


BMJ Open Early prediction of in-hospital mortality in patients with congestive heart failure in intensive care unit: a retrospective observational cohort study

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ABSTRACT

Objective Congestive heart failure (CHF) is a clinical syndrome in which the heart disease progresses to a severe stage. Early diagnosis and risk assessment of death of patients with CHF are critical to prognosis and treatment. The purpose of this study was to establish a nomogram that predicts the in-hospital death of patients with CHF in the intensive care unit (ICU).

Design A retrospective observational cohort study.

Setting and participants Data for the study were from 30 411 patients with CHF in the Medical Information Mart for Intensive Care database and the eICU Collaborative Research Database (eICU-CRD).

Primary outcome In-hospital mortality.

Methods Univariate logistic regression analysis was used to select risk factors associated with in-hospital mortality of patients with CHF, and multivariate logistic regression was used to build the prediction model. Discrimination, calibration and clinical validity of the model were evaluated by AUC, calibration curve, Hosmer-Lemeshow χ^2 test and decision curve analysis, respectively. Finally, data from 15 503 patients with CHF in the multicentre eICU-CRD were used for external validation of the established nomogram.

Results The inclusion criteria were met by 15 983 subjects, whose in-hospital mortality rate was 12.4%. Multivariate analysis determined that the independent risk factors were age, race, norepinephrine, dopamine, phenylephrine, vasopressin, mechanical ventilation, intubation, hepatic failure (HepF), heart rate, respiratory rate, temperature, systolic blood pressure (SBP), anion gap (AG), blood urea nitrogen (BUN), creatinine, chloride, mean corpuscular volume (MCV), red blood cell distribution width (RDW) and white cell count (WCC). The C-index of the nomogram (0.767, 95% CI 0.759 to 0.779) was superior to that of the traditional Sequential Organ Failure Assessment, Acute Physiology Score III and Get With The Guidelines Heart Failure scores, indicating its discrimination power. Calibration plots demonstrated that the predicted results are in good agreement with the observed results. The decision curves of the derivation and validation sets both had net benefits.

Conclusion The 20 independent risk factors for in-hospital mortality of patients with CHF were age, race, norepinephrine, dopamine, phenylephrine, vasopressin, mechanical ventilation, intubation, HepF, heart rate, respiratory rate, temperature, SBP, AG, BUN, creatinine,

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ Logistic regression analysis was used to select variables associated with in-hospital mortality of patients with congestive heart failure (CHF).
- ⇒ The nomogram to predict mortality of patients with CHF in the intensive care unit was built based on the included risk factors.
- ⇒ The application of the nomogram can provide clinical decision-making opinions for clinicians to improve the prognosis of inpatients with CHF.
- ⇒ Discrimination, calibration and clinical validity of the nomogram were evaluated by AUC, calibration curve, Hosmer-Lemeshow χ^2 test and decision curve analysis, respectively.

chloride, MCV, RDW and WCC. The nomogram, which included these factors, accurately predicted the in-hospital mortality of patients with CHF. The novel nomogram has the potential for use in clinical practice as a tool to predict and assess mortality of patients with CHF in the ICU.

INTRODUCTION

Congestive heart failure (CHF) is a severe clinical syndrome in which the cardiac structure and/or function are abnormal. Inadequate pumping or filling capacity of the ventricles, inability of the cardiac blood output to meet the body's metabolic demands, hypoperfusion of tissues and organs, and concomitant pulmonary and systemic congestion are common causes of CHF. Increased internal pressure causes typical symptoms such as dyspnoea and fatigue, and may also be accompanied by typical signs (eg, jugular vein distention, pulmonary rales and peripheral oedema).¹ Heart failure can be classified into left heart failure, right heart failure or whole heart failure depending on its location. In addition, according to severity, heart failure can be divided into acute heart failure and chronic heart failure.²

CHF is not a separate disease but a complicated phenomenon that occurs after various other heart diseases develop to a more serious level, with relatively high morbidity and mortality. Patients are usually admitted to the intensive care unit (ICU) for treatment. In the USA, approximately 10%–15% of hospitalised patients with heart failure are admitted to the ICU.^{3,4} Despite major breakthroughs in the diagnosis and treatment in recent years, mortality in heart failure remains high and the 5-year survival rate is similar to that of malignant tumours.⁵

There have been many predictive models for the prognosis of patients with CHF, but due to various reasons these models have not been widely used in clinical practice.^{6–8} The Get With The Guidelines Heart Failure (GWTGHF) risk score, previously proposed by Peterson *et al*,⁹ used commonly used clinical variables to predict in-hospital mortality and provided clinicians with a valid risk stratification tool, but was proposed for a non-contemporary cohort,¹⁰ which may have limited its applicability to current practice. Traditional critical care scoring systems for patients in the ICU, including the Sequential Organ Failure Assessment (SOFA) and the Acute Physiology Score III (APSO), are often not as accurate when applied to patients with CHF.

Due to the insufficiency of existing predictive models, a more simple, efficient and accurate clinical application tool is needed to predict mortality of hospitalised patients with CHF. Therefore, we aimed to establish a more authoritative, efficient and easy-to-follow in-hospital mortality prediction model for patients with CHF based on the data of patients with CHF in a large critical illness database (Medical Information Mart for Intensive Care, MIMIC-IV). This will provide some reference for medical staff to improve the poor prognosis of patients with CHF in the process of clinical practice (in the process of clinical practice, it can provide certain guiding value for medical staff to improve the poor prognosis of CHF patients).

METHODS

Data source

MIMIC-IV is a single-centre, free-access database that contains data on more than 40 000 ICU patients covering the period from 2008 to 2019.¹¹ Another intensive care database, the eICU Collaborative Research Database (eICU-CRD), was used to validate the findings. The eICU-CRD is a database of multiple, longitudinal, multi-centre retrospective cohort studies of patients in 335 ICUs in the USA from 2014 to 2015.¹² It includes demographic records, physiological indicators for bedside monitoring, diagnoses based on the International Classification of Disease-9 (ICD-9) code and other laboratory data.

