Validation and Derivation of short-term prognostic risk score in acute decompensated heart failure in China

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Abstract

Background: Few prognostic risk scores (PRSs) have been widely applied in acute decompensated heart failure (ADHF). We therefore externally validated three published PRSs (3A3B, AHEAD, and OPTIME-CHF) and derived a new PRS to predict the short-term prognosis in ADHF.

Methods: A total of 4550 patients from the Heb-ADHF registry in China were randomly divided into the derivation and validation cohort (3:2). Discrimination of each PRS was assessed by the area under the receiver operating characteristic curve (AUROC). Logistic regression was used to select the predictors and create the new PRS. Calibration of the new PRS was assessed by Hosmer-Lemeshow goodness-of-fit test.

Results: The AUROCs of the 3A3B, AHEAD, and OPTIME-CHF score in the derivation cohort were 0.55 (95% CI 0.53-0.57), 0.54 (95% CI 0.53-0.56), and 0.56 (95% CI 0.54-0.57), respectively. After logistic regression analysis, the new PRS computed as 1 × (diastolic blood pressure < 80 mmHg) + 2 × (lymphocyte > 1.11 × 10^9/L) + 1 × (creatinine > 80 μmol/L) + 2 × (blood urea nitrogen > 21 mg/dL) + 1 × [BNP 500 to < 1500 pg/mL (NT-proBNP 2500 to < 7500 pg/mL)] or 3 × [BNP ≥ 1500 (NT-proBNP ≥ 7500) pg/mL] + 3 × (QRS fraction of electrocardiogram < 55%) + 4 × (ACEI/ARB not used) + 1 × (rhBNP used), with a better AUROC 0.67 (95% CI 0.64-0.70) and a good calibration (Hosmer-Lemeshow χ^2=3.366, P=0.186). The results in validation cohort verified these findings.

Conclusions: The short-term prognostic values of 3A3B, AHEAD, and OPTIME-CHF score in ADHF patients were all poor, while the new PRS exhibited potential predictive ability. We firstly found the QRS fraction of electrocardiogram as a novel predictor for the short-term outcomes of ADHF. Our findings might help to recognize high-risk ADHF patients.

1. Background

Acute decompensated heart failure (ADHF) is a common clinical syndrome with poor prognosis at internal medicine and emergency department, and the majority of ADHF patients require hospitalization for further treatment [1,2]. Despite the remarkable therapeutic advances in treatments, the mortality and rehospitalization rates of ADHF remain high [3], most conspicuously during hospitalization and the early post-discharge period [4-6], which was called “the vulnerable phase” for heart failure (HF) [7]. Data from China show that ADHF is the main cause of hospitalization in patients > 65 years old, with the hospitalization mortality of 3% and the short-term readmission rate of about 50% [8].

Accurately predicting prognosis in patients with ADHF is important to improve the treatment decisions during and after hospitalization, thereby reducing readmissions and deaths [9]. For these purposes, several prognostic risk scores (PRSs) in patients with HF have been established [10-13]. However, most of these scores have not been fully externally validated and the effect values of predictors are different among races and regions [14,15]. Moreover, current scoring systems focused less attention on outcomes during the vulnerable phase in patients with ADHF, and it is unclear whether they can be directly applied to ADHF patients.

This study therefore aimed to validate whether the previously published PRSs (3A3B, AHEAD, and OPTIME-CHF) [10,12,13] could be used to predict the composite of in-hospital all-cause mortality, 30-day all-cause readmission, or 30-day all-cause mortality after discharge in patients with ADHF. Meanwhile, we derived a new PRS and compared it with the existing systems. We believe this will contribute to the prognostic risk assessment of ADHF patients.

2. Methods

2.1. *Study population.*

The study population consisted of hospitalized patients with ADHF enrolled in the Hebei Acute Decompensated Heart Failure (Heb-ADHF) registry (ChiCTR-POC-17014020) database, a prospective, multicenter, open study designed in real-world to assess risk predictors of influencing comprehensive treatment and short-term prognosis in patients with ADHF. Patients were consecutively recruited between March 2016 and December 2018 in 13 tertiary hospitals in Hebei Province, China.

ADHF was defined as new-onset acute HF (AHF) or decompensation of chronic HF (CHF) [16]. Patients were eligible for inclusion in the study if they were: (1) age ≥18years; (2) unplanned admission; (3) with typical symptoms or signs of ADHF; and (4) brain natriuretic peptide (BNP) >100 pg/mL or N-terminal pro-brain natriuretic peptide (NT-proBNP) > 300 pg/mL. Diagnosis and treatment of ADHF were determined by the cardiologist-physicians according to the clinical guideline [8]. Exclusion criteria were: (1) hospital stay < 24 hours; (2) heart transplantation; (3) on renal replacement therapy; (4) massive stroke; (5) concomitant terminal disease; or (6) patients lost to follow-up. All eligible subjects were randomly divided into two cohorts at a ratio of 3:2 as the derivation cohort and the validation cohort. The derivation cohort was used to validate the published PRSs and establish the new model, and the validation cohort was used to validate the findings.

2.2. *Data collection.*

We recorded the following clinical data on admission of each enrolled patient: (1) demographic characteristics; (2) previous clinical history; (3) physical examination; (4) laboratory tests; (5) chest radiography (6) electrocardiogram; (7) echocardiography; and (8) medical treatment. Variables analysis of outcome events group showed cut-offs as follows: age, 65 year-old; body mass index (BMI), 24 kg/m^2; length of hospital stay (LoHS), 10 days; systolic blood pressure (SBP), 130 mmHg; diastolic blood pressure (DBP), 80 mmHg; anemia, < 13.0 g/dL in men or < 12.0 g/dL in women; red blood cells (RBC), 4.15 × 10^{12}/L; neutrophil, 4.37 × 10^9/L; lymphocyte, 1.11 × 10^9/L; platelet, 155 × 10^9/L; total cholesterol (TC) 3.6 mmol/L; low density lipoprotein cholesterol (LDL-C), 2.0mmol/L; creatinine, 80 μmol/L; blood urea nitrogen (BUN), 21 mg/dL; aspartate aminotransferase (AST), 32 U/L; alanine aminotransferase (ALT), 59 U/L; QRS fraction, 55%; left ventricular ejection fraction (LVEF), 36%; left atrial diameter (LAD), 41 mm. Phase values were used for BNP (NT-proBNP), 100 to <500 (300 to <2500), 500 to <1500 (2500 to

<7500), and ≥1500 (≥7500) pg/mL, respectively. QRS fraction is defined as the sum of the R-wave amplitudes of the standard 12 leads (ΣR) dividing by the sum of the absolute values of the QRS wave amplitudes of the 12 leads (ΣQRS) in electrocardiogram, i.e. (ΣR/ ΣQRS) × 100%.

