A nomogram to predict the in-hospital mortality of patients with congestive heart failure and chronic kidney disease

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Abstract

Aims  Patients with congestive heart failure (CHF) may also suffer from chronic kidney disease (CKD), and the two conditions may interact to increase the risk of death. The purpose of this study was to investigate the risk factors contributing to in-hospital mortality in patients with CHF and CKD and to develop a nomogram to predict the risk of in-hospital mortality.

Methods and results  This retrospective study used data from the Marketplace for Medical Information in Intensive Care (MIMIC-IV, version 1.0). Patients diagnosed with CHF and CKD in MIMIC-IV were included in this study. The least absolute shrinkage and selection operator (LASSO) logistic regression is used to select risk variables for the nomogram model, and boot-strap is used for internal validation. Simplified Acute Physiology Score II (SAPS II) and Logistic Organ Dysfunction Score (LODS) were compared with the nomogram model by the area under the receiver operating characteristic curve (AUC) and decision curve analysis (DCA). A total of 4638 adult patients with CHF and CKD were included in the final cohort; of them, 707 (15.2%) died and 3931 (84.8%) survived during hospitalization. Our final model included the following 13 variables: age, acute kidney injury, myocardial infarction, anaemia, heart rate ≥ 100 b.p.m., systolic blood pressure ≥ 130 mmHg, anion gap (AG) ≥ 20 mEq/L, sodium ≥ 145 mEq/L, red blood cell distribution width (RDW) ≥ 15.5%, white blood cell count ≥ 10 K/μL, continuous renal replacement therapy (CRRT), angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, and beta-blocker. The corrected C-statistic of the nomogram was 0.767, and the calibration curve indicating good concordance between the predicted and observed values. The nomogram demonstrated good accuracy for predicting the in-hospital mortality with an AUC of 0.771 (95% CI: 0.752–0.790), while the AUC for SAPS II and LODS was 0.747 (95% CI: 0.726–0.767) and 0.752 (95% CI: 0.730–0.773), respectively. DCA found that when the threshold probability was 0.05 to 0.41, the nomogram model could provide a greater net benefit than SAPS II.

Conclusions  In this retrospective cohort analysis of patients with CHF and CKD, we identified 13 independent variables associated with in-hospital mortality using LASSO logistic regression. RDW, AG, and CRRT were reported to play a significant role in in-hospital mortality among patients with CHF and CKD for the first time. Based on a simplified model including 13 variables, a nomogram was drawn to predict the risk of in-hospital mortality. In comparison with SAPS II and LODS, the nomogram model performed well.

Keywords  Congestive heart failure; Chronic kidney disease; Nomogram; Red blood cell distribution width; Anion gap; Continuous renal replacement therapy; MIMIC-IV

Introduction

Heart failure (HF), a common clinical syndrome associated with high morbidity and mortality rates. It has a prevalence of approximately 1–2% of the adult population in developed countries, and its incidence in European and American countries is 1–9/1000 person-years. In Europe, the rate of 1 year all-cause mortality for hospitalized patients with heart
failure was 17%. About 40% to 50% of patients with heart failure also have chronic kidney disease. Even a mild reduction in the glomerular filtration rate is associated with an increased risk of all-cause mortality. An American study found that HF hospitalization rates were high among patients with CKD, and patients with CKD with HF had a higher risk of CKD progression and death. In conclusion, HF and CKD often occur together, increasing the risk of death for patients.

However, there are few studies on the risk factors of in-hospital mortality in patients with congestive heart failure (CHF) and CKD and no models have been developed specifically to predict in-hospital mortality in patients with these conditions. In patients with CHF and CKD, there can be various factors influencing in-hospital mortality, such as heart rate, blood pressure, medication treatment for HF, and so on; however, the relative contribution of each factor is unknown. As a visualization tool, a nomogram shows the weights of variables in a model and can be used to calculate probabilities of outcomes. Therefore, the purpose of this study was to identify the risk factors contributing to in-hospital mortality in patients with CHF and CKD and to develop a nomogram model for predicting in-hospital mortality using these risk factors.