Study population

In the MIMIC-IV database, the ICD-9 code for screening CHF is 4280. Similarly, the ICD-9 code for CHF was used to screen patients from the eICU-CRD. For patients with multiple ICU admissions, only data from the first

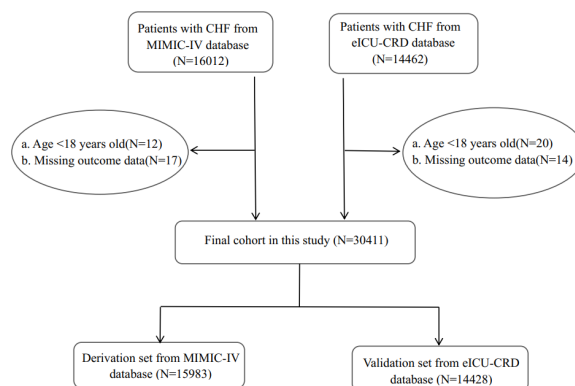


Figure 1 Flow chart of patient selection. CHF, Congestive heart failure; eICU-CRD, eICU Collaborative Research Database; MIMIC-IV, Medical Information Mart for Intensive Care.

admission were considered. Exclusion criteria were age <18 years and missing outcome data. After applying these criteria, the study included 15 983 and 14 428 patients with CHF in the derivation cohort and in the validation cohort, respectively. The selection process is demonstrated in figure 1.

Data retrieval and outcomes

Based on previous studies, the demographic characteristics included age, race, sex, severity score (SOFA and APSO scores), comorbidities (eg, chronic obstructive pulmonary disease (COPD), diabetes, hepatic failure (HepF) and acute myocardial infarction (AMI)), drug information (norepinephrine, dopamine, epinephrine, phenylephrine and vasopressin), mechanical ventilation and intubation, and vital signs first recorded on ICU admission (heart rate, respiratory rate, systolic blood pressure (SBP) and temperature). Laboratory test indexes on admission were also collected, including anion gap (AG), chloride, blood urea nitrogen (BUN), calcium, creatinine, potassium, sodium, mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC), mean corpuscular volume (MCV), platelet, haemoglobin, red blood cell distribution width (RDW), red blood cell (RBC) and white cell count (WCC). Demographic characteristics and vital signs in the first 24 hours after admission were recorded, and the results of the first measurement on admission were selected as laboratory examination indicators. To accurately compare data from the eICU-CRD for external validation, we attempted to extract the same variables as those from the MIMIC-IV.

The primary outcome was in-hospital mortality, which was defined based on survival status at discharge.

Statistical analyses

Continuous variables are expressed by mean±SD or median (IQR), and analysis was performed using Student's t-test or Mann-Whitney U test. Categorical variables are

Table 1 Baseline characteristics of patients with CHF on admission

Characteristics	Derivation cohort (MIMIC-IV)	Validation cohort (eICU-CRD)	P value
	n=15 983	n=14 428	
Age, years	74 (64–83)	72 (62–81)	<0.001
Gender (%)			<0.001
Male	8733 (54.6)	7562 (52.4)	
Female	7250 (45.4)	6866 (47.6)	
Ethnicity (%)			<0.001
White	11 056 (69.2)	10 806 (74.9)	
Black	2124 (13.3)	2785 (19.3)	
Other	2803 (17.5)	837 (5.8)	
COPD (%)			<0.001
No	6309 (39.5)	11 416 (79.1)	
Yes	9674 (60.5)	3012 (20.9)	
AMI (%)			<0.001
No	10 926 (68.4)	14 178 (98.3)	
Yes	5057 (31.6)	250 (1.7)	
Diabetes (%)			<0.001
No	8920 (55.8)	9896 (68.6)	
Yes	7063 (44.2)	4532 (31.4)	
HepF (%)			<0.001
No	15 545 (97.3)	14 286 (99.0)	
Yes	438 (2.7)	142 (1.0)	
Norepinephrine (%)			<0.001
No	12 095 (75.7)	13 724 (95.1)	
Yes	3888 (24.3)	704 (4.9)	
Dopamine (%)			<0.001
No	15 504 (97.0)	14 355 (99.5)	
Yes	479 (3.0)	73 (0.5)	
Epinephrine (%)			<0.001
No	15 245 (95.4)	14 344 (99.4)	
Yes	738 (4.6)	84 (0.6)	
Phenylephrine (%)			<0.001
No	14 781 (92.5)	14 147 (98.1)	
Yes	1202 (7.5)	281 (1.9)	
Vent (%)			<0.001
No	2275 (14.2)	6032 (41.8)	
Yes	13 708 (85.8)	8396 (58.2)	
Intubated (%)			<0.001
No	11 232 (70.3)	12 393 (85.9)	
Yes	4751 (29.7)	2035 (14.1)	
SOFA	4 (1–5)	3 (5–8)	<0.001
APSO	48 (37–63)	44 (32–62)	<0.001
Temperature, °C	36.7 (36.5–37.0)	36.4 (36.1–36.7)	<0.001
Respiratory rate, breaths per minute	19.0 (17.0–22.0)	29.0 (13.0–36.0)	<0.001
Heart rate, beats per minute	82.0 (73.0–94.0)	103.0 (85.0–120.0)	<0.001

Continued

Table 1 Continued

Characteristics	Derivation cohort (MIMIC-IV)	Validation cohort (eICU-CRD)	P value
	n=15983	n=14428	
SBP, mm Hg	113.0 (104.0–126.0)	119.0 (101.0–139.0)	<0.001
Chloride, mmol/L	103.0 (98.0–107.0)	101.0 (97.0–105.0)	<0.001
AG	15.0 (12.0–17.0)	11.0 (8.0–14.0)	<0.001
BUN, mg/dL	28.0 (18.0–46.0)	29.0 (19.0–46.0)	0.001
Creatinine, mg/dL	1.3 (0.9–2.1)	1.4 (1.0–2.2)	<0.001
Potassium, mmol/L	4.2 (3.8–4.7)	4.1 (3.8–4.6)	<0.001
Calcium, mg/dL	8.5 (8.0–8.9)	8.7 (8.2–9.1)	<0.001
Sodium, mmol/L	139.0 (135.0–141.0)	138.0 (135.0–141.0)	<0.001
Haemoglobin, g/dL	10.1 (8.6–11.6)	10.9 (9.4–12.7)	<0.001
MCH, pg	29.8 (28.0–31.3)	29.5 (27.7–31.0)	<0.001
MCHC, g/L	32.4 (31.2–33.5)	32.4 (31.4–33.3)	0.195
MCV, fL	91.0 (87.0–96.0)	90.8 (86.0–95.0)	<0.001
RDW	15.3 (14.1–17.0)	15.7 (14.4–17.5)	<0.001
WCC, $\times 10^9/L$	10.3 (7.4–14.3)	9.9 (7.3–13.4)	<0.001
Platelet, $\times 10^9/L$	193.0 (143.0–255.0)	201.0 (150.0–261.0)	<0.001
RBC, $\times 10^9/L$	3.4 (2.9–4.0)	3.8 (3.2–4.3)	<0.001