2.3. Validation for published predictive risk scores.

Considering the research background (population and regions), as well as availability of variables, we chose the 3A3B [13], AHEAD [12], and OPTIME-CHF [10] score as the alternative PRSs. The next sections go through each one in depth.

2.3.1. The 3A3B score.

The 3A3B score is developed for the Japanese HF preserved left ventricular ejection fraction (LVEF) (HFpEF). From a total of 14 covariates, age, albumin, anemia, BMI, BNP or NT-proBNP, and BUN were selected as long-term prognostic variables [13]. The predictive value was confirmed in the external validation in Asian cohorts. The discrimination abilities were all excellent in both derivation and validation cohorts (c-index=0.708). However, the accuracy of this score in predicting short-term prognosis in ADHF patients remains unknown.

2.3.2 The AHEAD score.

The AHEAD score is a simple tool based on 5 comorbidities (Atrial fibrillation, Hemoglobin (anemia), Elderly, Abnormal renal parameters (creatinine), Diabetes mellitus) used to predict the short and long term prognosis of hospitalized patients with AHF in the European population. It was derived from a multicenter prospective registry. The score was externally validated in the GREAT registry consisted of nine AHF cohorts from Italy, Spain, France, Argentina, Finland, Switzerland, USA, Tunisia, and Austria [12]. Nevertheless, its prognostic efficacy in Asian patients with ADHF has not been validated.

2.3.3. The OPTIME-CHF score.

The OPTIME-CHF score was suggested to predict the risk of 60-day mortality for hospitalized patients with decompensated HF. Using data from a cohort from the United States, 5 routine variables on admission, including age, SBP, sodium, New York Heart Association (NYHA) class IV, and BUN, were found to be independently associated with the prognosis. The discrimination of the current score was excellent (c-index=0.77). The author further developed a nomogram based on each factor for bedside application [10]. However, it was not externally validated.

We intended to evaluate the robustness of these scores on the composite of in-hospital all-cause mortality, 30-day all-cause readmission, or 30-day all-cause mortality after discharge in patients with ADHF. Moreover, we tried to develop a new PRS and compare it with the 3 PRSs.

2.4. *Study endpoint and follow-up*.

The primary endpoint was the composite of in-hospital all-cause mortality, 30-day all-cause readmission, or 30-day all-cause mortality after discharge. The follow-up programs for all patients were carried out according to the original plan of the Heb-ADHF study designs via medical record, physician's office visits, or telephone interviews from admission to 30 days after discharge.

2.5. *Statistical analysis*.

Continuous variables are presented as means ± standard deviations or medians with interquartile range whenever appropriate; categorical variables are presented as frequencies (*n*) and proportions (%). The few missing data are replaced by the expectation maximization method. The Student *t* test or Mann-Whitney *U* test was used to evaluate differences between groups for continuous variables and the Chi-square (χ^2) test for categorical variables whenever appropriate. To assess the existing PRSs' ability for predicting the endpoint, discrimination of each PRS was evaluated by the area under the receiver operating characteristic curve (AUROC) with a 95% confidence interval (CI). Univariate logistic regression analyses were firstly used to identify risk factors associated with outcome events. Variables with *P*-values of < 0.2 in univariate analyses were entered into the multivariable analysis. Then, variables with *P*-values of < 0.05 in the multivariate logistic regression were considered as independent variables for the new PRS. Odds ratios (ORs) with 95% CIs were calculated for the logistic regression analysis. The relative importance of each predictor within the final PRS model was evaluated by the value of the partial Wald χ^2 statistic minus the degrees of freedom (*df*) of predictors (χ^2−df). In the new PRS model, we assigned the scores (points) of each independent variables on the basis of their value of (χ^2-df): (χ^2-df) ≤ 5.0 assigned as 1 point, 5.0 < (χ^2-df) ≤ 10 assigned as 2 points, 10 < (χ^2-df) ≤ 15 assigned as 3 points, and (χ^2-df) > 15 as 4 points. Calibration was assessed using *Hosmer-Lemeshow* goodness-of-fit test. Using the *Z* test, we also compared the predictive accuracy of new PRS with that of the 3 previously published PRS by AUROCs. The correlation between different score-points and different outcome events were analyzed by *Mantel–Haenszel* trend test and *Pearson* correlation test. Two-sided *P* < 0.05 was deemed statistically significant. Statistical analyses were performed using SPSS software (version 26.0) and the AUROC curves were conducted using the Medcalc software (version 20.0.3).

3. Results

3.1. *Population characteristics*.

A total of 4550 patients from the Heb-ADHF registry were enrolled into this study, which were randomly divided into the derivation cohort (2,745) and the validation cohort (1,805) at a ratio of 3:2. The incidence of the composite of outcomes in the derivation and validation cohorts were 13.9% (381/2745) and 13.9% (249/1805) respectively. For both cohorts, the age, male, BMI, smoking, drinking, HF duration, number of hospitalizations for heart failure (NH-HF), LoHS, SBP, DBP, heart rate, etiology, heart function, comorbidities, urine protein, laboratory blood tests, chest radiography, electrocardiogram, echocardiography, medical treatment, and risk of outcome events were comparable without significant

difference ($P > 0.05$). The clinical characteristics of derivation and validation cohorts are summarized in Table 1.

3.2. *Validation of previous scores in the derivation cohort*.