**Methods**

**Source of data**

This retrospective study used data from the Marketplace for Medical Information in Intensive Care (MIMIC-IV, version 1.0), a large publicly available database comprising de-identified health-related data from patients who were admitted to the critical care units of the Beth Israel Deaconess Medical Center (BIDMC, Boston, MA, USA) in 2008–2019. The requirement for individual patient consent is not essential, access to the database is granted by passing the Collaborative Institutional Training Initiative (CITI) examination. One author (JM Chen) has completed the CITI examination (certification number: 46121351) and received permission to use the database for research.

**Study population and data extraction**

PgAdmin PostgreSQL (version 10.18, Bedford, USA) tools and Navicat Premium (version 15.0.12) were used for the raw data extraction. Inclusion criteria for the study population were as follows: (i) adult patients; (ii) patients admitted for the first time to the intensive care unit (ICU); and (iii) patients with CHF and CKD. The screening process is shown in Figure 1. Patients without ICU records were excluded from this study as only patients with ICU records had vital signs information. For patients with multiple ICU admissions, only the first ICU admission is considered to avoid duplication of information. The diagnosis information was taken from the table ‘diagnoses_icd’ and ‘d_icd_diagnoses’ in the database. Supporting Information, Table S1 provides the International Classification of Diseases (ICD) code of CHF and CKD.

The following variables are extracted in first-time ICU patients: (i) co-morbidities; Supporting Information, Table S1 provides the ICD code of the disease or a SQL query used to extract the ICD code; (ii) demographic data; (iii) the first vital signs within 24 h during the ICU admission; (iv) the first laboratory data obtained within 24 h during the ICU admission; (v) medications administered during the ICU admission; (vi) continuous renal replacement therapy (CRRT) records; (vii) serum creatinine values, used to calculate estimated glomerular filtration rate (eGFR); (vii) Simplified Acute Physiology Score II (SAPS II) and Logistic Organ Dysfunction Score (LODS). The code for data extraction is available on GitHub (https://github.com/MIT-LCP/mimic-iv). Each table in the MIMIC-IV database has a special ID (such as subject-id, hadm-id, and stay-id), and we use Stata (version 16.0, Texas, USA) to merge the tables based on these IDs to obtain a complete hospitalization information table.

**Statistical analysis**

R software (version 3.6.3; https://www.r-project.org/) was used for the raw data processing and statistical analysis. We used the predictive mean matching method of the ‘mouse’ package to impute the missing values in a single time since less than 1% of all key variables were missed. The 4638 patients included in the study were divided into two groups based on non-survival or survival during hospitalization, and variables are displayed and compared between groups. Shapiro–Wilk tests were used to assess the distribution of continuous variables, non-normally distributed continuous variables are summarized as the median and interquartile range (IQR), and categorical variables are expressed as n (%). The Wilcoxon rank-sum test was used to compare non-normally distributed continuous variables between the two groups, whereas the χ² test was used to compare normally distributed continuous variables.

**Model development phase**

(i) For clinical application and statistical analysis, continuous variables were classified into high and low levels according to the normal range provided in the database, heart rate and systolic blood pressure for which no normal range is
provided in the database are classified according to the clinical routine cut-off values. One continuous variable generated two dummy variables that will be incorporated into the multivariate logistic regression model as appropriate. (ii) As the number of events per variable\(^{10,11}\) of this study is \(\geq 20\), all variables were entered into the least absolute shrinkage and selection operator (LASSO) multivariate logistic regression analysis to obtain a simplified model for predicting the in-hospital mortality. The largest \(\lambda\) that is still within one standard error of the minimum binomial deviance was used for the variable selection. The odds ratios (ORs) are presented with 95% confidence intervals (CIs). (iii) A nomogram was used to visualize the results of the LASSO logistic regression. The calibration curve was used to confirm the calibration performance of the nomogram model. The discriminative ability of the models was determined by the area under the receiver operating characteristic curve (AUC), and decision curve analysis (DCA) was used to evaluate the clinical utility of the models for decision-making. (iv) Internal validation of the model’s performance was estimated using corrected C-statistic, which was obtained from the bootstrapping method (500 replications). Statistical significance was set at \(P < 0.05\).

