuracy of the model. An AUC between 0.7 and 0.9 indicates fair to good discrimination while a calibration curve close to the ideal $y = x$ line indicates good calibration.

We assessed the improvement in discrimination by comparing the AUC in the model with and without the novel inflammatory marker, using the method of Delong et al.[19] The SCORTEN served as the baseline model. We assessed the incremental prognostic value of the novel inflammatory marker using the category-free net reclassification improvement (NRI).[20] The NRI captures the relative improvement in classification associated with the additional predictive variable. Positive values of the event NRI indicate that the investigated marker aids in the detection of patients who will eventually die while hospitalized. On the other hand, positive values of the non-event NRI indicate the marker's value in correctly decreasing risk estimates for survivors. The overall NRI is the sum of the 2 underlying components above and is reported as a proportion (possible range, −2.0 to 2.0). The integrated discrimination improvement (IDI) is a complementary measure that considers the actual change in calculated risk for each individual for those with and without events with the addition of the new marker.[20] The IDI is the ability of the larger model in relation to the smaller model to improve average sensitivity without sacrificing average specificity. The *P* values associated with NRI and IDI indicate whether the reclassification was statistically significant. Statistical analysis was performed using IBM SPSS version 22 and R version 3.4. Statistical significance was defined as $P \leq .05$.

Results

Patient Characteristics

Between 2003 and 2019, 196 consecutive patients were recruited. Information concerning novel inflammatory markers on admission was missing for 4 patients (2%), who were excluded from the study. A comparison of patients with complete data on novel inflammatory markers vs those without did not reveal any significant differences with respect to demographics, comorbidities, disease classification, SCORTEN, and in-hospital mortality. Of the 192 patients with complete data, there were 65 patients with SJS (33.9%), 61 with SJS/TEN overlap (31.8%), and 66 with of TEN (34.4%). The median age was 56 years (interquartile range 42-70 years). Baseline characteristics of the 192 patients are summarized in **Table 1**. The overall in-hospital mortality rate was 43 out of 192 (22.4%).

Novel Inflammatory Markers for Prognostication of Mortality on Admission

Among the novel inflammatory markers calculated on admission, only RDW/Hb was statistically significant in predicting in-hospital mortality (median [IQR]: patients who survived, 1.09 [0.95-1.37], vs patients who died, 1.50 [1.27-2.04]; $P < .001$). The other markers, MPV/Plt (median [IQR]: patients who survived, 0.04 [0.03-0.06], vs patients who died, 0.04 [0.03-0.06]; $P = .89$), NLR (median [IQR]: patients who survived, 5.01 [3.33-9.09], vs patients who died, 6.18 [3.84-11.03]; $P = .13$), LMR (median [IQR]: patients who survived, 1.74 [1.11-2.50], vs patients who died, 1.84 [1.19-3.16]; $P = .69$), and PLR (median [IQR]: patients who survived, 233.59 [159.54-362.47], vs patients who died, 215.95 [127.05-330.76]; $P = .28$), were not significant in predicting in-hospital mortality. After adjusting for SCORTEN, RDW/Hb remained statistically significant in predicting in-hospital mortality (OR, 3.55; 95% CI, 1.76-7.16; $P < .001$).

Adjusting for SCORTEN and time period (2003-2010 vs 2011-2019), RDW/Hb remained significant in predicting in-hospital mortality (OR, 3.63; 95% CI, 1.78-7.40; $P < .001$). Adjusting for the comorbidities, multivariate analysis showed that RDW/Hb remains significant in predicting in-hospital mortality (OR, 4.73; 95% CI, 2.32-9.64; $P < .001$). Adjusting for disease severity (SJS, SJS/TEN, TEN), RDW/Hb remained significant in predicting in-hospital mortality (OR, 6.09; 95% CI, 2.79-13.32; $P < .001$).

The optimal cutoff for RDW/Hb based on ROC curve analysis was 1.19 (OR, 9.68; 95% CI, 3.83-24.42; $P < .001$). Further

Table 2. RDW/Hb in 4 Risk Groups in Prognostication of Mortality[a]

	Mortality, No (%)		Unadjusted		Adjusted for SCORTEN	
RDW/Hb	No (n = 149)	Yes (n = 43)	*P* value[b]	OR (95% CI)	*P* value[b]	OR (95% CI)
<1.19	91 (93.8)	6 (6.2)		1 [Reference]		1 [Reference]
1.20-1.38	22 (68.8)	10 (31.3)	.001	6.9 (2.3-21.0)	.004	5.4 (1.7-17.2)
1.39-1.74	20 (62.5)	12 (37.5)	<.001	9.1 (3.1-27.1)	.002	5.9 (1.9-18.4)
>1.75	16 (51.6)	15 (48.4)	<.001	14.2 (4.8-42.1)	.001	7.4 (2.3-23.7)

Abbreviations: OR, odds ratio; RDW/Hb, red cell distribution width to hemoglobin ratio; SCORTEN, Severity-of-Illness Score for Toxic Epidermal Necrolysis.

