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ORIGINAL ARTICLE

Role of depressive symptoms in the prognosis of heart failure and its potential clinical predictors

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Abstract

Aims This study aims to analyse the factors associated with prognosis in hospitalized patients with heart failure, particularly the role of depressive symptoms, and to develop a prediction model for depressive symptoms based on clinical characteristics in hospitalized patients with heart failure.

Methods and results Baseline information was collected at admission, and patients were followed up after discharge. The endpoint events were being hospitalized for heart failure or all-cause death. Depressive symptoms were evaluated and defined via the Patient Health Questionnaire (PHQ)-2 and PHQ-9. The bidirectional elimination was used to screen independent predictors of heart failure with depression symptoms. The least absolute shrinkage and selection operator (LASSO) optimized the predictor variables, and the prediction model was constructed. The model was internally validated by the bootstrap sampling method (Bootstrap), and its performance was assessed by discrimination and calibration. The mean age of patients with heart failure was 69.43 ± 12.15 years, and the proportion of males was 66.67%. The prevalence of depressive symptoms in hospitalized patients with heart failure was 46.83%, and the prevalence of moderate/severe depressive symptoms was 11.62%. Eighty cases (30.30%) were readmitted for heart failure, and 13 cases (4.92%) were all-cause deaths. Depressive symptoms (HR = 2.43, 95% CI: 1.55–3.80) and the PHQ-9 score (HR = 1.11, 95% CI: 1.06–1.16) were both independent risk factors for endpoint events ($P < 0.001$). For heart failure patients combined with depressive symptoms, obesity (OR = 0.27, 95% CI: 0.09–0.77, $P = 0.015$), *N*-terminal brain natriuretic peptide precursor (NT-proBNP) level (lnNT-proBNP: OR = 1.55, 95% CI: 1.20–2.01, $P < 0.001$) and red blood cell distribution width (RDW) (OR = 1.26, 95% CI: 1.08–1.47, $P = 0.004$) were the independent factors. Six variables, including cardiovascular disease hospitalization history, obesity, renal insufficiency, NT-proBNP level, neutrophil ratio and RDW, were included to construct the prediction model. The area under the curve (AUC) was 0.730 in the original data, and the calibration curve was approximately distributed along the reference line in Bootstrap (500 resamplings), indicating the high level of discrimination and calibration of this model.

Conclusions Depressive symptoms and the PHQ-9 score are both independent risk factors for the prognosis of hospitalized patients with heart failure. In hospitalized patients with heart failure, the risk prediction model developed in this study has good predictive power for depressive symptoms.

Keywords Heart failure; Prognosis; Depression symptoms; Patient Health Questionnaire-9; Prediction model

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Introduction

Heart failure (HF) is the terminal stage of cardiovascular diseases (CVDs). Despite significant advances in the diagnosis, treatment and management of HF,[1,2] patients with HF are still at a high risk of mortality and readmission.[3] Recently, studies have shown that the incidence of mortality and readmission is 17.4% and 43.9% for patients with acute heart

failure and 7.2% and 31.9% for patients with chronic heart failure (CHF), respectively.[4] Therefore, the identification of risk factors for prognosis in patients with HF is vital for their clinical treatment and long-term prognosis.

Patients with HF are at high risk for depression,[5] and depression can worsen cardiac function through various mechanisms, including inflammatory responses, endothelial dysfunction, platelet hyperactivation, hypothalamic–pituitary–adrenal axis hyperfunction and autonomic dysfunction.[6,7] In a meta-analysis of 4012 patients with HF,[8] those with depression had a significantly higher risk of all-cause mortality than those without depression (HR = 1.51, 95% CI: 1.19–1.91). In a subgroup analysis, major depression was found to be associated with a higher risk of all-cause mortality in patients with HF (HR = 1.98, 95% CI: 1.23–3.19), compared with mild depression, which was not associated with a higher risk of all-cause mortality (HR = 1.04, 95% CI: 0.75–1.45). Similarly, a 20-year follow-up study found that major depression significantly increased the risk of all-cause mortality in patients with HF when compared with the non-depression group (adjusted HR = 1.64, 95% CI: 1.27–2.11, P = 0.001), suggesting that depression is an independent risk factor for long-term prognosis in patients with HF.[9]