**Results**

**Baseline characteristics**

As shown in Figure 1, 67,855 patients were diagnosed with CHF in the MIMIC-IV database; of them, 20,840 (30.7%) had CKD. After screening, a total of 4638 adult patients with CHF and CKD were included in the final cohort, of whom 707 (15.2%) died and 3931 (84.8%) survived during hospitalization. Table 1 shows the baseline characteristics of patients who died versus those who survived, and Supporting Information, Table S2 shows the baseline characteristics of the transformed variables. In the preliminary statistical analysis, non-survivors were older than survivors, with a median age of 80.99 (IQR, 73.46–87.33) in non-survivors and 76.99 (IQR, 67.98–84.77) in survivors. Regarding co-morbidities, we unexpectedly found that patients who died were less likely to suffer from anaemia and diabetes but not MI, AKI, and infection than surviving patients. Furthermore, the non-survivors displayed higher heart rates, AG, BUN, potassium, WBC, and RDW, and lower SBP, DBP, haemoglobin, and RBC. Non-survivors had a lower eGFR than survivors. Additionally, the proportion of CRRT treatment in non-survivors was higher.

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**Figure 1** Flow chart of inclusion and exclusion process of patients admitted with CHF and CKD. CHF, congestive heart failure; CKD, chronic kidney disease; ICU, intensive care unit.
Table 1 Baseline characteristics of patients with CHF and CKD

| Variables | Overall | Survivor | Non-Survivor | P    |
|-----------|---------|----------|-------------|------|
| Age (median [IQR]) | 77.7 [68.7, 85.2] | 77.0 [68.0, 84.8] | 81.0 [73.5, 87.3] | <0.001 |
| Gender, % (F) | 19.8 [39.2] | 15.4 [39.2] | 27.5 [38.9] | 0.096 |
| Anaemia (%) | 1671 [36.0] | 1390 [35.4] | 281 [39.7] | 0.028 |
| Diabetic (%) | 2652 [57.2] | 2281 [58.0] | 371 [52.5] | 0.007 |
| Infection (%) | 2498 [53.9] | 2154 [54.8] | 344 [48.7] | 0.003 |
| CRRT (%) | 363 [7.8] | 240 [6.1] | 123 [17.4] | <0.001 |
| Beta-blocker (%) | 1472 [31.7] | 1376 [35.0] | 96 [13.6] | 0.081 |
| WBC (median [IQR]) | 2806 [60.5] | 2497 [63.5] | 309 [43.7] | <0.001 |
| RBC (median [IQR]) | 2928 [63.1] | 2525 [64.2] | 403 [57.0] | <0.001 |
| Potassium (median [IQR]) | 13 [1.5, 1.8] | 13 [1.5, 1.8] | 14 [1.6, 1.9] | <0.001 |
| BUN (median [IQR]) | 41 [28, 62] | 40 [27, 60] | 49 [32, 74] | 0.001 |
| Glucose (median [IQR]) | 136 [107, 183] | 135 [107, 181] | 139 [106, 193] | 0.001 |
| Potassium (median [IQR]) | 30.0 [17.5, 43.3] | 30.9 [17.9, 44.1] | 25.4 [15.2, 38.6] | <0.001 |
| CRRT (%) | 363 [7.8] | 240 [6.1] | 123 [17.4] | <0.001 |
| Beta-blocker (%) | 1472 [31.7] | 1376 [35.0] | 96 [13.6] | 0.081 |
| ACEI/ARB (%) | 13 [1.5, 1.8] | 13 [1.5, 1.8] | 14 [1.6, 1.9] | <0.001 |
| CRRT (%) | 363 [7.8] | 240 [6.1] | 123 [17.4] | <0.001 |
| Diabetic (%) | 2806 [60.5] | 2497 [63.5] | 309 [43.7] | <0.001 |
| RBC (median [IQR]) | 2928 [63.1] | 2525 [64.2] | 403 [57.0] | <0.001 |
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| BUN (median [IQR]) | 41 [28, 62] | 40 [27, 60] | 49 [32, 74] | 0.001 |
| Glucose (median [IQR]) | 136 [107, 181] | 135 [107, 181] | 139 [106, 193] | 0.001 |
| Potassium (median [IQR]) | 30.0 [17.5, 43.3] | 30.9 [17.9, 44.1] | 25.4 [15.2, 38.6] | <0.001 |
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ACEI/ARB, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers; AG, anion gap; AKI, acute kidney injury; BUN, blood urea nitrogen; CRRT, continuous renal replacement therapy; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; F, female; HR, heart rate; LODS, Logistic Organ Dysfunction Score; WBC, white blood cell count; M, male; MI, myocardial infarction; MRAs, mineralocorticoid receptor antagonists; RBC, red blood cell count; RDW, red blood cell distribution width; SBP, systolic blood pressure; SAPS II, Simplified Acute Physiology Score II.