[a] Percentages are calculated with the denominator being the total number of patients in each RDW/Hb group.

[b] *P* value ≤.05; variable is significant for predicting mortality during the hospital stay.

stratification beyond RDW/Hb of 1.19 carried prognostic significance—OR of mortality increased in tandem with a higher risk tier (**Table 2**). As applied in 4 risk groups, RDW/Hb had good discrimination (AUC [95% CI]: 0.76 [0.69-0.84]) and a good performance on the basis of the calibration plot (**Figure 1**). The maximum absolute error was low (0.024), indicating the model was a good fit for the data. The discrimination of RDW/Hb in the 4 risk groups was similar to the discrimination of SCORTEN (AUC [95% CI]: RDW/Hb in 4 groups, 0.76 [0.69-0.84], vs SCORTEN, 0.78 [0.70-0.85], *P* = .89).

Trend of RDW/Hb Across the First 5 Days of Hospitalization

Red cell distribution width to hemoglobin ratio across days 1, 3, and 5 of hospitalization was compared between patients who died and those who survived. Red cell distribution width to hemoglobin ratio retained its predictive power across the first 5 days of hospitalization (eTable 1 in the Supplement). As can be seen from the eFigure in the Supplement, RDW/Hb was consistently higher among patients who died compared with those who survived over the first 5 days of hospitalization. Mean difference (95% CI) in RDW/Hb between patients who died and survived was 0.44 (0.26-0.61, *P* < .001).

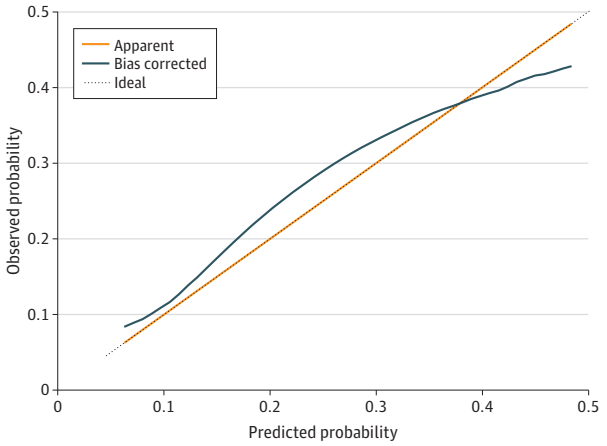
Incorporation of RDW/Hb Into SCORTEN (Re-SCORTEN)

Multivariate analysis yielded a score of 2 (derived by rounding the corresponding regression coefficient) for RDW/Hb 1.19 or higher when it was added to SCORTEN. The combination Re-SCORTEN had good discrimination (AUC, 0.83; 95% CI, 0.77-0.89) and good calibration as demonstrated in the calibration plot (**Figure 2**). The maximum absolute error is low (0.019), supporting its good calibration. Re-SCORTEN had a significantly better discrimination than SCORTEN alone (AUC [95% CI]: Re-SCORTEN, 0.83 [0.77-0.89] vs SCORTEN, 0.78 [0.70-0.85], *P* = .02).

For patients who died, the addition of RDW/Hb resulted in 37 (86.0%) being correctly reclassified as higher risk and 6 (14.0%) being incorrectly reclassified as lower risk, resulting in a net 72.0% (51.4%-92.8%) of the cohort being correctly classified. Conversely, for patients who survived, 91 (61.1%) were correctly reclassified as lower risk and 58 (38.9%) were incorrectly reclassified as higher risk, yielding a net of 22.2% (6.5%-37.8%) correctly classified. The overall NRI was 0.94 (95% CI, 0.68-1.20; *P* < .001). The IDI was 0.06 (95% CI, 0.03-0.08; *P* < .001). A positive IDI indicated that the new model with the addition of RDW/Hb is an improved model over the old model.