AG, anion gap; AMI, acute myocardial infarction; APSIII, Acute Physiology Score III; BUN, blood urea nitrogen; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; eICU-CRD, eICU Collaborative Research Database; HepF, hepatic failure; MCH, mean corpuscular haemoglobin; MCHC, mean corpuscular haemoglobin concentration; MCV, mean corpuscular volume; MIMIC-IV, Medical Information Mart for Intensive Care; RBC, red blood cell; RDW, red blood cell distribution width; SBP, systolic blood pressure; SOFA, Sequential Organ Failure Assessment; WCC, white cell count.

presented as numbers (percentages), and comparisons were performed using χ^2 test or Fisher's exact test.

Univariate logistic regression analysis showed that all significant risk factors were entered into the multivariate logistic regression analysis. The nomogram was constructed based on the results of the multivariate logistic regression analysis. Calibration plots and the Hosmer-Lemeshow χ^2 test are usually used to assess the degree of calibration of the model.¹³ The discriminative ability of a model is usually evaluated using the C-index or the Receiver Operating Characteristic (ROC) curve.¹⁴ Decision curve analysis (DCA) assessed the clinical usefulness of the model.¹⁵ In addition, the prediction accuracy of the model was assessed by computing the net reclassification improvement (NRI) and the integrated discriminant improvement (IDI).¹⁶

SPSS software (V.21.0) and R software (V.4.0.1) were used for statistical analysis. $P < 0.05$ was considered statistically significant.

Patient and public involvement

Patients and the public were not directly involved in this study.

RESULTS

Baseline characteristics

We selected 15 983 patients with CHF based on the MIMIC-IV. For nomogram construction and external validation, 14 428 patients with CHF were selected from the multicentre eICU-CRD. The following characteristics were, respectively, recorded in the derivation and validation sets: median age of patients (74 years and 72 years), male (54.6.0% and 52.4%), white (69.2% and 74.9%), and had comorbidities of COPD (60.5% and 20.9%), AMI (31.6% and 1.7%), diabetes (44.2% and 31.4%) and HepF (2.7% and 1.0%). The proportion of patients who received mechanical ventilation and intubation in the derivation and validation sets was 85.8% and 7.5%, respectively. Overall in-hospital mortality was 12.4% and 12.8% in the MIMIC-IV and eICU-CRD, respectively. The baseline data of the derivation and validation sets were similar. The baseline characteristics of the patients are shown in [table 1](#).

Prognostic factors for in-hospital mortality

Prognostic factors significantly related to in-hospital mortality of patients with CHF were age, race, norepinephrine, dopamine, epinephrine, phenylephrine, vasopressin, mechanical ventilation, intubation, AMI, HepF, heart rate, respiratory rate, temperature, SBP, AG, BUN, creatinine, calcium, chloride, haemoglobin, potassium, MCHC, MCV, RDW, RBC and WCC. Multivariate logistic

Table 2 Logistic regression analysis for patients with CHF

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Age	1.027 (1.023 to 1.031)	<0.001	1.041 (1.036 to 1.046)	<0.001
Gender, n (%)				
Male	Reference			
Female	1.026 (0.934 to 1.128)	0.589		
Race, n (%)				
White	Reference			
Black	0.817 (0.701 to 0.951)	0.009	1.029 (0.854 to 1.236)	0.759
Other	1.325 (1.178 to 1.490)	<0.001	1.310 (1.136 to 1.509)	<0.001
COPD, n (%)				
No	Reference			
Yes	0.996 (0.905 to 1.096)	0.933		
AMI, n (%)				
No	Reference			
Yes	1.242 (1.126 to 1.371)	<0.001	1.097 (0.975 to 1.234)	0.123
Diabetes, n (%)				
No	Reference			
Yes	0.958 (0.871 to 1.053)	0.372		
HepF, n (%)				
No	Reference			
Yes	2.599 (2.089 to 3.233)	<0.001	2.321 (1.750 to 3.059)	<0.001
Norepinephrine, n (%)				
No	Reference			
Yes	6.572 (5.950 to 7.258)	<0.001	2.075 (1.789 to 2.407)	<0.001
Dopamine, n (%)				
No	Reference			
Yes	8.569 (7.114 to 10.322)	<0.001	2.178 (1.733 to 2.738)	<0.001
Epinephrine, n (%)				
No	Reference			
Yes	4.455 (3.802 to 5.219)	<0.001	0.869 (0.696 to 1.083)	0.212
Phenylephrine, n (%)				
No	Reference			
Yes	7.059 (6.223 to 8.008)	<0.001	1.753 (1.475 to 2.083)	<0.001
Vasopressin, n (%)				
No	Reference			
Yes	10.976 (9.660 to 12.470)	<0.001	3.123 (2.607 to 3.744)	<0.001
Mechanical ventilation, n (%)				
No	Reference			
Yes	2.915 (2.405 to 3.534)	<0.001	1.606 (1.295 to 2.009)	<0.001
Intubation, n (%)				
No	Reference			
Yes	2.496 (2.268 to 2.746)	<0.001	1.902 (1.671 to 2.164)	<0.001
Heart rate, beats per minute	1.020 (1.017 to 1.023)	<0.001	1.100 (1.006 to 1.014)	<0.001
Respiratory rate, breaths per minute	1.113 (1.100 to 1.126)	<0.001	1.091 (1.074 to 1.107)	<0.001

