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Red blood cell distribution width provides additional prognostic value beyond severity scores in adult critical illness

Yan-Qiu Han[a], Li Yan[b], Lei Zhang[a], Pei-Heng Ouyang[a], Peng Li[a], Hemant Goyal[c], Zhi-De Hu[a,*]

[a] Department of Laboratory Medicine, The Affiliated Hospital of Inner Mongolia Medical University, Hohhot, China
[b] Department of Respiratory and Critical Care Medicine, The Affiliated Hospital of Inner Mongolia Medical University, Hohhot, China
[c] The Wright Center for Graduate Medical Education, 111 North Washington Avenue, Scranton, PA, 18503, USA.

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ABSTRACT

Background: The prognostic value of red blood cell distribution width (RDW) in critical illness remains controversial. The aim of this study was to investigate the prognostic value of on-admission RDW for in-hospital and 4-year mortality in adults with critical illness.

Methods: This is a retrospective cohort study from the Medical Information Mart for Intensive Care III (MIMIC III) database (version 1.4). Patients admitted to the intensive care unit (ICU) for the first time were included. Their on-admission RDW and severity scores were extracted with the Structured Query Language (SQL). The patients were categorized into a training set and a validation set. The relation of RDW to in-hospital and 4-year all-cause mortality was analyzed using receiver operating characteristic (ROC) curve, Kaplan-Meier curve, Cox model, net reclassification index (NRI), integrated discriminatory index (IDI) and nomogram.

Results: A total of 36,532 patients (21,090 in training and 15,442 in validation set) were included in this study. Increased RDW was significantly associated with higher in-hospital and 4-year mortality. The prognostic value of RDW for 4-year mortality was independent of conventional severity scores. Using conventional severity scores as covariates the continuous NRI and IDI of RDW for in-hospital mortality were around 0.3–0.5 and 0.01–0.03, respectively. For 4-year mortality the NRI was around 0.2–0.3 and IDIs was around 0.03–0.08.

Conclusions: Admission RDW predicts both in-hospital and 4-year mortality in adult patients with critical illness admitted in the ICU, and can provide additional prognostic values beyond conventional clinical severity scores.

1. Introduction

Red blood cell distribution width (RDW) can be automatically measured by modern hematological analyzers, and is reported along with other hematological parameters. It is a parameter that reflects the size variation among the red blood cells [1]. Traditionally, it is used as a practical and effective test to differentiate thalassemia and iron deficiency anemia [2]. However, accumulated published studies have revealed that RDW can also serve as a prognostic factor in various hematological and non-hematological diseases such as multiple myeloma [3], heart failure [4], solid cancers [5,6] and gastrointestinal diseases [7]. Although some studies with small sample size have reported that increased RDW is associated with worse short-term outcomes in patients with critical illness [8–13], it remains unclear whether RDW can improve the prognostic value of conventional prognostic scores [14,15]. In addition, the long-term prognostic value of RDW in critical illness is unclear. Here, we performed a study to investigate the long-term prognostic value of RDW in the adult critical illness.

2. Methods

2.1. Database and subjects

Similar to our previous studies [16,17], this is a retrospective cohort study from the Medical Information Mart for Intensive Care III (MIMIC III) database (version 1.4). The MIMIC III is a clinical database comprising the information of 38,645 adults and 7875 neonates with over 58,000 hospital admissions. All the subjects were admitted to the intensive care units (ICUs) of Beth Israel Deaconess Medical Center between 2001 and 2012 [18,19]. The Institutional Review Boards (IRB) of the Massachusetts Institute of Technology (MIT) approved the establishment of this database. Therefore, informed consent was waived for our study. The database is publicly accessible, and an online training course is required before accessing it.

* Corresponding author.
E-mail address: hzdlj81@163.com (Z.-D. Hu).

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The patients' information in this database is anonymous and deidentified, and the dates (e.g., admission time, date of birth) are shifted into the future by a random offset to protect privacy. The diagnoses, laboratory tests, fluid balance, demographic characteristics and medications of each patient are recorded in the database. Out-of-hospital mortality date is acquired from the social security death registry. Two types of clinical information systems, named *metavision* and *carevue*, are used to obtain data in this database. *Metavision* records the date of death up to 90 days and *carevue* records the dates of death up to 4 years. In this study, we defined the *carevue* patients as a training set and *metavision* patients as a validation set.