The results showed that discriminations of 3A3B, AHEAD, and OPTIME-CHF score were all poor on the composite of in-hospital all-cause mortality, 30-day all-cause readmission, or 30-day all-cause mortality after discharge in the derivation cohort, with AUROCs of 0.55 (95% CI 0.53-0.57), 0.54 (95% CI 0.53-0.56), and 0.56 (95% CI 0.54-0.57), respectively. Only the specificity of 3A3B score was acceptable (85.3%), but the sensitivities was unsatisfactory (22.0%).

3.3. *Logistic regression analysis and the new risk score model*.

Logistic regression analysis was performed in the derivation cohort (Table 2). After univariate analysis, there were 27 variables ($P < 0.2$) entered into the multivariable analysis: sex (male), BMI, LoHS, DBP, anemia, RBC, neutrophil, lymphocyte, platelet, TC, LDL-C, creatinine, BUN, AST, ALT, cTnI/T, BNP (NT-proBNP), QRS fraction, pulmonary congestion (X-ray), LVEF, LAD, ACEI/ARB, β-blocker, Tolvaptan, recombinant human brain natriuretic peptide (rhBNP), calcium channel blockers, and Statin. However, multivariate analysis showed only 8 variables ($P < 0.05$) [DBP, lymphocyte, creatinine, BUN, BNP (NT-proBNP), QRS fraction of electrocardiogram, ACEI/ARB, and rhBNP] maintained an independent correlation with the composite endpoint, which were included into the development of the final model.

We calculated the relative importance of each independent predictor by the value of (χ^2 − df) (Figure 1). Then, the score was assigned based on the (χ^2 − df) value of each independent predictor (Table 2). The new scoring system was as follows:

1 × (DBP < 80 mmHg) + 2 × (lymphocyte > 1.11 × 10^9/L) + 1 × (creatinine > 80 μmol/L) + 2 × (BUN > 21 mg/dL) + 1 × [BNP 500 to < 1500 pg/mL (NT-proBNP 2500 to < 7500 pg/mL)] or 3 × [BNP ≥ 1500 (NT-proBNP ≥ 7500) pg/mL] + 3 × (QRS fraction of electrocardiogram < 55%) + 4 × (ACEI/ARB not used) + 1 × (rhBNP used).

3.3. *Discrimination, calibration, and comparison of the new risk score*.

The discrimination ability of the new PRS model was suitable, whose AUROC for the derivation cohorts was 0.67 (95%CI 0.64-0.70) (Figure 2A), and it had good calibration (the *Hosmer-Lemeshow* test χ^2=3.366, P=0.186). The discrimination was validated by the AUROC for the validation cohorts [0.65 (95% CI 0.61-0.69)] (Figure 2B), and the calibration was also good (the *Hosmer-Lemeshow test* χ^2=9.751, P=0.283). In addition, the AUROCs of the new PRS in both the derivation and validation cohorts were the highest compared with the 3A3B score, AHEAD score, and OPTIME-CHF score system (Figure 2), those differences were statistically significant ($P < 0.001$; Table 3).

3.4. *The risk stratification of the new risk score model in the entire cohort.*

The new PRS was then used to classify patients into 3 groups: 0-4 points, low-risk group; 5-8 points, medium-risk group; ≥ 9 points, high-risk group. The incidence of in-hospital all-cause mortality in low-, medium-, and high-risk group were 1.86% (14/754), 4.07% (74/1820), and 5.57% (110/1976), respectively (Figure 3A). The incidence of 30-day readmission in low-, medium-, and high-risk group were 3.18% (24/754), 6.43% (117/1820), and 11.03% (218/1976), respectively (Figure 3B). The incidence of 30-day all-cause mortality after discharge were 0.53% (4/754), 1.04% (19/1820), and 2.53% (50/1976), respectively (Figure 3C) and the composite of outcome events were 5.57% (42/754), 11.54% (210/1820), and 19.13% (378/1976), respectively (Figure 3D). *Mantel-haenszel* test showed a linear trend between the risk stratification and the incidence of outcomes events (χ^2=38.14, P < 0.001). *Pearson* correlation test indicated that the incidence of outcomes events increased with increase of the risk stratification (R=0.480, P < 0.001).

4. Discussions

From the data of Heb-ADHF registry, we externally validated 3 previously published risk models (3A3B, AHEAD, OPTIME-CHF) to predict the composite of in-hospital all-cause mortality, 30-day all-cause readmission, or 30-day all-cause mortality after discharge in patients with ADHF. The current findings revealed that all the 3 models performed poorly. We also developed a new PRS based on clinical characteristics on admission. The new scoring system comprised a combination of variables, including DBP, lymphocyte, creatinine, BUN, BNP (NT-proBNP), QRS fraction, ACEI/ARB, and rhBNP. We found that the new PRS had moderate ability to predict the short-term prognosis and outperformed the 3A3B, AHEAD, and OPTIME-CHF score. More importantly, we firstly demonstrated that the QRS fraction is an independent predictor for short-term prognosis of patients with ADHF. In addition, it was interesting that low DBP, lymphocyte count and rhBNP used were positive predictors of poor short-term outcomes in patients with ADHF in our study.

The short-term risks of death or readmission for ADHF remain very high, at 13.9% in our study. This also resulted in huge direct and indirect economic losses [1,8,17,18]. Short-term prognosis assessment for patients with ADHF remains one of the major challenges for clinicians. Previous studies have shown that the risk score can effectively predict the adverse outcomes of HF. Nevertheless, validation in different cohorts is a crucial step in providing evidence for the performance of scores, which must be considered in the context of different studies [19,20]. The success of any PRS depends on the availability of the included variables [11]. Likewise, when validating the original score in an external population, it is necessary to assess whether the existing population can obtain the effective variables of the original score. We have considered employing other well-known scores for the validation in our population. Unfortunately, we failed since our sample group lacked key variables contained in other scores. Besides the availability of variables, we chose the 3A3B, AHEAD, and OPTIME-CHF score because their study populations involved: the OPTIME-CHF model from the United States [10], the AHEAD from Europe [12], and the 3A3B model from Asian [13]. We attempted to locate one of the existing risk models from different regions to evaluate their short-term prediction abilities for ADHF patients. Disappointingly, it did

not work out. Despite the fact that our endpoint-positive group had higher scores than the endpoint-negative group, the 3A3B, AHEAD, and OPTIME-CHF score performed poorly in the population of Heb-ADHF. The difference in the results may be attributed to differences in study populations and endpoints design. In other words, the direct application of previously published HF risk scores to the ADHF population is debatable. This implies that the development and implementation of risk scores for different populations, as well as the variables included in these scores, should be specific and targeted.