(17.4% vs. 6.1%). Regarding SAPS II and LODS, non-survivors scored higher. Finally, the survivors exhibited a higher use frequency of ACEIs/ARBs, beta-blockers, and diuretics.

Development of a prediction nomogram

The multivariate regression analysis (full model) contained 34 variables, including 22 categorical variables generated from continuous variables. The most important variables related to in-hospital mortality of patients with CHF and CKD identified by LASSO multivariable logistic regression are presented in the simplified model (Table 2). In the multivariate regression analysis, age, AKI, MI, HR ≥ 100 b.p.m., SBP ≤ 90 mmHg, DBP ≥ 80 mmHg, sodium ≥ 145 mEq/L, RDW ≥ 15.5%, WBC ≥ 10 K/μL, CRRT, ACEI/ARB, and beta-blocker. All of these variables were significantly associated with in-hospital mortality in patients with CHF and CKD. Based on the simplified model, a nomogram was plotted to predict the probability of in-hospital mortality in patients with CHF and CKD (Figure 2).

Prediction nomogram validation and comparison

Figure 3 shows that the calibration curve constructed by bootstrap (500 bootstrap resamples), apparent line and bias-corrected line deviated only slightly from the ideal line, indicating good concordance between the predictions and observations. In Figure 4A, the nomogram demonstrated good accuracy for predicting the in-hospital mortality of patients with CHF and CKD with an AUC of 0.771 (95% CI: 0.726–0.790), while the AUC for SAPSII and LODS was 0.747 (95% CI: 0.726–0.767) and 0.752 (95% CI: 0.730–0.773), respectively. The corrected C-statistic of the nomogram model obtained from bootstrap resampling was 0.767, indicating good internal validation. The DCA curve (Figure 4B) was drawn to demonstrate a clinical application of the
SBP simplification in MIMIC-IV. The following 13 variables were included in the simplification analysis to identify independent risk factors of in-hospital mortality in patients with CHF and CKD in the clinical utility of this nomogram. The contribution of AKI, MI, anaemia, HR ≥ 100 b.p.m., SBP ≥ 130 mmHg, AG, anion gap; AKI, acute kidney injury; ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blockers; BUN, blood urea nitrogen; CRRT, continuous renal replacement therapy; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; F, female; HR, heart rate; M, male; MI, myocardial infarction; MRAs, mineralocorticoid receptor antagonists; RBC, red blood cell count; RDW, red blood cell distribution width; SBP, systolic blood pressure; WBC, white blood cell count.

Discussion

This retrospective cohort analysis used LASSO logistic regression analysis to identify independent risk factors of in-hospital mortality in patients with CHF and CKD in MIMIC-IV. The following 13 variables were included in the simplified model: age, AKI, MI, anaemia, HR ≥ 100 b.p.m., SBP ≥ 130 mmHg, AG ≥ 20 mEq/L, sodium ≥ 145 mEq/L, RDW ≥ 15.5%, WBC ≥ 10 K/μL, CRRT, ACEI/ARB, and beta-blocker. A nomogram based on a simplified model was developed to predict the risk of in-hospital mortality in patients with CHF and CKD. This nomogram has a good calibration; compared with SAPS II and LODS, it has a good calibration and clinical utility.