2.2. Data extraction

Patients aged > 18 years old were included in this study. Patients without the estimation of RDW value within 24 h after ICU admission were excluded. If a patient was admitted to ICU for more than once, only the data during their first admission during the study period were included which was called the index set. If a patient underwent multiple RDW tests during the first 24 h of ICU admission, then only the first RDW value was used.

We used the structured query language (SQL) to extract the data within the first 24 h after the ICU admission. Following data were extracted: RDW, comorbidities, demographic characteristics, severity scores such as Acute Physiology Score III (APS III) [20], Simplified Acute Physiology Score (SAPS II) [21], Systemic Inflammatory Response Syndrome (SIRS) [22], Sequential Organ Failure Assessment (SOFA) [23], Oxford Acute Severity of Illness Score (OASIS) [24], Modified Logistic Organ Dysfunction System (MLODS) [25] and Quick Sequential Organ Failure Assessment (qSOFA) [26]. All the scripts used to calculate these severity scores and comorbidities were available from GitHub website (https://github.com/MIT-LCP/mimic-code/tree/master/concepts, date of access: January 2019).

2.3. Statistical analysis

Normal distribution of continuous variables was tested using the Kolmogorov-Smirnov test. The Mann-Whitney *U* test was used to compare continuous variables in two groups. Receiver operating characteristic (ROC) curve analysis was used to analyze the relation between RDW and in-hospital mortality. Kaplan-Meier curve and Cox hazard proportional model were used to analyze the relationship between baseline RDW and 4-year mortality. Because some variables (e.g., age, renal function) in the conventional severity scores are overlapped, and including too many covariates in a multivariable model may increase the risk of overfitting [27], we only adjusted one score at each multivariable analysis. Net reclassification index (NRI) and integrated discriminatory index (IDI) were used to analyze whether RDW provides additional prognostic value beyond the conventional scores [28]. Time-dependent ROC curve was used to analyze the predictive accuracy of RDW for all-cause mortality RDW with different follow-up time [29]. R (version 3.5.0) software with packages of *CBCgrps* [30], *smoothHR* [31], *predictABEL* [32], *survIDINRI*, *rms* [33] and *survAUC* were used to analyze data. *P* value of < 0.05 was defined to have statistical significant in the analysis.

3. Results

3.1. Characteristics of the subjects

We included 36,532 subjects in this study. A total of 21,090 of the included subjects were categorized into the training set, and the remaining15,442 subjects were categorized into the validation set. The clinical characteristics of the training and validation sets were summarized in Table 1. The in-hospital mortality rates in the training and validation sets were 11.5% and 9.5%, respectively.

Table 1
Clinical characteristics of the subjects.

	Training set (n = 21,090)	Validation set (n = 15,442)
Age, years	66 (52–78)	66 (53–78)
Gender, Male%	12,050 (57%)	8674 (56%)
Ethnicity, White%	14,740 (70%)	11,161 (72%)
Admission type		
Emergency	16,876 (80%)	12,766 (83%)
Elective	3401 (16%)	2483 (16%)
Urgent	813 (4%)	193 (1%)
Comorbidity		
Congestive heart failure	5523 (26%)	3367 (21%)
Hypertension	10,383 (49%)	9152 (59%)
Chronic pulmonary disease	3831 (18%)	3508 (23%)
Renal failure	2110 (10%)	2395 (16%)
Liver disease	1636 (8%)	1711 (11%)
AIDS	145 (1%)	64 (0%)
Anemia	887 (4%)	694 (4%)
Coagulopathy	1928 (9%)	1917 (12%)
Weight loss	582 (3%)	810 (5%)
Alcohol abuse	1506 (7%)	1541 (10%)
Cancer	1796 (9%)	1638 (11%)
Hypothyroidism	1667 (8%)	1806 (12%)
Diabetes	5082 (24%)	4014 (26%)
Severity score		
qSOFA	2 (1–2)	2 (1–2)
OASIS	31 (25–37)	31 (25–37)
SAPS II	32 (24–42)	33 (25–42)
SOFA	3 (2–6)	3 (2–6)
SIRS	3 (2–4)	3 (2–3)
MLODS	2 (1–4)	2 (1–4)
APS III	38 (28–50)	38 (29–51)
Outcome		
In-hospital mortality	2433 (11.5%)	1467(9.5%)

Note: Continuous variables were presented as median (quartile), and categorical variables were presents as an absolute number (percentage). APS III, Acute Physiology Score III; SAPS II, Simplified Acute Physiology Score; SIRS, Systemic Inflammatory Response Syndrome; SOFA, Sequential Organ Failure Assessment; OASIS, Oxford Acute Severity of Illness Score; MLODS, Modified Logistic Organ Dysfunction System; qSOFA, Quick Sequential Organ Failure Assessment.