In our study, the new PRS got better predictive value than the 3 previous scoring systems in predicting the composite outcomes. Furthermore, our results suggested that there was a linear correlation between the new PRS and outcome events. The higher the risk stratification, the higher the incidence of adverse outcome events (*P*-for-trend < 0.001), namely high risk stratification increased the incidence of in-hospital all-cause mortality, 30-day all-cause readmission, 30-day all-cause mortality after discharge, or the composite outcomes. Although the discrimination (AUROC) results were not excellent, it still has potential predictive value. In particular, our PRS contained some specific predictors with independent predictive value for the endpoint, such as the DBP, lymphocyte, rhBNP, and QRS fraction.

“Risk scores are multivariate predictive models in which relative weights are assigned to each variable in order to calculate the probability that a specific event (e.g. death, rehospitalization) will occur in the future” [9]. Therefore, risk variables are the basic elements of PRS, and different variables may play different roles in different PRS. In general, the same patient may have multiple risk variables coexisted [21]. BNP or NT-proBNP [22], BUN or creatinine [23,24], and/or ACEI/ARB use [25] have been recognized as common variables affecting the prognosis of patients with ADHF. In our new PRS model, ACEI/ARB use and high BNP (NT-proBNP) level are the two variables with the highest weights [(χ^2 – df) value] (Figure. 1). Additionally, more studies have suggested that low SBP is closely related to adverse outcomes in ADHF patients [26,27]. However, studies of relationship between DBP and the prognosis of patients with ADHF are relatively rare. Our results indicated that low DBP (< 80mmHg), not SBP, was an independent variable of short-term adverse outcomes in patients with ADHF. Similarly, many studies have shown that hemoglobin (anemia) [12,13], red blood cell distribution width [28], white blood cells, and/or hematocrit [29] are associated with poor prognosis in patients with ADHF, while the lymphocyte is rarely used as predictor. In our new PRS, lymphocytes as an independent predictor could predict short-term poor prognosis for ADHF patients. More interesting and meaningful, rhBNP used and low QRS fraction were also predictors of related adverse events.

It is known that rhBNP is a synthetic drug widely used in the clinical treatment of patients with ADHF and recommended by many major guidelines [1,8,30]. Generally speaking, rhBNP has protective effects on the heart and kidney [1,8,30,31]. Studies on patients with ADHF have shown that the use of rhBNP could reduce the 30-day mortality and readmission rate [32,33]. However, the use of rhBNP in our study actually increased the composite outcomes. The result was somewhat surprising. We do not think the truth is what it looks like. Although the accurate proportion of rhBNP used in ADHF patients is clearly unknown, it is certainly more common in severe patients. The most likely reason that treatment with rhBNP increased the composite endpoints in our study was the proportion of critical patients included in our cohort. They

may need rhBNP more than those with less severe conditions. This phenomenon needs further exploration.

A rather new finding of our study was the QRS fraction included into our PRS as a novel independent predictor for the endpoints. The previously published QRS scoring systems have been proved to be related to left ventricular function [34-36], but their computational complexity makes them inconvenient for clinical application. Different from previous QRS scores, our novel QRS fraction is simpler and easier to achieve, which is defined as (ΣR/ΣQRS) × 100%. More importantly, we have found in our previous studies that QRS fraction were significantly positively correlated with LVEF in patients with cardiovascular disease (including HF). This result was further verified in the Heb-ADHF registry. Studies have shown that LVEF is significantly associated with in-hospital mortality and 30-day all-cause readmission in patients with ADHF [37,38]. This may be the reason why QRS fraction can predict the prognosis of our cohort. To the best of our knowledge, this study is the first one using this method to assess the prognosis in patients with ADHF. After correction for confounding variables, low QRS fraction was still an independent predictor of the composite of in-hospital all-cause mortality, 30-day all-cause readmission, or 30-day all-cause mortality after discharge for patients with ADHF. Excitingly, our results indicate that low QRS fraction (< 55%) have a higher weight in our new PRS (Figure. 1). The new PRS performed better than the 3A3B, AHEAD and OPTIME-CHF score, which was largely related to the introduction of QRS score. This issue also needs to be further discussed and we believe that the combination of QRS fraction in future PRS will show us its real value in the short-term prognosis of ADHF patients.

In fact, the application of PRSs for ADHF in clinical practice is far from enough. One PRS is unlikely to generalize widely to all ADHF populations. However, if effective and simple PRSs are actively applied in daily clinical work, incorporated into electronic health records like the application of CHA_2DS_2-VASc score in atrial fibrillation [39] or GRACE score in acute myocardial infarction [40], we believe that patients with ADHF will get better treatment and have a better prognosis. Clinicians and researchers still have a long way to go to achieve this goal.

5. Study Limitations

There exist several limitations in the present study. First, patients' socio-economic background may strongly influence treatment. Some diagnostic and therapeutic approaches such as the detection of interleukin-1 receptor-like 1 (ST2), the use of sodium-glucose cotransporter 2 (SGLT2) inhibitors or Levosimendan, and the application of implantable cardioverter defibrillator (ICD) or cardiac resynchronization therapy-defibrillator (CRT-D), etc. were relatively less in the our study population, which may affect the inclusion of valuable variables and the discrimination for our new PRS. In the future, it is necessary to add more updated variables to improve its predictive accuracy. Second, because our research was carried out in multi-centers, some centers only tested BNP, while others only tested NT-proBNP, which may have a certain impact on the results. Third, other than the 3A3B, AHEAD and OPTIME-CHF score, we have considered comparing the predictive accuracy of the new PRS with other scores in

our population. Unfortunately, we failed since our cohort lacked key variables contained in other scores. Four, the clinical data collected for patients on admission without considering pre-hospital management and we had a small amount of data missing, which may have a certain impact on the results. Besides, our PRS still needs external validation.