To the best of our knowledge, this is the first visual nomogram with the ability to predict the risk of in-hospital mortality for patients with CHF and CKD. Benefitting from the 10 year data collection of the MIMIC-IV database, our study included a total of 4638 patients, a larger sample size than those of previous studies by Bansal et al.12,13 In addition, all variables in the simplified model are easily available, which guarantees the clinical utility of this nomogram. The contribution of RDW, AG, and CRRT to in-hospital mortality among patients with CHF and CKD was reported for the first time.

A comparison of the nomogram model with SAPS II and LODS has shown that the nomogram model discriminates
better than SAPS II and LODS and has a higher net clinical benefit than SAPS II. Also, our nomogram model has the following advantages: (i) it is simpler and more intuitive than SAPS II and LODS; and (ii) it was designed specifically for patients with CHF and CKD, unlike other score models that were designed for all ICU patients. It can be utilized not only to predict the risk of in-hospital mortality of patients with CHF and CKD but also to identify whether the variables in the model are risk or protective factors, which will have an impact on the physician’s decision-making.
In our study, AKI was independently associated with in-hospital mortality, with a prevalence of 60.8% in patients with CHF and CKD, a surprising figure compared with approximately 30.6% in patients with HF and CKD reported by Juan et al.\textsuperscript{14} Patients with AKI were more likely to be referred to the ICU, which may have contributed to this increase. In this study, patients with AKI had a 1.65-fold increased risk of death. Among the 13 selected variables, CRRT accounted for the largest weight in the simplified model (OR, 3.47; 95% CI, 2.66–4.54). CRRT is required when AKI or acute renal failure occurs\textsuperscript{15}; however, it does not appear to reduce the risk of in-hospital death in patients with CHF and CKD. Instead, patients receiving CRRT have a 3.47-fold increased risk of death. There may have been an existing critical condition when the physician decided on CRRT, which may have contributed to a higher risk of death, but CRRT failed to alleviate the crisis. Similarly, the results of a meta-analysis showed a lack of conclusive evidence of a definite advantage of CRRT in terms of patient survival.\textsuperscript{16}

As shown in Table 1, the median eGFR of overall patients was 30.0 mL/min/1.73 m\textsuperscript{2}, indicating that half of the patients had a renal function at stage IV or stage V. The median eGFR of patients who died was even lower, about 25.4 mL/min/1.73 m\textsuperscript{2}. The prevalence of metabolic acidosis increases as eGFR decreases,\textsuperscript{17} and AG divides metabolic acidosis into two categories: high AG metabolic acidosis and hyperchloraemic metabolic acidosis.\textsuperscript{18} In our research, the AG of the dead patients was higher than that of the surviving patients, while the bicarbonate level decreased, indicating that the dead patients were prone to acid–base imbalance. AG ≥ 20 mEq/L was finally included in the simplified model after LASSO logistic regression, suggesting that compared with bicarbonate, an increased AG was a stronger predictor of death in patients with CHF and CKD. The role of AG in-hospital mortality in patients with HF and CKD has not been studied, but it has been shown that an elevated AG is a risk factor for death in patients with advanced CKD.\textsuperscript{19}

Laboratory indicators such as RDW, WBC, and blood sodium were incorporated into the final model. RDW is a parameter used to reflect the degree of red blood cell volume heterogeneity, but recent studies have shown that it plays a greater role than that.\textsuperscript{20} A 13 year cohort study confirmed that RDW is a predictor of all-cause mortality in patients with CKD\textsuperscript{21} and associated with long-term mortality in patients with HF.\textsuperscript{22} Our study showed that elevated RDW increased the risk of death in patients with CHF and CKD by 1.81-fold after correcting for other confounding factors. Moreover, a meta-analysis showed that RDW is related to the prognosis of multiple diseases as well as the overall mortality of the general population.\textsuperscript{20} Heart failure is characterized by sodium retention and extracellular volume overload, which can be further exacerbated by concomitant renal dysfunction.\textsuperscript{23} Serum sodium imbalance (hypernatraemia or hyponatraemia) is a risk factor for death in patients with HF.\textsuperscript{24} However, in our study, only hypernatraemia was an independent risk factor for hospital mortality in patients with CHF and CKD. Elevated WBC is an indicator of poor prognosis in patients with HF as well as those with CKD.\textsuperscript{25,26}