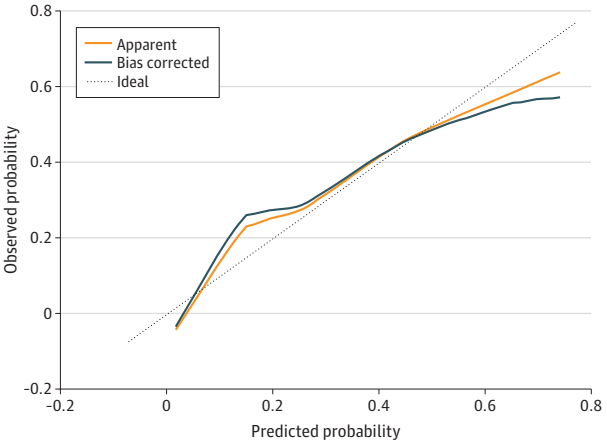
Table 3 summarizes the predicted probability of mortality for each score of Re-SCORTEN. The maximum score among

Figure 1. Calibration Curve of RDW/Hb in 4 Risk Groups



Abbreviation: RDW/Hb, red cell distribution width to hemoglobin ratio.

Figure 2. Calibration Curve of Re-SCORTEN, a Combination Score Integrating RDW/Hb into SCORTEN



Abbreviations: RDW/Hb, red cell distribution width to hemoglobin ratio; SCORTEN, Severity-of-Illness Score for Toxic Epidermal Necrolysis.

Table 3. Predicted Probability of Mortality for Each Score of Re-SCORTEN[a]

	No. of patients	Predicted probability of mortality, % (95% CI)
Re-SCORTEN		
0	13	1.9 (0.7-5.2)
1	31	4.3 (2.0-8.8)
2	32	8.7 (5.2-14.3)
3	28	14 (9.5-20.3)
4	33	23 (16.7-30.8)
5	25	35.3 (26.1-45.6)
6	21	54.5 (39.5-68.7)
7	7	73.2 (53.9-86.4)
8-9	2	86.1 (67.2-95.0)

Abbreviations: RDW/Hb, red cell distribution width to hemoglobin ratio; SCORTEN, Severity-of-Illness Score for Toxic Epidermal Necrolysis.

[a] Re-SCORTEN, composite score calculated by adding 2 points for RDW/Hb ≥1.19 to SCORTEN.

patients in the present study cohort was 8. Scores 8 and 9 were combined into 1 category due to rarity of events and for completeness, following the approach of the original SCORTEN article.[6]

Prediction of Development of Bacteremia During Hospitalization Using RDW/Hb

Red cell distribution width to hemoglobin ratio was also statistically significant in predicting bacteremia ($P < .001$). Using a similar cutoff of 1.19, RDW/Hb strongly predicted bacteremia (OR 5.94, 95% CI 2.81-12.54, $P < .001$). Further stratification beyond RDW/Hb of 1.19 carried prognostic significance—OR of bacteremia increased in tandem with a higher risk tier (eTable 2 in the Supplement).

Prediction of 1-Year Mortality After Discharge Using RDW/Hb

A total of 19 patients (9.9%) were lost to follow-up. Among patients who died within 1 year of discharge, the median time of death was 127 days (interquartile range [IQR], 65-296) after discharge. Mortality rates at 6 and 12 months after discharge were 11/130 (8.5%) and 19/130 (14.6%), respectively (eTable 3 in the Supplement). The RDW/Hb strongly predicted mortality up to 1 year from discharge (6 months: OR 4.71; 95% CI, 1.61-13.81; $P = .005$; vs 12 months: OR, 3.94; 95% CI, 1.52-10.25; $P = .005$). The RDW/Hb had good discrimination (6 months: AUC, 0.80; 95% CI, 0.69-0.91; vs 12 months: AUC, 0.75; 95% CI, 0.64-0.85) and calibration for postdischarge mortality.

Discussion

In the current study, we have evaluated various inflammatory indices and have demonstrated that RDW/Hb was a good prognostic marker for SJS/TEN with good calibration and discrimination. In addition, when incorporated with SCORTEN, the predictive accuracy improves. Prognostic performance of risk scores becomes increasingly inaccurate as time between their development and application increases. Risk models, hence, require periodic revalidation and when their predictive accuracy deteriorates, additional markers which have demonstrated prognostic significance should be tested for inclusion. A similar approach is used in the Acute Physiology and Chronic Health Evaluation (APACHE) score, one of the most commonly used intensive care unit prognostic scores, now in its fourth iteration.[21] While SCORTEN maintains good discrimination, its calibration has deteriorated with time.[10] Evaluation and incorporation of novel risk markers such as RDW/Hb are thus important in maintaining the predictive accuracy of mortality prognostication in patients with SJS/TEN.