6. Conclusions

Collectively, the present study validated 3A3B, AHEAD, and OPTIME-CHF score in ADHF patients from the Heb-ADHF registry, but their discriminations were all poor to predict the composite of in-hospital all-cause mortality, 30-day all-cause readmission, or 30-day all-cause mortality after discharge. We proposed a new short-term PRS (included DBP, lymphocyte, creatinine, BUN, BNP (NT-proBNP), QRS fraction, ACEI/ARB, and rhBNP) that performed moderate predictive capability with the larger AUROC than the 3A3B, AHEAD, and OPTIME-CHF score. When the risk score reaches ≥ 9 points, particular attention must be paid and clinical decision-making needs to be formulated and adjusted more actively. More new variables and larger multicenter studies are needed make our PRS become a practical and reliable tool for evaluating the short-term adverse events for ADHF patients.

7. Declarations

Ethics approval and consent to participate

All methods were performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. The study was approved by the ethics committee of the Second Hospital of Hebei Medical University (2015110). All patients signed informed consent to participate in Hebei Acute Decompensated Heart Failure (Heb-ADHF) registry study.

Consent for publication

Not applicable.

Availability of data and materials

The authors confirm that the data supporting the findings of this study are available within the article. The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

All the authors have no conflicts of interest and had access to the data and wrote the manuscript.

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Authors' contributions

HLZ and XLG, and WC designed the study, analyzed and interpreted the patient data, and were major contributors in writing the manuscript. XL, YHL, SLL, QZ, WCS, QZ, JZ, YZL, LL, NG, HST, QMW, XTH, YKC, XG, QW collected and assembled the patient data. All authors read and approved the final manuscript.

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Tables

Table 1. Comparison of clinical characteristics between the derivation and validation cohorts.

Characteristic	Derivation cohort (*n* = 2745)	Validation cohort (*n* = 1805)	*P*-Value
Age, years	67.8 ± 12.9	67.2 ± 13.0	0.126
Male, *n* (%)	1603 (58.4)	1057 (58.6)	0.913
BMI, kg/m^2	24.5 ± 4.5	24.5 ± 3.9	1.000
Smoking, *n* (%)	651 (23.7)	411 (22.8)	0.461
Drinking, *n* (%)	575 (20.9)	347 (19.2)	0.157
LoHS, days	10.9 ± 5.8	11.2 ± 6.9	0.114
SBP, mmHg	132.6 ± 24.4	132.7 ± 25.0	0.893
DBP, mmHg	80.4 ± 15.5	80.7 ± 16.2	0.530
Heart rate, times/min	87.8 ± 23.5	88.4 ± 23.7	0.401
Etiology: ischemic, *n* (%)	1499 (54.6)	957 (53.0)	0.293
Heart function, *n* (%)			
NYHA class IV	1257 (45.8)	836 (46.3)	0.729
Killip class IV	40 (1.5)	39 (2.2)	0.076
Comorbidities, *n* (%)			
Atrial fibrillation	870 (31.7)	549 (30.4)	0.362
Hypertension	1580 (57.6)	1068 (59.2)	0.281
Coronary artery disease	1376 (50.1)	860 (47.6)	0.101
Diabetes mellitus	706 (25.7)	493 (27.3)	0.233
Chronic kidney disease	189 (6.9)	111 (6.1)	0.328
Stroke	501 (18.3)	299 (16.6)	0.144
Urine protein +, *n* (%)	315 (11.5)	243 (13.5)	0.046
Blood findings			
Red blood cells, 10^{12}/L	4.30 (3.86, 4.69)	4.29 (3.82, 4.70)	0.868
Hemoglobin, g/L	130.3 ± 22.8	130.3 ± 23.2	1.000
Hematocrit, %	39.11 ± 8.94	39.32 ± 8.36	0.427
white blood cells, 10^9/L	7.10 (5.69, 9.04)	7.10 (5.64, 9.10)	0.883
Neutrophil, 10^9/L	4.83 (3.69, 6.62)	4.81 (3.60, 6.70)	0.875

Lymphocyte, 10^9/L	1.40 (1.00, 1.82)	1.39 (1.00, 1.84)	0.696
Platelet, 10^9/L	200.6 ± 70.4	201.9 ± 71.8	0.545
Glucose, mmol/L	5.80 (4.91, 7.34)	5.80 (4.94, 7.28)	0.954
Creatinine, μmol/L	82.0 (66.3, 103.0)	83.1 (67.0, 106.0)	0.135
BUN, mg/dL	20.5 (15.5, 29.2)	20.5 (15.8, 30.4)	0.240
Na⁺, mEq/L	138.9 ± 4.9	139.2 ± 4.5	0.037
Total cholesterol, mmol/L	3.96 (3.30, 4.69)	3.92 (3.30, 4.62)	0.564
LDL-C, mmol/L	2.42 ± 0.88	2.33 (1.84, 2.91)	0.592
ALT, U/L	24.0 (15.0, 40.4)	24.1 (15.0, 42.0)	0.546
AST, U/L	25.0 (18.5, 41.0)	25.4 (19.0, 42.1)	0.184
Albumin, g/L	38.28 ± 5.35	38.48 ± 5.37	0.218
BNP, pg/mL△	797.0 (400.2, 1540.0)	855.5 (382.5, 1620.0)	0.451
NT-proBNP, pg/mL▲	4644.9 (2408.6, 8794.6)	4893.5 (2351.0, 9189.3)	0.663
cTnI/T (higher than normal), *n* (%)			
1 to <3 times	149 (5.4)	94 (5.2)	0.746
≥ 3 times	556 (20.3)	380 (21.1)	0.515
Electrocardiogram, *n* (%)			
Ventricular premature beat	236 (8.6)	153 (8.5)	0.886
Left bundle branch block	165 (6.0)	102 (5.7)	0.613
QRS fraction, % ‡	54.24 ± 13.48	53.82 ± 14.00	0.311
SPC (X-ray), *n* (%)			
pulmonary congestion	708 (25.8)	445 (24.7)	0.388
Pulmonary edema	670 (24.4)	451 (25.0)	0.658
Cardiothoracic ratio >50%, *n* (%)	1285 (46.8)	810 (44.9)	0.200
Echocardiogram			
LVEF, %	45.2 ± 12.7	45.2 ± 12.9	1.000
Left atrial diameter, mm	43.2 ± 9.0	43.3 ± 8.7	0.710
LVEDD, mm	55.0 (48.1, 62.7)	55.0 (49.0, 62.0)	0.794