Several other variables in the nomogram were associated with in-hospital mortality among patients with CHF and CKD. In our study, the median age of not-surviving patients was greater than that of surviving patients. Aging was associated with an increased risk of death in patients with heart failure,\textsuperscript{27–29} as well as patients with CHF and CKD. In addition to this, we noted that ICU patients with CHF and CKD have a median age of 77 years, which is much higher than the median age of ICU patients or AHF patients in other studies, which was 62–65 years.\textsuperscript{30–32} The chronic, long-term nature of CKD may explain this difference. ACEIs/ARBs and beta-blockers are commonly used to treat HF and can decrease HF hospitalizations and improve survival\textsuperscript{33}; in patients with CHF and CKD, beta-blockers have been shown to reduce all-cause mortality.\textsuperscript{34} HR above 100 b.p.m. is a risk factor for in-hospital mortality among patients with CHF and CKD, further demonstrating the importance of beta-blockers. In

Figure 4 Comparison of the nomogram with SAPS II and LODS. (A) Receiver operating characteristic curves, (B) decision curve analysis.
In line with previous studies, it has been shown that patients with acute and chronic heart failure suffer from an elevated heart rate that is associated with adverse outcomes. As for elevated SBP, although hypertension is well known to induce the development of HF, a higher SBP appears to have a protective effect on survival in patients with established HF. Among the co-morbidities, MI is an independent risk factor for in-hospital mortality in patients with CHD and CKD, a finding that is consistent with those of current studies in patients with HF. Anaemia is the second most common complication of patients with CHF and CKD, with a prevalence of 57.2%, but it does not increase the risk of in-hospital mortality; on the contrary, it is protective. Studies have also shown that the administration of erythropoietin to increase haemoglobin levels increases the risk of mortality in patients with HF and CKD, and a large randomized controlled trial also showed that increasing haemoglobin with an erythrocyte stimulant (darbepoetin alfa) increased the risk of stroke in HF patients with anaemia. Although the mechanism of the role of anaemia in patients with CHF and CKD has not been investigated, in patients with CKD, chronic moderate anaemia reduces glomerular damage, while elevated haemoglobin accelerates glomerulosclerosis. This may partly explain why anaemia reduces the risk of death in patients with CHF and CKD.

This study has some limitations: First, selection bias may have been caused by the use of data from a single-centre database. Second, some candidate variables were discarded because the missing values were greater than 20%, such as brain natriuretic peptide, NT-pro-brain natriuretic peptide, and first 24 h urine output in the ICU. Third, the patients included in this study were all admitted to the ICU, meaning that patients with a low disease severity may have been excluded from the study. Fourth, unlike the MIMIC-III, MIMIC-IV does not provide follow-up data, so the long-term mortality of patients with CHF and CKD is unknown. Fifth, although internal validation of model performance is estimated using the bootstrap method, our predictive model lacks validation of an external population. Finally, the nature of observational research indicates that unknown confounding factors may affect our results.

## Conclusions

In this retrospective cohort analysis of patients with CHF and CKD, we identified 13 independent variables associated with in-hospital mortality using LASSO logistic regression. RDW, AG, and CRRT were reported to play a significant role in in-hospital mortality among patients with CHF and CKD for the first time. Based on a simplified model including 13 variables, a nomogram was drawn to predict the risk of in-hospital mortality. In comparison with SAPS II and LODS, the nomogram model performed well. The model performed well in internal validation, but external validation is still required.

## Conflict of interest

None declared.

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## Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

### Table S1. ICD codes or SQL queries for obtaining ICD codes.

### Table S2. Basic characteristics of the transformed continuous variable. RBC, red blood cell count; RDW, red blood cell distribution width; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; AG, anion gap; BUN, blood urea nitrogen; WBC, white blood cell count; eGFR, estimated glomerular filtration rate; F, female; M, male.

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