Currently, depression symptoms are majorly evaluated by questionnaire scales, including the Patient Health Questionnaire (PHQ)-9, Beck Depression Inventory (BDI), Self-Rating Depression Scale and Hamilton Depression Scale (HAMD).[10,11] However, because of the variability of different scales and individual subjectivity, they still partially weaken the accuracy of screening and diagnosis of depression in patients with HF.[8] For example, a meta-analysis showed distinct diagnostic rates in the same cohort of patients with HF via evaluation of BDI (62%) and the Center for Epidemiological Survey-Depression Scale (CES-D, 31%).[12] Notably, there is a causal linkage between the severity of depression and cardiac events. Even mild depressive symptoms might still increase the risk.[13] Patients with mild depressive symptoms, on the other hand, may be classified as non-depressed using widely used depression questionnaires. As a result, a simple classification of depression severity (e.g. non-depression vs. depression) may reduce the strength of the association between depression and HF patient prognosis. Therefore, objective indicators for assessing depressive symptoms in hospitalized patients with HF are necessary.

A predictive model is of great value for early screening of diseases, clinical treatment and prognosis guidance. Thus, building a predictive model through clinically objective variables may be a more effective and earlier way to identify depressive symptoms than the conventional subjective scales. This study aims to analyse the factors associated with the prognosis of hospitalized patients with HF and to investigate the correlation between the PHQ-9 score and the prognosis in patients with HF. Meanwhile, it aims to develop a reliable prediction model for depressive symptoms in hospitalized patients with HF and to provide objective indicators for the early detection and treatment of these patients' depressive symptoms.

Methods

Study design and participants

The study is a single-centre cohort study enrolling patients with HF who were hospitalized in the Department of Cardiology at the Third Affiliated Hospital of Soochow University from December 2019 to August 2021. The study was approved by the Ethics Committee of the Third Affiliated Hospital of Soochow University and registered with the China Clinical Trials Centre Registry (registration number ChiCTR2000029968).

Inclusion and exclusion criteria

This study included hospitalized patients with HF who met the diagnostic criteria for the disease.[14] Exclusions mainly considered recent organic brain injury or psychosomatic disorders, a history of depression or psychiatric disorders, current use of antidepressants or other antipsychotics, conditions that might affect the patients' survival expectations and personal history and other diseases that might affect the patients' psychosomatic status. The following are the specific inclusion and exclusion criteria.

Inclusion criteria include (i) age ≥18 years; (ii) ability to express and comprehend voluntarily written the informed consent; (iii) presence of HF-related symptoms or signs, and necessary ancillary investigations, such as plasma *N*-terminal brain natriuretic peptide precursor (NT-proBNP) level and echocardiography to confirm cardiac insufficiency[14]; and (4) New York Heart Association (NYHA) II–IV at screening.

Exclusion criteria include (i) stroke or transient ischaemic attack within the previous 3 months; (ii) history of malignancy; (iii) history of depression or other mental diseases; (iv) recent significant mental stress, or taking antidepressants and other antipsychotics; (v) difficulty communicating; (vi) history of substance abuse; (vii) heart transplant recipient or listed for a heart transplant; (viii) alcoholic and hyperthyroid heart failure; and (ix) already participating in other clinical trials.