Medical therapy, *n* (%)			
Loop diuretics	2489 (90.7)	1618 (89.6)	0.250
ARA	2331 (84.9)	1506 (83.4)	0.178
Hydrochlorothiazide	248 (9.0)	164 (9.1)	0.953
Tolvaptan	35 (1.3)	20 (1.1)	0.614
β-blocker	1916 (69.8)	1268 (70.2)	0.746
ACEI/ ARB	1595 (58.1)	1005 (55.7)	0.106
Calcium channel blockers	422 (15.4)	260 (14.4)	0.370
Nitrates	1339 (48.8)	902 (50.0)	0.431
Digitalis	863 (31.4)	541 (30.0)	0.295
rh-BNP	235 (8.6)	183 (10.1)	0.072
Levosimendan	130 (4.7)	88 (4.9)	0.829
Antiplatelets	1830 (66.7)	1184 (65.6)	0.455
Statin	1831 (66.7)	1172 (64.9)	0.217
Anticoagulants	338 (12.3)	238 (13.2)	0.387
Outcome events, *n* (%)	381 (13.9)	249 (13.9)	1.000
all-cause in-hospital mortality	130 (4.7)	68 (3.8)	
all-cause 30-day readmission	210 (7.7)	149 (8.3)	
all-cause 30-day mortality after discharge	41 (1.5)	32 (1.8)	

BMI, body mass index; TH-HF, times of hospitalizations for heart failure; LoHS, length of hospital stay; SBP, systolic blood pressure; DBP, diastolic blood pressure; BUN, blood urea nitrogen; LDL-C, low density lipoprotein cholesterol; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BNP, brain natriuretic peptide; NT-proBNP, N-terminal pro-brain natriuretic peptide; cTnI/T, cardiac troponin I/T; SPC, signs of pulmonary congestion; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter; ARA, aldosterone receptor antagonists; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; rh-BNP, recombinant human brain natriuretic peptide

‡ QRS fraction is calculated by sum of the R-wave amplitudes of the standard 12 leads (ΣR) and dividing by the sum of the absolute values of the QRS wave amplitudes of the 12 leads (ΣQRS), i.e. (ΣR/ ΣQRS) × 100%.

△ The data of BNP were available in 2,916 patients, including 1,796 in derivation cohort and 1,120 in validation cohort.

▲ The data of NT-proBNP were available in 1638 patients, including 950 patients in derivation cohort and 688 in validation cohorts.

Table 2. Logistic regression analysis of the composite outcomes in the derivation cohort

Variables	Univariate analysis		Multivariate analysis		Model selection	
	OR (95% CI)	*P-Value*	OR (95% CI)	*P-Value*	χ^2-df	Score
Age ≥ 65 years	0.916 (0.734-1.144)	0.440				
Sex (meal)	1.183 (0.951-1.470)	0.131	1.074 (0.851-1.356)	0.546		
BMI < 24 kg/m^2	1.160 (0.934-1.442)	0.180	1.061 (0.842-1.338)	0.615		
LoHS ≥ 10 days	1.256 (1.007-1.567)	0.043	1.206 (0.960-1.517)	0.108		
SBP < 130mmHg	1.150 (0.926-1.428)	0.206				
DBP < 80mmHg	1.264 (1.017-1.570)	0.034	1.286 (1.021-1.619)	0.032	4.58	1
NYHA (Killip) class □	1.000 (0.805-1.242)	0.998				
Diabetes mellitus	1.032 (0.807-1.321)	0.800				
Anemia	1.188 (0.953-1.481)	0.125	0.988 (0.718-1.361)	0.943		
Red blood cells ≤ 4.15 × 10^{12}/L	1.278 (1.028,1.588)	0.027	0.653 (0.184-2.315)	0.510		
Neutrophil > 4.37 × 10^9/L	1.301 (1.046-1.617)	0.018	2.013 (0.562-7.214)	0.283		
Lymphocyte > 1.11 × 10^9/L	1.832 (1.423-2.358)	< 0.001	1.738 (1.220-2.475)	0.002	9.37	2
Platelet ≥ 155 × 10^9/L	1.305 (1.004-1.696)	0.046	1.282 (0.967-1.700)	0.084		
Total cholesterol < 3.6 mmol/L	1.429 (1.147-1.781)	0.001	1.362 (0.981-1.890)	0.065		
LDL-C < 2.0mmol/L	1.319 (1.054-	0.015	1.103	0.564		