A component of the complete blood cell count, RDW is a measure of the heterogeneity in the size of the circulating red blood cells. This measure has been shown to be strongly associated with all-cause mortality both in critically ill patients[22] and in community dwelling adults[23]—higher RDW has predicted mortality related to the cardiovascular system, cancer,[24] and sepsis.[25] This association was shown to be independent of anemia.[22-24] Although the biological mechanisms underlying the association between RDW and mortality are unclear, systemic factors that alter erythrocyte homeostasis such as inflammation have been proposed.[23]

Previous studies have demonstrated that independent of hemoglobin, RDW is positively related with inflammatory markers, such as C-reactive protein and erythrocyte sedimentation rate, indicating that anisocytosis may be reflective of an underlying inflammatory response.[26] Inflammatory cytokines such as tumor necrosis factor-alpha can alter erythropoiesis in a variety of ways: they can promote erythrophagocytosis or red cell apoptosis, induce myelosuppression of erythroid precursors, interfere with iron homeostasis, or inhibit erythropoietin production.[27,28] Both SJS and TEN are driven by cell-mediated cytotoxic reactions against keratinocytes, with various cytokines for keratinocyte apoptosis involved including tumor necrosis factor-alpha.[29] Therefore, RDW may be a reflection of the severity of inflammation in the disease, and correlate with mortality.

The model with RDW/Hb divided into 4 risk tiers is comparable with SCORTEN in terms of discrimination and calibration. The simplicity of the RDW/Hb score, which is easily computed from components of the complete blood cell count, carries certain advantages. While SCORTEN incorporates a comprehensive array of biochemical markers, the converse is that any missing marker would compromise the use of the score in patients. In aggregated cohorts with SJS/TEN, missing values may be a potential problem. Out of 369 European patients between 2003 and 2005, only 166 patients (45%) had complete data on the parameters of SCORTEN.[30] The degree of missing values was most severe for the 4 vital and laboratory parameters, with only 49% of patients having values for serum bicarbonate. The reason was attributed to different health care systems in different countries; for example, bicarbonate testing is hardly ever performed in German dermatology departments.[30] Red cell distribution width to hemoglobin ratio is a readily available biomarker that can be calculated based on the complete blood cell count, a test routinely done

in clinical practice. It does not require expensive instruments, complex calculations, or additional costs.

The integration of RDW/Hb with SCORTEN was associated with significant improvements in risk reclassification and enhanced predictive accuracy of SCORTEN. Through the use of RDW/Hb, a net 72.0% of patients with in-hospital mortality were reclassified as higher risk and a net 22.2% of patients who survived as lower risk. This reclassification was statistically significant. Using Re-SCORTEN, identification of patients at higher risk of mortality will be more precise, which could improve outcomes.

Strengths and Limitations

The retrospective study design with its inherent biases and the potential for referral bias are limitations. This study was also performed in an Asian population treated in a reference center. Further studies would be needed to validate the utility of RDW/Hb in other populations and settings.

Nonetheless, there were certain strengths to this study. To our knowledge, this is the first study that found an independent association and dose response relationship of RDW/Hb with mortality in patients with SJS/TEN. A total of 3 complementary techniques were used to evaluate the incremental prognostic value of RDW/Hb to SCORTEN—improvement in AUC, NRI, and IDI. In addition, study patients were managed in the same center under the same protocol, thereby reducing biases attributed to the center effect.

Conclusions

Although SCORTEN continues to be used in different domains in the treatment of SJS/TEN, its prognostic ability has deteriorated with time. Red cell distribution width to hemoglobin ratio is a novel biomarker, which is inexpensive and readily available, that can help to fill the gap. It not only shows similar predictive accuracy with SCORTEN, but when used in combination with SCORTEN, it also helps to augment its prognostic ability further. Accurate risk stratification is integral in improving patient evaluation and management and more precise estimation of survival benefits associated with immunomodulatory therapy. Future studies may consider validating the use of RDW/Hb and the composite model of Re-SCORTEN in prognostication of mortality in other cohorts of SJS/TEN.

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Concept and design: Koh, Lee.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Koh.
Critical revision of the manuscript for important intellectual content: All authors.
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