Physical and clinical examination

Baseline data on admitted patients were obtained through interviews, medical records and actual measurements and included (i) demographic baseline information, including

gender, age, body mass index (BMI), blood pressure, education and CVD hospitalization history, and (ii) comorbidities, including hypertension, diabetes mellitus (DM), coronary artery disease (CAD), atrial fibrillation, renal insufficiency and anaemia. Renal insufficiency was defined as an estimated glomerular filtration rate (eGFR) $<$ 90 mL/min, calculated using the Modification of Diet in Renal Disease formula[15]; anaemia was defined as haemoglobin (Hb) $<$ 120 g/L in men and $<$110 g/L in women; (3) echocardiogram was completed within 48 h of admission (ultrasound equipment: EPIQ7C; Philips; Netherlands), left ventricular ejection fraction (LVEF) was measured by biplane Simpson method, and LV end-diastolic diameter and LV end-systolic diameter were measured by M-mode echocardiogram; (iv) ECG-related parameters, such as heart rate (HR) and QRS interval; (v) blood was drawn to detect routine laboratory parameters, such as *N*-terminal brain natriuretic peptide precursor (NT-proBNP), biochemical parameters and blood lipids tests.

Assessment of depression symptoms

In this study, hospitalized patients with HF were screened for depression using PHQ-2 and PHQ-9 as previously reported.[11,16] Depressive symptoms are defined as a positive manifestation of PHQ-2 and the PHQ-9 score $\geq$ 10. The non-depressive symptom group was further divided into the non-depressive tendency group (PHQ-9 score $<$ 5) and the depressive tendency group (5 $\leq$ PHQ-9 score $<$10).

Follow-up and study endpoint events

All patients with HF were discharged from the hospital on standardized HF medication unless contraindicated. Patients were followed up at 1, 3, 6, 12, 18 and 24 months. The study's endpoint events were being hospitalized for heart failure or all-cause death.

Statistical analysis

Normally distributed data were expressed as mean ± SD, whereas non-normally distributed data were expressed as median and interquartile range. Categorical variables were expressed as frequency or rate (%). The chi-square test (categorical variable), one-way analysis of variance (normally distributed continuous variable) and Mann–Whitney *U* tests (skew continuous variable) were used to analyse the differences between groups. Kaplan–Meier curves were used to analyse the differences in the risk of endpoint events between the groups, and log-rank tests were used to assess the statistical significance of the differences. Variables with $P < 0.10$ in the univariate Cox regression were included in the multivariate regression analysis, and variables were screened by bidirectional elimination ($P < 0.05$ and $P > 0.10$ were set as entry and exit criteria, respectively). Considering the skewed distribution of NT-proBNP, a natural logarithm-transformation (ln) was performed on it. A Cox regression analysis was used to determine the association of depressive symptoms and PHQ score with the endpoint events in hospitalized patients with HF, with the degree of the association expressed as a hazard ratio and 95% confidence interval (CI). A two-sided $P < 0.05$ was considered a statistically significant difference.

Logistic regression analysis was used to determine the correlation between clinical characteristics and depressive symptoms, with the degree of correlation expressed as an odds ratio (OR) and a 95% CI. Variables with $P < 0.10$ in the univariate logistic regression were included in the multivariate regression analysis, which used bidirectional elimination to screen variables ($P < 0.05$ and $P > 0.10$ were set as entry and exit criteria, respectively). The prediction model was further optimized by the least absolute shrinkage and selection operator (LASSO), and the final predictor variables were screened and incorporated into a multivariate logistic regression model. The prediction model's accuracy and predictive power were evaluated using the area under the receiver operating curve (AUC). The prediction model was validated internally by the bootstrap sampling method (Bootstrap), and the calibration curve of the prediction model was further plotted to evaluate the difference between the predicted and actual values (statistical analysis was performed using R3.6.1).