Continued

Table 2 Continued

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Temperature, °C	0.674 (0.618 to 0.736)	<0.001	0.692 (0.626 to 0.765)	<0.001
SBP, mm Hg	0.965 (0.962 to 0.969)	<0.001	0.990 (0.986 to 0.994)	<0.001
Chloride, mmol/L	0.985 (0.978 to 0.991)	<0.001	0.988 (0.979 to 0.996)	0.005
AG	1.129 (1.118 to 1.140)	<0.001	1.054 (1.039 to 1.070)	<0.001
BUN, mg/dL	1.014 (1.013 to 1.016)	<0.001	1.009 (1.006 to 1.011)	<0.001
Creatinine, mg/dL	1.103 (1.079 to 1.127)	<0.001	0.952 (0.910 to 0.995)	0.032
Calcium, mmol/L	0.825 (0.778 to 0.876)	<0.001	0.956 (0.894 to 1.020)	0.177
Sodium, mmol/L	0.995 (0.986 to 1.004)	0.253		
Potassium, mmol/L	1.255 (1.187 to 1.326)	<0.001	1.014 (0.945 to 1.089)	0.694
Haemoglobin, g/dL	0.963 (0.942 to 0.984)	0.001	0.985 (0.792 to 1.229)	0.462
MCH, pg	1.005 (0.988 to 1.022)	0.566		
MCHC, g/L	0.822 (0.800 to 0.844)	<0.001	0.941 (0.870 to 1.018)	0.251
MCV, fL	1.034 (1.028 to 1.041)	<0.001	1.034 (1.010 to 1.059)	0.005
RDW	1.178 (1.158 to 1.199)	<0.001	1.128 (1.101 to 1.157)	<0.001
WCC, $\times 10^9/L$	1.030 (1.025 to 1.035)	<0.001	1.007 (1.002 to 1.012)	0.008
Platelet, $\times 10^9/L$	1.000 (0.999 to 1.000)	0.521		
RBC, $\times 10^9/L$	0.907 (0.852 to 0.966)	0.002	1.180 (0.615 to 2.238)	0.302

AG, anion gap; AMI, acute myocardial infarction; BUN, blood urea nitrogen; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; HepF, hepatic failure; MCH, mean corpuscular haemoglobin; MCHC, mean corpuscular haemoglobin concentration; MCV, mean corpuscular volume; RBC, red blood cell; RDW, red blood cell distribution width; SBP, systolic blood pressure; WCC, white cell count.

regression analysis was then performed on these variables to control for confounding effects as much as possible. Finally, age, race, norepinephrine, dopamine, phenylephrine, vasopressin, mechanical ventilation, intubation, HepF, heart rate, respiratory rate, temperature, SBP, AG, BUN, creatinine, chloride, MCV, RDW and WCC were determined as the prognostic factors for patients with CHF. Detailed data are shown in table 2.

A nomogram for predicting in-hospital mortality

A novel nomogram (figure 2) was developed using multivariate logistic regression analysis. Higher total scores for all risk factors indicated higher risk of in-hospital mortality. The nomogram indicates that age is the factor with the most significant effect on prognosis, followed by respiratory rate, RDW, temperature, AG, BUN, WCC, SBP, MCV, heart rate, creatinine, vasopressin, chloride, dopamine, HepF, norepinephrine, intubation, phenylephrine, mechanical ventilation and race. SOFA, APSIII and GWTGHF scores were compared with our novel nomogram.

Performance of the nomogram

The C-index of the nomogram was 0.839 (95% CI 0.829 to 0.848), indicating good discrimination ability. The ROC curves of the SOFA, APSIII and GWTGHF scores and the novel nomogram used to predict in-hospital mortality are presented in figure 3. The Area Under Curve (AUC) values indicated that our novel nomogram model is better than the SOFA, APSIII and GWTGHF score models.

The Hosmer-Lemeshow χ^2 value of the novel nomogram was 6.6 ($p=0.677$), showing no significant difference. The calibration curves showed good consistency between the predicted and actual probability (figure 4). The net benefit from the DCA curve of the novel nomogram was greater than the SOFA, APSIII and GWTGHF scores in the derivation set (figure 5).

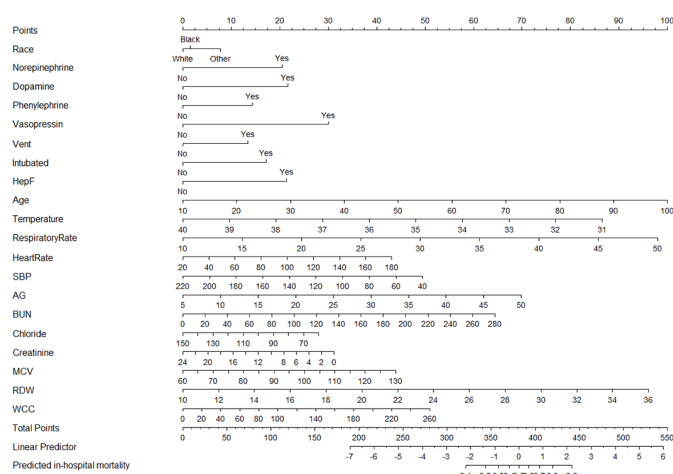


Figure 2 Nomogram for predicting in-hospital mortality in patients with congestive heart failure. AG, anion gap; BUN, blood urea nitrogen; HepF, hepatic failure; MCV, mean corpuscular volume; RDW, red blood cell distribution width; SBP, systolic blood pressure; WCC, white cell count.