	1.650)		(0.790-1.541)			
Creatinine > 80 μmol/L	1.386 (1.115-1.722)	0.003	1.272 (1.013-1.598)	0.038	4.29	1
BUN > 21 mg/dL	1.711 (1.373-2.132)	< 0.001	1.346 (1.063-1.703)	0.013	6.12	2
AST > 32 U/L	1.384 (1.108-1.728)	0.004	1.050 (0.790-1.395)	0.739		
ALT > 59 U/L	1.585 (1.194-2.104)	0.001	1.256 (0.880-1.795)	0.210		
cTnI/T elevated	1.405 (1.123-1.757)	0.003	1.244 (0.971-1.594)	0.084		
BNP (NT-proBNP) pg/ml						
BNP 100 to < 500 (NT-proBNP 300 to < 2500)	Reference		Reference			
BNP 500 to < 1500 (NT-proBNP 2500 to < 7500)	1.679 (1.251-2.254)	0.001	1.460 (1.074-1.983)	0.016	5.85	1
BNP ≥ 1500 (NT-proBNP ≥ 7500)	2.649 (1.962-3.577)	< 0.001	1.785 (1.281-2.488)	0.001	11.69	3
QRS fraction ‡ < 55%	1.593 (1.279-1.985)	< 0.001	1.458 (1.156-1.839)	0.001	10.15	3
Pulmonary congestion (X-ray)	1.496 (1.201-1.863)	< 0.001	0.909 (0.667-1.238)	0.544		
LVEF < 36%	1.224 (0.962-1.558)	0.100	0.955 (0.733-1.245)	0.735		
Left atrial diameter > 41 mm	1.367 (1.094-1.707)	0.006	1.232 (0.971-1.563)	0.086		
ACEI/ARB not used	1.670 (1.343-2.076)	< 0.001	1.588 (1.260-2.003)	< 0.001	15.30	4
β-blocker not used	1.357 (1.081-1.703)	0.009	1.150 (0.900-1.470)	0.264		

Tolvaptan not used	2.522 (1.201-5.293)	0.014	1.935 (0.890-4.209)	0.096		
rhBNP used	1.629 (1.160-2.288)	0.005	1.474 (1.019-2.131)	0.039	4.25	1
CCB used	1.458 (1.045-2.034)	0.026	1.230 (0.868-1.744)	0.244		
Statin used	1.291 (1.032-1.615)	0.025	1.226 (0.963-1.559)	0.098		

BMI, body mass index; LoHS, length of hospital stay; SBP, systolic blood pressure; DBP, diastolic blood pressure; BUN, blood urea nitrogen; LDL-C, low density lipoprotein cholesterol; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BNP, brain natriuretic peptide; NT-proBNP, N-terminal pro-brain natriuretic peptide; cTnI/T, cardiac troponin I/T; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blockers; rh-BNP, recombinant human brain natriuretic peptide; χ^2-df, Wald Chi-squared (χ^2) statistic minus the degrees of freedom (df) of predictors.

‡ QRS fraction is calculated by the sum of the R-wave amplitudes of the standard 12 leads (ΣR) and dividing by the sum of the absolute values of the QRS wave amplitudes of the 12 leads (ΣQRS), i.e. (ΣR/ΣQRS) × 100%.

Table 3. Comparison of AUROCs between the new risk score and previous risk scores for predicting outcomes.

Cohort	Comparison	Difference between AUROCs	95% CI	*Z*-statistic	*P*-value
Derivation	New risk score *vs.* 3A3B	0.122	0.019 (0.086-0.158)	6.595	< 0.001
	New risk score *vs.* AHEAD	0.125	0.019 (0.089-0.163)	6.515	< 0.001
	New risk score *vs.* OPTIME-CHF	0.114	0.018 (0.078-0.150)	6.174	< 0.001
Validation	New risk score *vs.* 3A3B	0.111	0.023 (0.066-0.156)	4.808	< 0.001
	New risk score *vs.* AHEAD	0.136	0.025 (0.087-0.185)	5.455	< 0.001
	New risk score *vs.* OPTIME-CHF	0.086	0.024 (0.040-0.132	3.663	< 0.001