Results

Analysis of aetiology of heart failure and prevalence of depressive symptoms in hospitalized patients with heart failure

Of the 317 hospitalized patients with HF, 37 were excluded: 16 had a history of malignancy, six had a cerebrovascular event within 3 months, three had a communication disorder, two had a history of heart transplantation, two were alcoholic heart failure, two were hyperthyroid heart failure, and six failed to complete the PHQ-9 assessment. As assessed by the PHQ-9, 150 (53.57%) had no depressive symptoms, 99 (35.36%) had mild depressive symptoms, and 31 (11.07%) had moderate/severe depressive symptoms. Sixteen of the 280 patients were lost during the follow-up (lost rate of 5.71%), and the remaining 264 cases had 93 endpoint events (35.22%) after 1–24 months of follow-up (median time: 9.02 months). Eighty (30.30%) were readmitted for heart failure, and 13 (4.92%) were all-cause deaths (Supporting Information, *Figure S1*).

Based on medical history and clinical information on admission, the aetiology of hospitalized patients with HF was classified as follows: 76 cases of ischaemic heart failure (28.79%), 22 cases of hypertensive heart disease (8.33%), 21 cases of valvular disease (7.95%),18 cases of dilated cardiomyopathy (6.82%), 7 cases of congenital heart disease (2.65%), 2 cases of hypertrophic cardiomyopathy (0.76%), 2 cases of pulmonary heart disease (0.76%), and 116 cases of unclear aetiology (43.94%) (Supporting Information, *Figure S2*).

Comparison of clinical characteristics between non-depressive and depressive symptoms groups

Table 1 shows the differences in clinical characteristics between the non-depressive symptom group and the depressive symptom group. In terms of categorical variables, the depressive symptom group had significantly higher rates of CVD hospitalization history (P = 0.002) and renal insufficiency (P = 0.002) and a significantly lower incidence of obesity (P = 0.005) than the non-depressive symptom group. In terms of continuity variables, age (P = 0.006), NT-proBNP level ($P < 0.001$), N (%) (P = 0.007) and RDW ($P < 0.001$) were significantly higher in the depressive symptoms group than in the non-depressive symptoms group, and L (%) (P = 0.011), TC (P = 0.008), LDL (P = 0.010), ApoA1 (P = 0.028) and ApoB (P = 0.029) were significantly lower than in the non-depressive symptoms group.

Comparison of clinical characteristics between non-endpoint and endpoint events groups

Supporting Information, *Table S1* demonstrates the differences in clinical characteristics between the non-endpoint events group and the endpoint events group. In terms of categorical variables, the endpoint events group had significantly higher rates of depressive symptoms ($P < 0.001$), CVD hospitalization history (P = 0.008), NYHA Class IV (P = 0.009), DM (P = 0.002), renal insufficiency (P = 0.023), anaemia (P = 0.002) and diuretic use (P = 0.024) than the non-endpoint events group. In terms of continuity variables, age (P = 0.012), length of hospitalization (P = 0.005), PHQ-9 score ($P < 0.001$) and NT-proBNP levels (P = 0.003) were significantly higher in the endpoint events group than in the non-endpoint events group.

Correlation between depressive symptoms and prognosis in hospitalized patients with heart failure

Univariate Cox regression showed a positive association between depressive symptoms and endpoint events

Table 1 Clinical characteristics of HF patients with or without depressive symptoms

	Non-depressive symptoms group (n = 141)	Depressive symptoms group (n = 123)	P
Age (years)	67.64 ± 12.67	71.48 ± 11.24	0.006
Male (%)	98 (69.50%)	78 (63.41%)	0.295
Education (%)			0.053
<12 year	95 (67.38%)	96 (78.05%)	
≥12 year	46 (32.62%)	27 (21.95%)	
CVD hospitalization history (%)	63 (44.68%)	78 (63.41%)	0.002
Obesity (%)	22 (15.60%)	6 (4.88%)	0.005
SBP (mmHg)	134.00 ± 23.06	129.08 ± 23.81	0.057
DBP (mmHg)	80.40 ± 15.35	77.03 ± 14.40	0.093
NYHA class (%)			0.138
II class	29 (20.57%)	22 (17.89%)	
III class	70 (49.65%)	50 (40.65%)	
IV class	42 (29.79%)	51 (41.46%)	
NT-proBNP (pg/mL)	2320.00 (1217.00–5330.00)	3850.00 (2250.00–9585.00)	<0.001
AF (%)	49 (34.75%)	56 (45.53%)	0.074
CAD (%)	73 (51.77%)	57 (46.34%)	0.379
Renal insufficiency (%)	96 (68.09%)	104 (84.55%)	0.002
TC (mmol/L)	4.24 ± 1.10	3.91 ± 0.95	0.008
LDL (mmol/L)	2.49 ± 0.88	2.24 ± 0.74	0.010
ApoA1 (g/L)	1.14 ± 0.77	1.03 ± 0.22	0.028
ApoB (g/L)	0.94 ± 0.66	0.82 ± 0.26	0.029
N (%)	63.29 ± 13.84	68.24 ± 9.2	0.007
L (%)	24.55 ± 9.15	21.67 ± 8.47	0.011
RDW (%)	13.58 ± 1.45	14.39 ± 2.20	<0.001