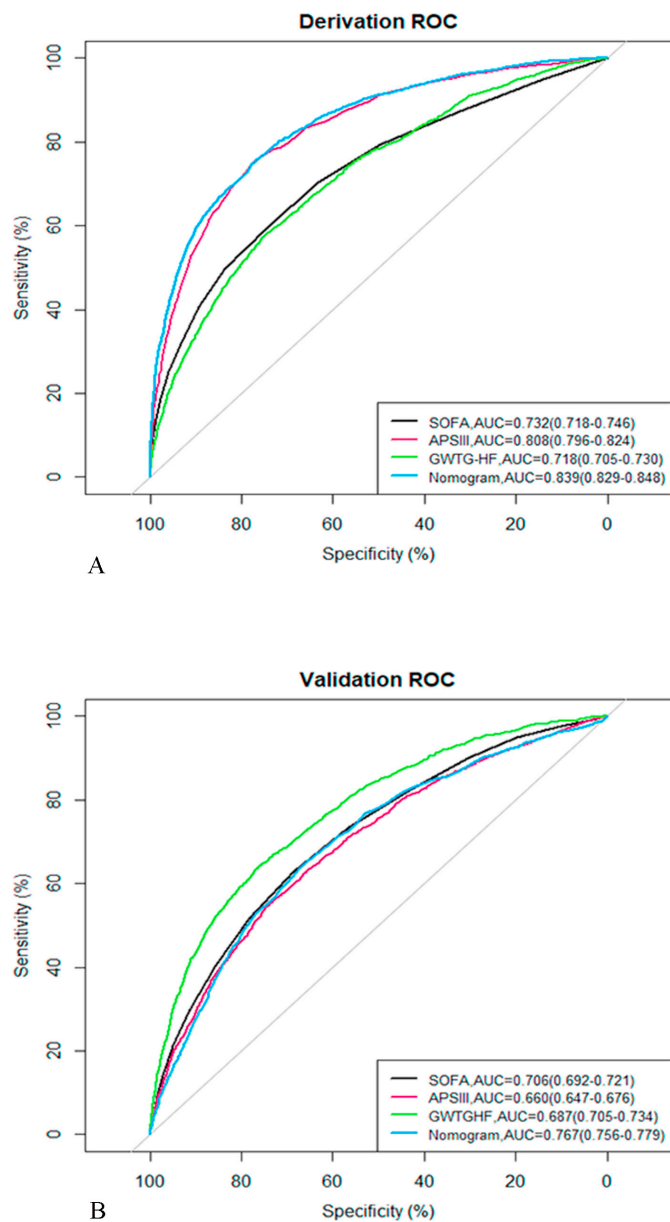


Figure 3 ROC curves of the SOFA, APSIII, GWTGHF scores and the nomogram in the derivation set (A) and the validation set (B). APSIII, Acute Physiology Score III; AUC, Area Under Curve; GWTGHF, Get With The Guidelines Heart Failure; ROC, Receiver Operating Characteristic; SOFA, Sequential Organ Failure Assessment.

The novel nomogram model had an NRI and IDI of 0.601 (95% CI 0.522 to 0.651) and 0.176 (95% CI 0.165 to 0.187) in the derivation set (table 3). All values indicate that the nomogram's prediction performance represented considerable improvement.

External validation of the nomogram

This study also identified 14428 eligible patients with CHF in the eICU-CRD. Applying the prediction nomogram to this validation set indicated similar prediction effects, with a C-index of 0.767 (95% CI 0.756 to 0.779). The ROC curves for predicting in-hospital mortality are presented in figure 3. The AUC values indicated that our

novel nomogram model has better predictive ability than the SOFA, APSIII and GWTGHF score models.

The Hosmer-Lemeshow χ^2 value of the novel nomogram was 12.1 ($p=0.210$), showing no significant difference. The calibration curves indicate that it is well calibrated for clinical application in the validation set (figure 4). Through data verification of eICU-CRD, the DCA also shows the high clinical application value of the nomogram (figure 5). The NRI and IDI of the validation set are presented in table 3.

DISCUSSION

CHF is the final manifestation of various cardiovascular diseases. The structure or function of the myocardium becomes dysfunctional, leading to restricted ventricular ejection or filling. With acute exacerbation or progression of the disease, insufficient tissue and organ perfusion results and ultimately leads to death.¹⁷ The disease has a relatively rapid onset and affected patients are in a relatively serious condition. Although some scoring systems and models for prognostic research or risk factor analysis of ICU patients are available, there is none specifically for the prognosis of patients with CHF. We therefore planned to establish a more comprehensive and accurate prognostic nomogram for patients with CHF in the ICU.

A nomogram is an effective tool for risk assessment.^{18 19} It provides a simple graphical representation for complex statistical prediction models, and is also suitable for prognostic analysis of individual patients.²⁰ The present multivariate logistic regression indicated that age, race, norepinephrine, dopamine, phenylephrine, vasopressin, mechanical ventilation, intubation, HepF, heart rate, respiratory rate, temperature, SBP, AG, BUN, creatinine, chloride, MCV, RDW and WCC are prognostic factors for survival of patients with CHF. The main advantages of the novel nomogram are its simplicity, efficiency and accuracy of application. The nomogram uses 20 clinical variables that are easy to obtain and do not require complex calculations, making it easy for clinicians to use.

Glasgow Coma Scale (GCS) and APSIII scores are commonly used severity scores for ICU patients, and patients with CHF in the ICU tend to be more severe. The GCS score is used to determine the state of consciousness of patients with CHF,²¹ and the SOFA and APSIII scores determine the physiological state of patients in the ICU.²² The GWTGHF risk score is a well-validated and widely accepted heart failure scoring system that is commonly used to risk-stratify in-hospital mortality.²³⁻²⁵ This predictive model was validated in our research group and compared with the model we developed. The performance of our nomogram is superior to other scores.

Several variables have been indicated to be associated with mortality in patients with heart failure, such as age, gender, body mass index, diabetes, COPD, low SBP and creatinine.²⁶ The study showed that heart rate, respiratory rate, temperature, SBP, AG, BUN, creatinine, chloride,