3.2. RDW and hospital mortality

As shown in Fig. 1A, subjects in the training set who died in the hospital had significantly higher RDW than survivors. The ROC curves for RDW, SOFA, SAPS II, OASIS, MLODS, SIRS, APSII had the highest AUC, followed by APS III, OASIS, MLODS, SOFA, and RDW. These results indicate that the predictive accuracy of RDW for in-hospital mortality is inferior to that of APS III, OASIS, MLODS, and SOFA.

Next, we analyzed whether RDW can improve the predictive values of these severity scores for in-hospital mortality using NRI and IDI. The results are summarized in Table 2. Notably, RDW could improve the predictive values of these severity scores for in-hospital mortality.

3.3. RDW and 4-year mortality

We categorized the patients into four groups according to their RDW quartiles. Fig. 2A is the Kaplan-Meier curve depicting the relationship between RDW and 4-year all-cause mortality of the patients. The patients with higher RDW had significantly higher 4-year mortality ($p < .01$). Fig. 2B is a curve that depicts the hazard ratio of APSIII adjusted RDW for all-cause mortality. Other severity scores adjusted RDW's curves were also found to be similar (data not shown). Fig. 2C is a time-dependent ROC curve depicting the relationship between AUC of RDW for predicting all-cause mortality and follow up time. Notably, the AUC of RDW increased with follow up time while the AUCs of severity scores decreased. Fig. 3 is a nomogram incorporating RDW and APS III

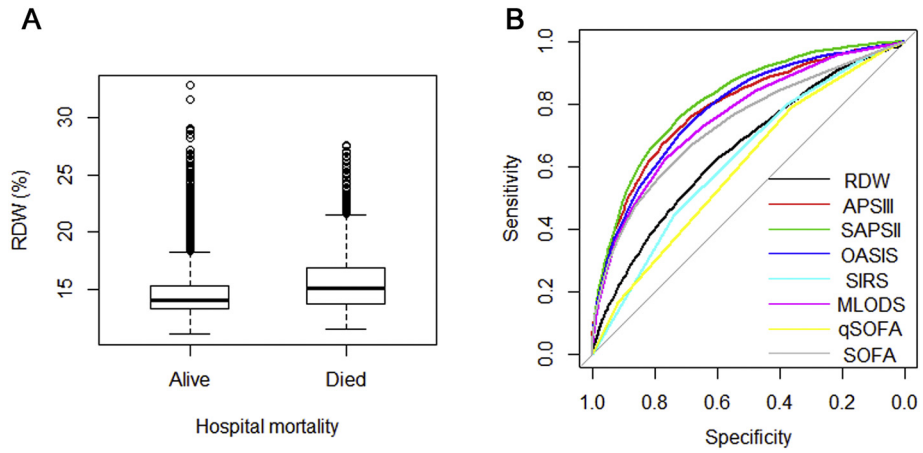

Fig. 1. RDW and the in-hospital mortality of the subjects in the training set.
Note: Abbreviations of severity scores were listed in Table 1.

as predictors of all-cause mortality.

Results of multivariable Cox model, NRI and IDI are summarized in Table 3. RDW was independently associated with 4-year all-cause mortality after the conventional severity scores were adjusted. NRI and IDI analysis revealed that RDW could improve the prognostic value of conventional severity scores.

4. Discussion

Some interesting findings have been obtained in this study. First, increased RDW was associated with higher in-hospital mortality, which is consistent with previous studies [10,13,34]. Although the predictive accuracy of RDW for in-hospital mortality is inferior to that of APS III, SAPS II, OASIS and MLODS, the addition of RDW could improve the predictive accuracy of these scores, as indicated by NRI and IDI analyses. Second, increased RDW was associated with 4-year mortality in the critical illness. Even within the reference interval (11.5% ~ 14.5% [35]), RDW was able to predict the all-cause mortality of the critical illness. Third, the prognostic value of RDW was independent of severity scores, as indicated by the results of Cox regression analysis. Furthermore, RDW could provide additional prognostic information beyond these conventional severity scores. Last but not least, we constructed a nomogram to depict the relationship between RDW and 4-year all-cause mortality, which may help identify the patients at higher risk of long-term mortality after critical illness.