Figures

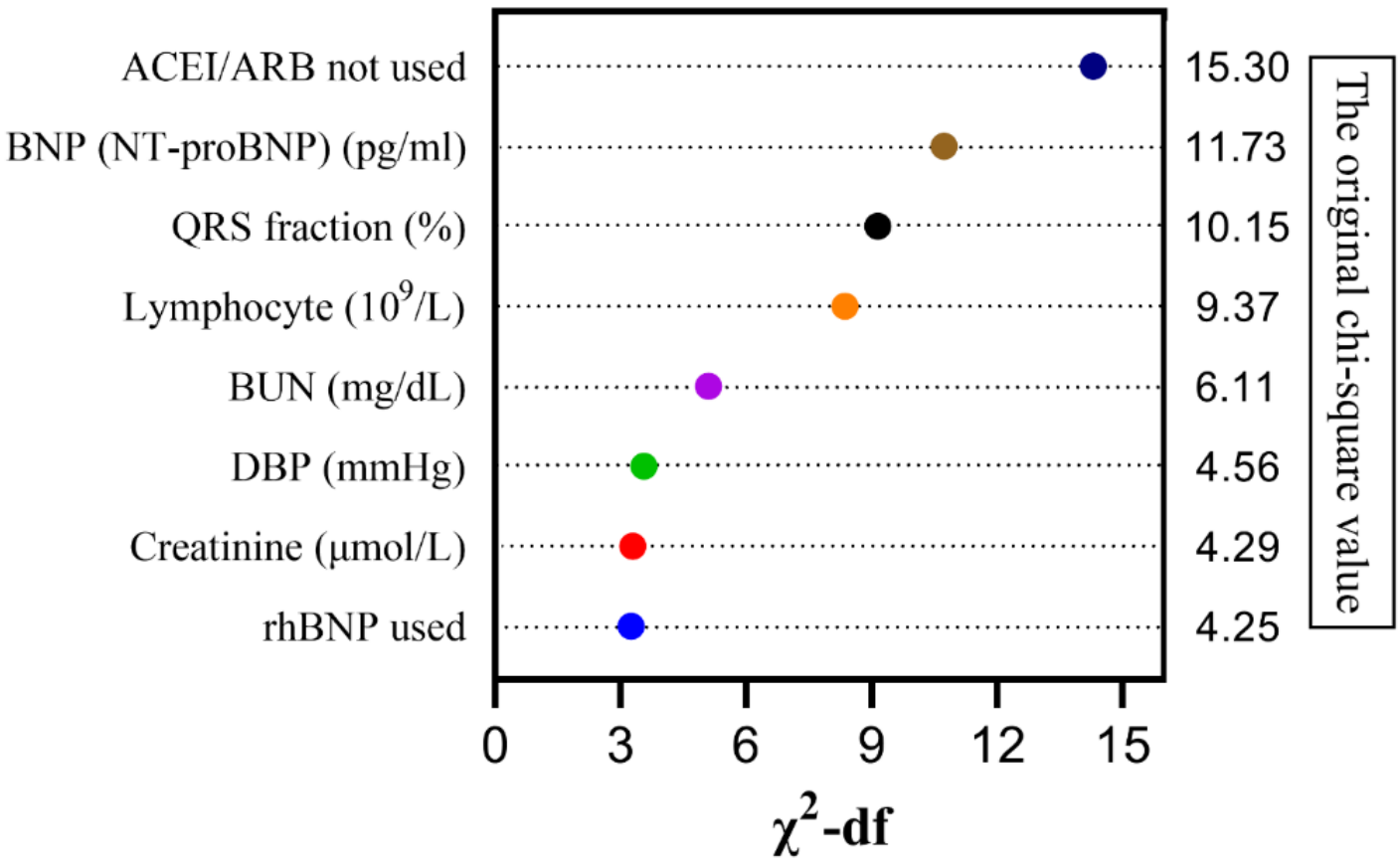

Figure 1

Relative importance of individual predictors within the final risk model. The relative importance of each predictor was calculated from the Wald chi-square (χ^2) minus the predictor's degrees of freedom (*df*) (χ^2-*df*).

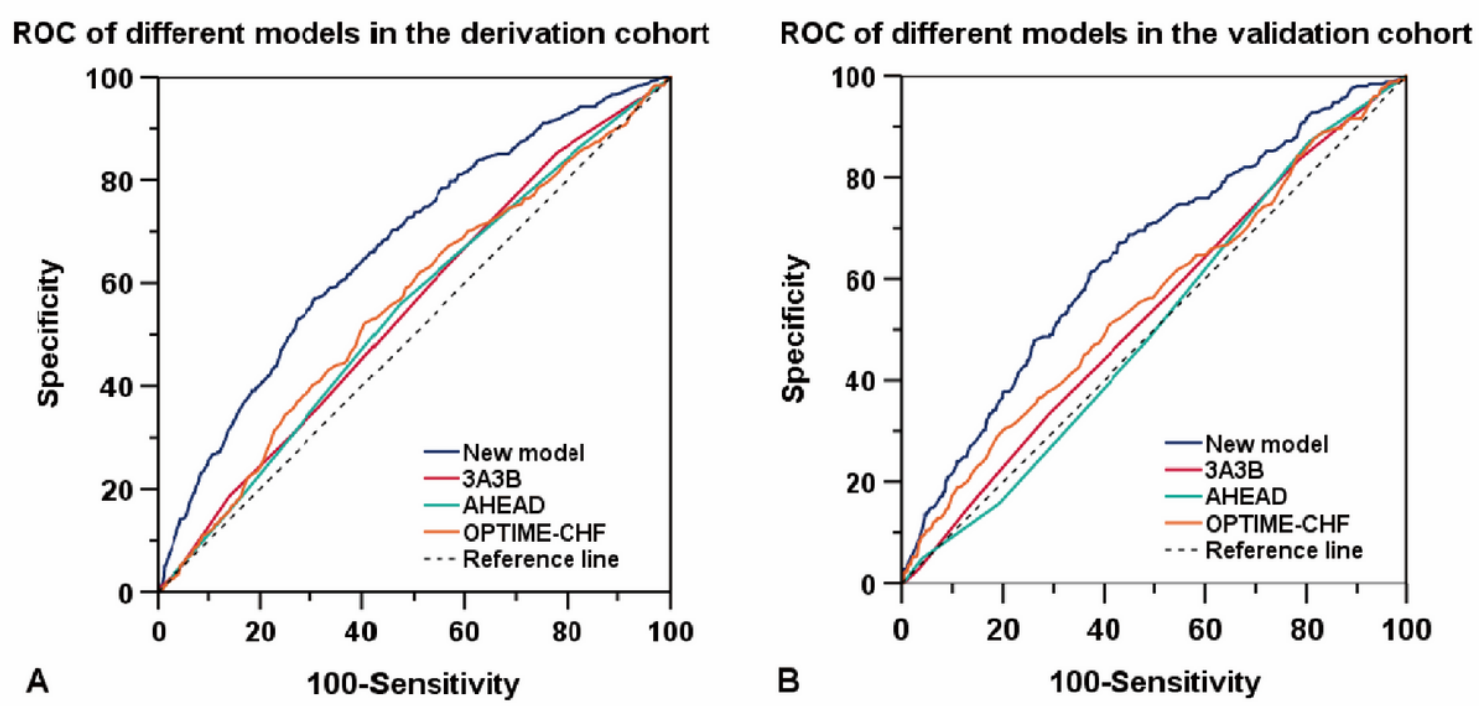

Figure 2

The receiver operating characteristic curve (ROC) for scoring models in the derivation and validation cohort.

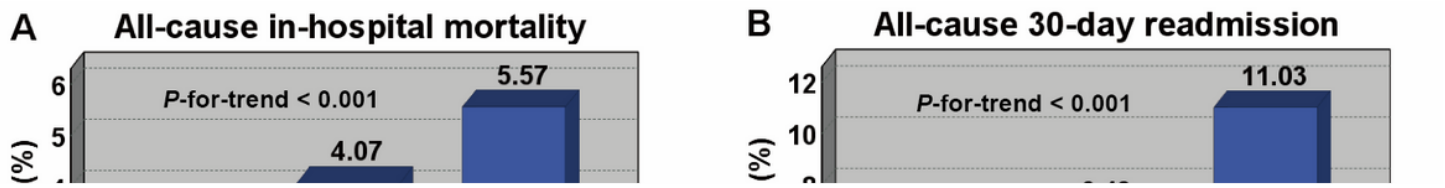

Figure 3

The incidence of outcome events for patients with different risk stratification in the entire cohort. The points of 0-4, 5-8, and ≥ 9 represent the low-, medium-, and high-risk stratification respectively.