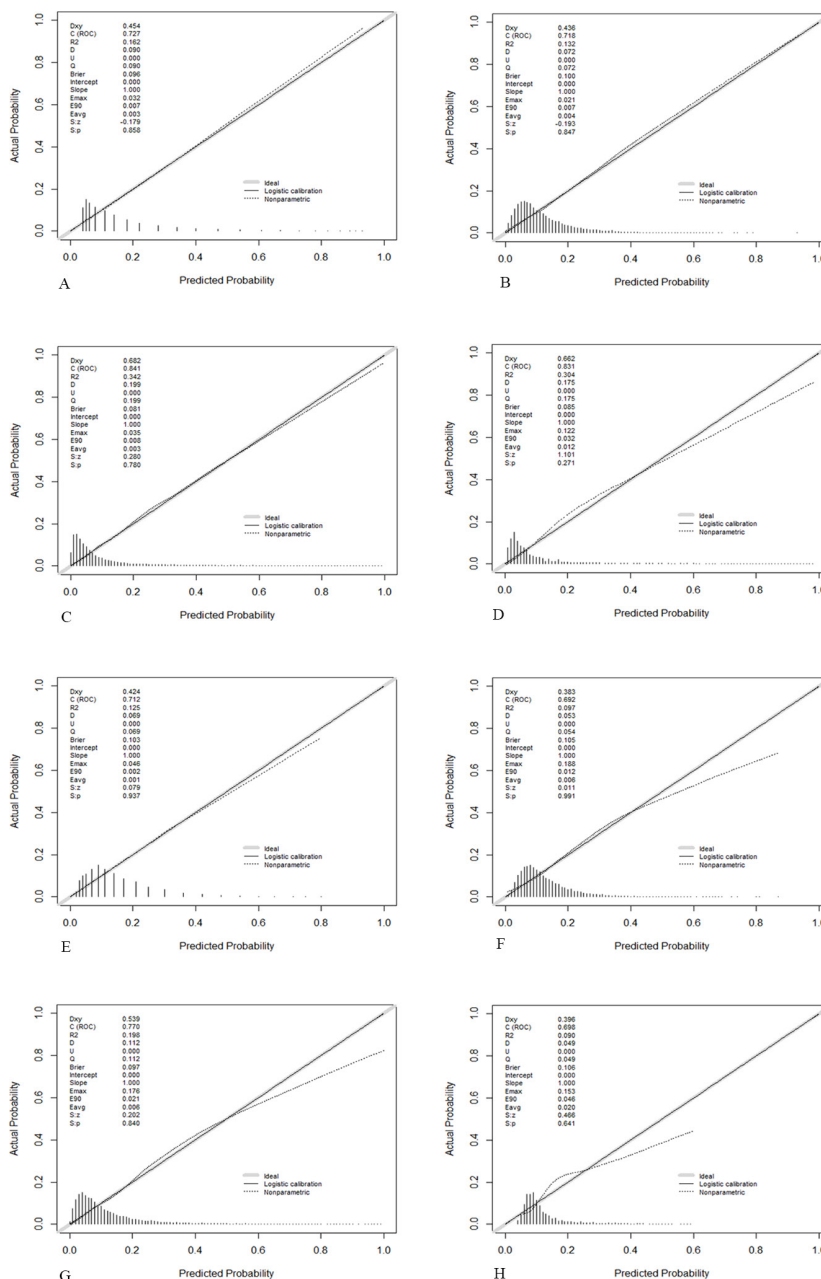


Figure 4 Calibration curves of the SOFA, APSIII, GWTGHF scores and the nomogram in the derivation set (A–D) and the validation set (E–H). APSIII, Acute Physiology Score III; GWTGHF, Get With The Guidelines Heart Failure; SOFA, Sequential Organ Failure Assessment.

MCV, RDW and WCC were predictors of in-hospital mortality.

The number of elderly patients admitted to the ICU has increased rapidly in recent years. The median age of ICU patients in many Western countries has increased to over 65 years.²⁷ Age is often considered an important indicator of prognosis of diseases. Many recognised prediction models have used age to predict the severity or mortality of CHF.^{28–29} Similarly, our results also indicate that age is a risk factor for patients with CHF, which may be due to older patients having more comorbidities and poor response to treatment. In addition, our finding that non-African American ethnicity has an increased CHF mortality risk is consistent with previous research.³⁰

Clinically, patients with CHF are treated with cardiac strengthening, diuresis, oxygen and other treatment measures. Although these treatment methods can achieve certain effects, for patients with relatively rapid disease development, ventilation function cannot be improved and ultimately the treatment effect will be reduced. Our study shows that use of catecholamines is associated with an increased risk of poor outcome in patients with CHF, which is similar to previous studies.^{31–33} In addition, our study also demonstrated mechanical ventilation and intubation increased the risk of in-hospital death of patients with CHF. This is consistent with previous research.¹⁰ The reason may be that early mechanical ventilation has a significant inhibitory effect on cardiac function and

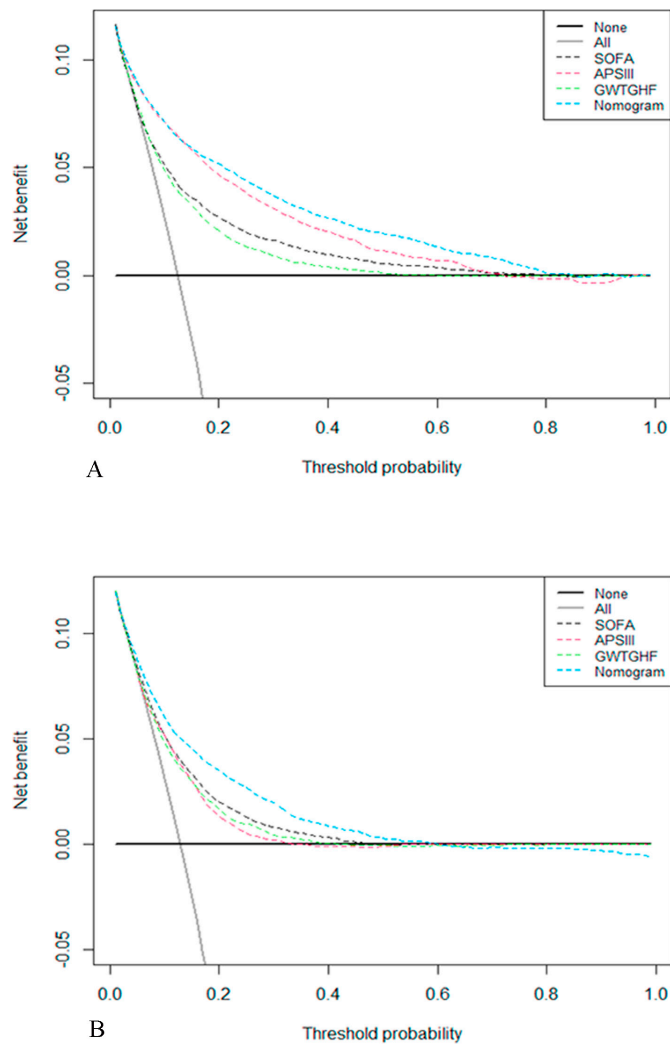


Figure 5 Decision curve analysis of the SOFA, APSIII, GWTGHF scores and the nomogram in the derivation set (A) and the validation set (B). APSIII, Acute Physiology Score III; GWTGHF, Get With The Guidelines Heart Failure; SOFA, Sequential Organ Failure Assessment.

may induce AMI or further enlarge the infarction area, resulting in poor prognosis.