Although some studies have investigated the prognostic value of RDW in critical illness [9,10,13,34], our study has its strength. First, to the best of our knowledge, the sample size of our study is larger than other similar studies. Therefore, the statistical power in our study was sufficient, and our results might be more reliable. Second, although some studies have investigated the long-term prognostic value of RDW in adult critical illness, the follow-up time in these studies was less than one year. By contrast, the follow-up duration in our study was four years. Therefore, our study extends the current knowledge about the long-term prognostic value of RDW in critical illness. Third, we used a training set and validation set to investigate the prognostic value of RDW, and the short-term prognostic value of RDW was reproduced in the validation set. These results also indicated that the results of our study are valid. Fourth, previous studies only reported that RDW can provide additional prognostic information beyond SAPII [9], acute physiology, age, chronic health evaluation (APACHE score) [15]. We found that RDW also provides added prognostic information beyond

Table 2
Analyzing the incremental prognostic value of RDW beyond severity scores with NRI and IDI.

	NRI				IDI			
	Estimate (95% CI)	p	Event	Nonevent	Estimate (95% CI)	p	Event	Nonevent
Training set (n = 21,090)								
SAPS II	0.28 (0.24–0.32)	< 0.01	−0.11	0.39	0.0098 (0.0075–0.0122)	< 0.01	0.0087	0.0011
APS III	0.27 (0.22–0.31)	< 0.01	−0.10	0.37	0.0084 (0.0063–0.0105)	< 0.01	0.0075	0.0010
OASIS	0.39 (0.35–0.43)	< 0.01	−0.03	0.41	0.0239 (0.0202–0.0276)	< 0.01	0.0211	0.0028
MLODS	0.34 (0.30–0.38)	< 0.01	−0.06	0.40	0.0166 (0.0136–0.0195)	< 0.01	0.0147	0.0019
SOFA	0.28 (0.24–0.32)	< 0.01	−0.07	0.35	0.0114 (0.0091–0.0138)	< 0.01	0.0101	0.0013
SIRS	0.44 (0.40–0.48)	< 0.01	0.02	0.42	0.0340 (0.0303–0.0377)	< 0.01	0.0300	0.0039
qSOFA	0.43 (0.39–0.47)	< 0.01	0.01	0.42	0.0341 (0.0305–0.0377)	< 0.01	0.0302	0.0039
Validation set (n = 15,442)								
SAPS II	0.33 (0.28–0.38)	< 0.01	−0.08	0.41	0.0111 (0.0080–0.0142)	< 0.01	0.0100	0.0010
APS III	0.31 (0.26–0.36)	< 0.01	−0.09	0.40	0.0094 (0.0065–0.0123)	< 0.01	0.0085	0.0009
OASIS	0.40 (0.36–0.45)	< 0.01	−0.02	0.42	0.0200 (0.0158–0.0243)	< 0.01	0.0181	0.0019
MLODS	0.39 (0.34–0.44)	< 0.01	−0.04	0.43	0.0187 (0.0148–0.0226)	< 0.01	0.0169	0.0018
SOFA	0.30 (0.25–0.36)	< 0.01	−0.06	0.36	0.0109 (0.0078–0.0139)	< 0.01	0.0098	0.0010
SIRS	0.46 (0.40–0.51)	< 0.01	0.02	0.44	0.0297 (0.0256–0.0338)	< 0.01	0.0269	0.0028
qSOFA	0.45 (0.40–0.51)	< 0.01	0.01	0.45	0.0305 (0.0265–0.0346)	< 0.01	0.0276	0.0029

Each score listed in the table was used as a basic model. We added RDW to the basic model to create a new model, and analyzed whether the new model provides additional prognostic information beyond the basic model with NRI and IDI. Considering that the scores are highly correlated, we only used one score at each NRI and IDI analyses. The abbreviations of severity scores were the same as Table 1.NRI, net reclassification index; IDI, integrated discriminatory index; CI, confidence interval.