Previous studies have also found high respiratory rate to be related to poor heart failure prognosis.⁴ Our results similarly indicated that increased respiratory rate was a risk factor for increased in-hospital mortality. Changes in body temperature and WCC reflect the body's inflammatory status, and values that are abnormal may be risk factors for poor prognoses. Our study indicated that lower body temperature, elevated WCC, higher AG and elevated MCV increased the risk of mortality of patients with CHF, which is consistent with the findings of previous studies.^{34,35} RDW is a parameter that reflects the heterogeneity of RBC volume and is expressed by the coefficient of variation of RBC volume.³⁶ Results from a previous study showed that higher RDW was an independent predictor of poor prognosis,³⁷ which is similar to our findings.

An ideal clinical prognostic model should be reliable and easy to use. For example, some clinically accessible, reliable and non-invasive clinical and laboratory indicators are usually used to construct prognostic models. Moreover, the performance of novel nomogram was superior to GWTGHF and other severity scores.

Most previous studies on the risk and prognostic factors for CHF have been limited by their relatively small samples.³⁸ This study is therefore the first that we know of to have simultaneously analysed patients with CHF in MIMIC-IV and eICU-CRD and to obtain a large sample to develop a prognostic nomogram. This retrospective clinical study involved multiple research centres, and the results provide significant reference information to guide clinical practice.

Inevitably, this study also had some limitations. First, the retrospective research design may reduce the validity of our findings, which could be validated in future prospective case-control studies. Second, although as many confounders as possible were adjusted for some covariates, residual confounders could not be completely

Table 3 Validation of the nomogram

Variables	Derivation set	Validation set
NRI (95% CI)		
SOFA and nomogram	0.539 (0.478 to 0.618)	0.267 (0.036 to 0.212)
GWTGHF and nomogram	0.601 (0.552 to 0.651)	0.380 (0.321 to 0.418)
APSIII and nomogram	0.142 (0.085 to 0.215)	0.429 (0.387 to 0.498)
IDI (95% CI)		
SOFA and nomogram	0.142 (0.131 to 0.153)	0.055 (0.046 to 0.063)
GWTGHF and nomogram	0.176 (0.165 to 0.187)	0.078 (0.070 to 0.086)
APSIII and nomogram	0.032 (0.019 to 0.045)	0.075 (0.068 to 0.081)

APSIII, Acute Physiology Score III; GWTGHF, Get With The Guidelines Heart Failure; IDI, integrated discrimination improvement; NRI, net reclassification improvement; SOFA, Sequential Organ Failure Assessment.



removed and some key comorbidity data were missing from the data set, and the relationships between certain variables (ie, temperature and WCC) and the outcome were treated as linear when they were likely to be bimodal. Third, MIMIC-IV and eICU-CRD contain data from 2008 to 2019 and from 2014 to 2015, respectively. The sample is old and some characteristics of the disease may have changed over time, which may affect our findings. Finally, due to the limitations of public databases, many other variables that may affect the model and its results, such as smoking and alcohol consumption, and detailed information on patient treatment and medication were not collected.

CONCLUSION

We have determined that the important risk factors for in-hospital mortality of patients with CHF are age, race, norepinephrine, dopamine, phenylephrine, vasopressin, mechanical ventilation, intubation, HepF, heart rate, respiratory rate, temperature, SBP, AG, BUN, creatinine, chloride, MCV, RDW and WCC. We developed and validated a prognostic nomogram for CHF that is highly accurate. The nomogram constructed in this study provides a method and choice for evaluation of the survival prognosis of patients with CHF in the ICU, and may become an auxiliary predictive tool for use in clinical practice to predict and evaluate patients and understand their in-hospital survival status.

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Contributors DH and FX conceptualised the research aims, planned the analyses and guided the literature review. LZ and RY extracted the data from the MIMIC-IV database. DH, SZ and TH participated in data analysis and interpretation. DH and RY wrote the first draft of the paper and the other authors provided comments and approved the final manuscript. HY and JL participated in project administration, supervision and visualisation. JL was regarded as the guarantor. The interpretation and reporting of these data were the sole responsibility of the authors.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval The clinical data used to support the findings of this study were provided by the MIMIC-IV and the eICU database. Although the database is publicly and freely available, researchers must complete the National Institutes of Health's web-based course known as Protecting Human Research Participants to apply for permission to access the database. The establishment of the MIMIC-IV database was approved by the Massachusetts Institute of Technology (Cambridge, Massachusetts) and Beth Israel Deaconess Medical Center (Boston, Massachusetts). eICU was made available by Philips Healthcare in partnership

with the MIT Laboratory for Computational Physiology. Consent was obtained for the original data collection. Therefore, ethical approval and the need for informed consent were waived for the studies on this database. The study was an analysis of two third-party anonymised publicly available databases with pre-existing institutional review board (IRB) approval. Informed consent was unnecessary because the MIMIC-IV and eICU data are anonymous and publicly available.

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Data availability statement Data are available in a public, open access repository. Publicly available data sets were analysed in this study and these data can be found at <https://mimic-iv.mit.edu/> and <https://eicu-crd.mit.edu/>. Extra data can be accessed via the Dryad data repository at <http://datadryad.org/> with the doi: 10.5061/dryad.tx95x6b18.