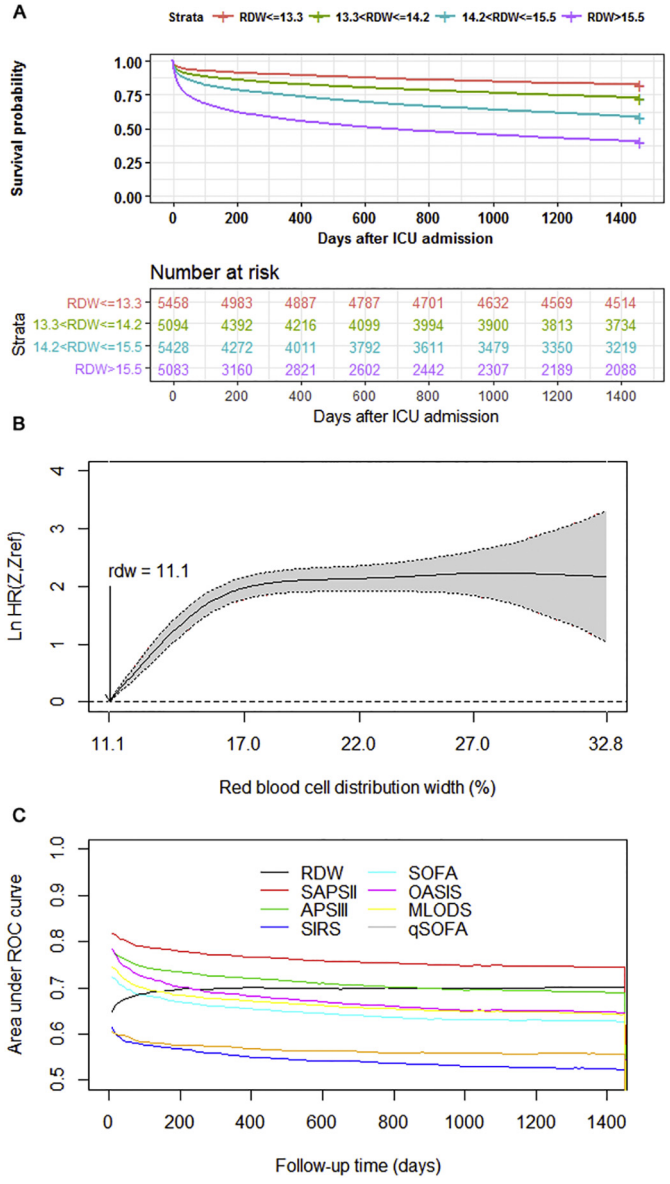

Fig. 2. RDW and 4-year all-cause mortality.
A, Kaplan-Meier curves of RDW; B, smoothed HR curve for RDW after adjusting APS III; C, time-dependent ROC curves of RDW and severity scores. Note: For abbreviations of severity scores, please refer Table 1.NRI, net reclassification index; IDI, integrated discriminatory index; CI, confidence interval.

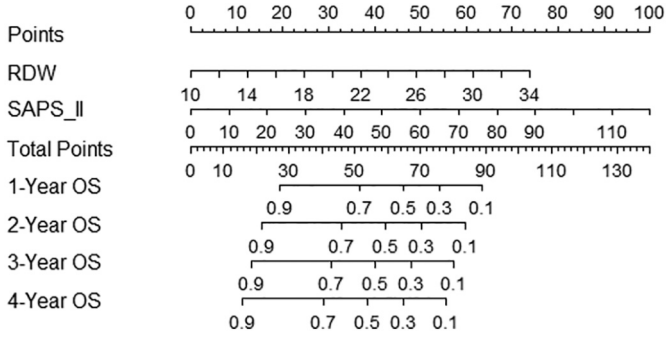

Fig. 3. A nomogram depicting RDW, SAPSII score and 4-year mortality.

other conventional severity scores, including MLODS, OASIS, SIRS, SOFA, and qSOFA. Fifth, we found that RDW could negatively affect the long-term outcomes of critical illness even within the reference interval. This has not been revealed by previous studies. Sixth, as indicated by the time-dependent ROC curve, we found that although the short-term prognostic value of RDW is inferior to that of conventional severity scores, its prognostic value increased with the duration of the follow-up time. By contrast, the prognostic value of conventional severity scores decreased. These results indicate that the effect of acute events on the long-term prognosis of critical illness may be weak and RDW represent a reliable test to predict long-term prognosis in critical illness. Seventh, we constructed a nomogram to depicting the relationship between long-term outcomes of critical illness, which has not been adopted by previous studies.

Estimating the prognosis of critical illness can significantly affect the treatment approach selection and is thus crucial for their management. Some severity scores have been developed to predict the outcome of critical illness. However, some limitations of these severity scores should be noted. First, these scores are far from perfect to predict the outcomes of critical illness. Therefore, more tools are needed to better predict the outcomes of critical illness. Second, these scores are cumbersome as they encompass various clinical information including patients' symptoms, signs, laboratory tests, microbiology findings etc. In the absence of any of this information, these scores cannot be used. Compared with these scores, RDW is an easily obtained, inexpensive test with short turnaround time (TAT), which may facilitate its use in the clinical practice. Furthermore, although the predictive accuracy of RDW for short-term prognosis is inferior to some of the conventional severity scores, its predictive accuracy for long-term prognosis was superior to these scores.

The possible mechanisms between RDW and prognosis of critical illness remains unknown. RDW is affected by various factors such as renal function [36], anemia [37], age [38] and inflammation response [39]. These factors may mediate the relationship between RDW and prognosis of critical illness. Increased RDW is caused by perturbation of erythrocyte biology, which have a crucial role in the onset and progression of several human disorders, such as liver disease, heart failure and caner [40].

Our work has some limitations. First, it is a retrospective cohort study and the representativeness of the study cohort may be a problem. Second, we only considered severity scores as the confounding factors when analyzing the prognostic value of RDW. More confounding factors, especially the treatment approach, should be considered by further studies. Third, our study subjects were adult critical illness, which encompass various types of disease states. Further studies are needed to clarify the prognostic value of RDW in a specified type of critical illness.

5. Conclusions

In conclusion, our study revealed that RDW prognosticate both in-hospital and 4-year mortality of adult critical illness, and it can provide additional prognostic values beyond conventional severity scores. Further prospective cohort studies are needed to validate our findings.

Authors' contributions

ZD Hu conceived and designed the study; ZD Hu extracted the data. ZD Hu, L Zhang, L Yan, PH Ouyang, P Li and YQ Han analyzed the data; L Zhang, L Yan, PH Ouyang, P Li and YQ Han drafted the manuscript; ZD Hu and Goyal H critically reviewed and revised the manuscript. All authors approved for submission.

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Table 3
RDW and 4-year mortality.

Adjusted severity scores	HR (1%)		NRI				IDI			
	Estimate (95% CI)	p	Estimate (95% CI)	p	Events	Nonevents	Estimate (95% CI))	p	Events	Nonevents
SAPS II	1.17 (1.16–1.18)	< 0.01	0.22 (0.21–0.24)	< 0.01	0.49	−0.27	0.035 (0.029–0.039)	< 0.01	0.021	0.013
APS III	1.17 (1.16–1.18)	< 0.01	0.23 (0.22–0.25)	< 0.01	0.50	−0.27	0.041 (0.035–0.046)	< 0.01	0.025	0.016
OASIS	1.21 (1.20–1.22)	< 0.01	0.26 (0.25–0.27)	< 0.01	0.51	−0.25	0.059 (0.053–0.064)	< 0.01	0.036	0.023
MLODS	1.19 (1.18–1.20)	< 0.01	0.26 (0.24–0.27)	< 0.01	0.51	−0.26	0.053 (0.048–0.058)	< 0.01	0.033	0.021
SOFA	1.19 (1.18–1.20)	< 0.01	0.24 (0.23–0.26)	< 0.01	0.50	−0.26	0.049 (0.042–0.055)	< 0.01	0.030	0.020
SIRS	1.22 (1.21–1.23)	< 0.01	0.28 (0.27–0.30)	< 0.01	0.52	−0.24	0.076 (0.069–0.083)	< 0.01	0.047	0.028
qSOFA	1.22 (1.21–1.23)	< 0.01	0.28 (0.27–0.29)	< 0.01	0.53	−0.24	0.075 (0.067–0.081)	< 0.01	0.047	0.028

Note: HR, hazard ratio; CI, confidence interval; IDI, integrated discriminatory index; CI, confidence interval; NRI, net reclassification index. The abbreviations of severity scores were the same as Table 1. Because some variables (e.g., age, renal function) in the conventional severity scores are overlapped, and including too many covariates in a multivariable model may increase the risk of overfitting, we only adjusted one score at each multivariable analysis.

Declaration of Competing Interest

The funding organization(s) played no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the report for publication.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cca.2019.08.008.

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