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REFERENCES

- Hernandez AV, Jeon A, Denegri-Galvan J, *et al*. Use of adaptive servo ventilation therapy as treatment of sleep-disordered breathing and heart failure: a systematic review and meta-analysis. *Sleep Breath* 2020;24:49–63.
- Nakade T, Adachi H, Murata M, *et al*. Relationship between exercise oscillatory ventilation loop and prognosis of heart failure. *Circ J* 2019;83:1718–25.
- Acharya P, Ranka S, Sethi P, *et al*. Incidence, predictors, and outcomes of In-Hospital cardiac arrest in COVID-19 patients admitted to intensive and Non-Intensive care units: insights from the AHA COVID-19 CVD registry. *J Am Heart Assoc* 2021;10:e21204:4116–9.
- GBD 2015 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015: a systematic analysis for the global burden of disease study 2015. *Lancet* 2016;388:1545–602.
- Zhang W, Wang Y, Wang J, *et al*. Association between red blood cell distribution width and long-term mortality in acute respiratory failure patients. *Sci Rep* 2020;10:21–185.
- Felker GM, Leimberger JD, Califf RM, *et al*. Risk stratification after hospitalization for decompensated heart failure. *J Card Fail* 2004;10:460–6.
- Pocock SJ, Wang D, Pfeffer MA, *et al*. Predictors of mortality and morbidity in patients with chronic heart failure. *Eur Heart J* 2006;27:65–75.
- Brophy JM, Dagenais GR, McSherry F, *et al*. A multivariate model for predicting mortality in patients with heart failure and systolic dysfunction. *Am J Med* 2004;116:300–4.
- Peterson PN, Rumsfeld JS, Liang L, *et al*. A validated risk score for in-hospital mortality in patients with heart failure from the American heart association get with the guidelines program. *Circ Cardiovasc Qual Outcomes* 2010;3:25–32.
- Lee DS, Austin PC, Rouleau JL, *et al*. Predicting mortality among patients hospitalized for heart failure: derivation and validation of a clinical model. *JAMA* 2003;290:2581–7.
- Bulgarelli L, Pollard T, Johnson A. *MIMIC-IV*. version 0.4. PhysioNet, 2020.
- Pollard TJ, Johnson AEW, Raffa JD, *et al*. The eICU collaborative research database, a freely available multi-center database for critical care research. *Sci Data* 2018;5:180178.
- Hosmer DW, Hosmer T, Le Cessie S, *et al*. A comparison of goodness-of-fit tests for the logistic regression model. *Stat Med* 1997;16:965–80.
- DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics* 1988;44:837–45.
- Yang J, Li Y, Liu Q, *et al*. Brief introduction of medical database and data mining technology in big data era. *J Evid Based Med* 2020;13:57–69.
- Wu W-T, Li Y-J, Feng A-Z, *et al*. Data mining in clinical big data: the frequently used databases, steps, and methodological models. *Mil Med Res* 2021;8:44.

- 17 Sun D, Zhang F, Ma T, *et al.* Atorvastatin alleviates left ventricular remodeling in isoproterenol-induced chronic heart failure in rats by regulating the RhoA/Rho kinase signaling pathway. *Pharmacol Rep* 2020;72:903–11.
- 18 Han Q, Ren J, Tian J, *et al.* A nomogram based on a patient-reported outcomes measure: predicting the risk of readmission for patients with chronic heart failure. *Health Qual Life Outcomes* 2020;18:290.
- 19 Lin Z, Yan S, Zhang J, *et al.* A nomogram for distinction and potential prediction of liver metastasis in breast cancer patients. *J Cancer* 2018;9:2098–106.
- 20 Balachandran VP, Gonen M, Smith JJ, *et al.* Nomograms in oncology: more than meets the eye. *Lancet Oncol* 2015;16:e173–80.
- 21 Mehta R, Chinthapalli K, *et al.* GP trainee. Glasgow coma scale explained. *BMJ* 2019;365:11296
- 22 Le Gall JR, Loirat P, Alperovitch A, *et al.* A simplified acute physiology score for ICU patients. *Crit Care Med* 1984;12:975–7.
- 23 Pandey A, Patel KV, Liang L, *et al.* Association of hospital performance based on 30-day risk-standardized mortality rate with long-term survival after heart failure hospitalization: an analysis of the get with the guidelines-heart failure registry. *JAMA Cardiol* 2018;3:489–97.
- 24 Suzuki S, Yoshihisa A, Sato Y, *et al.* Clinical significance of get with the guidelines-heart failure risk score in patients with chronic heart failure after hospitalization. *J Am Heart Assoc* 2018;7:e8316.
- 25 Pocock SJ, Ariti CA, McMurray JJV, *et al.* Predicting survival in heart failure: a risk score based on 39 372 patients from 30 studies. *Eur Heart J* 2013;34:1404–13.
- 26 Flaatten H, de Lange DW, Artigas A, *et al.* The status of intensive care medicine research and a future agenda for very old patients in the ICU. *Intensive Care Med* 2017;43:1319–28.
- 27 Harjola V-P, Follath F, Nieminen MS, *et al.* Characteristics, outcomes, and predictors of mortality at 3 months and 1 year in patients hospitalized for acute heart failure. *Eur J Heart Fail* 2010;12:239–48.
- 28 Krittayaphong R, Karaketklang K, Yindeengam A, *et al.* Heart failure mortality compared between elderly and non-elderly thai patients. *J Geriatr Cardiol* 2018;15:718–24.
- 29 Perne A, Schmidt FP, Hochadel M, *et al.* Admission heart rate in relation to presentation and prognosis in patients with acute myocardial infarction. treatment regimens in German chest pain units. *Herz* 2016;41:233–40.
- 30 Powers FM, Pifarre R, Thomas JX. Ventricular dysfunction in norepinephrine-induced cardiomyopathy. *Circ Shock* 1994;43:122–9.
- 31 Cohn JN, Levine TB, Olivari MT, *et al.* Plasma norepinephrine as a guide to prognosis in patients with chronic congestive heart failure. *N Engl J Med* 1984;311:819–23.
- 32 Jin Y-T, Hasebe N, Matsusaka T, *et al.* Magnesium attenuates isoproterenol-induced acute cardiac dysfunction and beta-adrenergic desensitization. *Am J Physiol Heart Circ Physiol* 2007;292:H1593–9.
- 33 White CM. Catecholamines and their blockade in congestive heart failure. *Am J Health Syst Pharm* 1998;55:676–82.
- 34 Vogenberg FR. Predictive and prognostic models: implications for healthcare decision-making in a modern recession. *Am Health Drug Benefits* 2009;2:218–22.
- 35 Salvagno GL, Sanchis-Gomar F, Picanza A, *et al.* Red blood cell distribution width: a simple parameter with multiple clinical applications. *Crit Rev Clin Lab Sci* 2015;52:86–105.
- 36 Wang B, Gong Y, Ying B, *et al.* Relation between red cell distribution width and mortality in critically ill patients with acute respiratory distress syndrome. *Biomed Res Int* 2019;2019:1–8.
- 37 Zhang Y, Guo F, Li S, *et al.* Decreased high density lipoprotein cholesterol is an independent predictor for persistent organ failure, pancreatic necrosis and mortality in acute pancreatitis. *Sci Rep* 2017;7:8064.
- 38 Sies H. Oxidative stress: a concept in redox biology and medicine. *Redox Biol* 2015;4:180–3.