AF, atrial fibrillation; ApoA1, apolipoprotein A1; ApoB, apolipoprotein B; CAD, coronary artery disease; CVDs, cardiovascular diseases; DBP, diastolic blood pressure; L (%), lymphocyte ratio; LDL, low-density lipoprotein; N (%), neutrophil ratio; NT-proBNP, *N*-terminal brain natriuretic peptide precursor; NYHA, New York Heart Association; RDW, red blood cell distribution width; SBP, systolic blood pressure; TC, total cholesterol.

(HR = 2.63, 95% CI: 1.71–4.02, $P < 0.001$). Survival curves showed that patients in the depressive symptoms group had significantly higher endpoint events than those in the non-depressive symptoms group ($P < 0.001$) (*Figure 1A*). The multivariate Cox regression model suggested that depressive symptoms were an independent risk factor for endpoint events in hospitalized patients with HF (HR = 2.46, 95% CI: 1.57–3.86, $P < 0.001$) (Supporting Information, *Table S2*). Furthermore, the non-depressive symptoms group was divided into the non-depressive tendency group and the depressive tendency group according to the PHQ-9 score. Survival curves suggested that the higher propensity to depression is associated with the higher risk of endpoint events in hospitalized patients with HF ($P < 0.001$) (*Figure 1B*).

Correlation between Patient Health Questionnaire-9 score and prognosis in hospitalized patients for heart failure

Univariate Cox regression analysis showed that the PHQ-9 score was positively associated with the endpoint events (HR = 1.12, 95% CI: 1.07–1.16, $P < 0.001$). The variables age, NYHA classification, NT-proBNP (lnNT-proBNP) level, DM, length of hospitalization, diuretics and PHQ-9 score were screened by bidirectional elimination and included in a multivariate proportional risk Cox regression model; after adjusting for the variables, the PHQ-9 score was an independent risk factor for endpoint events in hospitalized patients with HF (HR = 1.10, 95% CI: 1.05–1.15, $P < 0.001$). All potential risk factors for endpoint events in hospitalized patients with HF: gender, age, NYHA classification, NT-proBNP (lnNT-proBNP) level, DM, CAD, renal insufficiency, anaemia, length of hospitalization, previous cardiac hospitalization, blood pressure and standardized medications (diuretics, beta-blockers and ACEI/ARB/ARNI) were included in a multivariate Cox regression model, and PHQ-9 score was still an independent risk factor for endpoint events in hospitalized patients with HF (HR = 1.11, 95% CI: 1.06–1.16, $P < 0.001$) (*Table 2*).

Construction of a predictive model for depressive symptoms in hospitalized patients with heart failure

Using bidirectional elimination, variables with $P < 0.10$ in the univariate logistic regression were included in the multivariate regression analysis. Although gender did not show a significant difference in the univariate logistic regression

Figure 1 Survival curves of the effect of depressive symptoms and PHQ-9 score on endpoint events in hospitalized HF patients. PHQ-9, Patient Health Questionnaire-9.

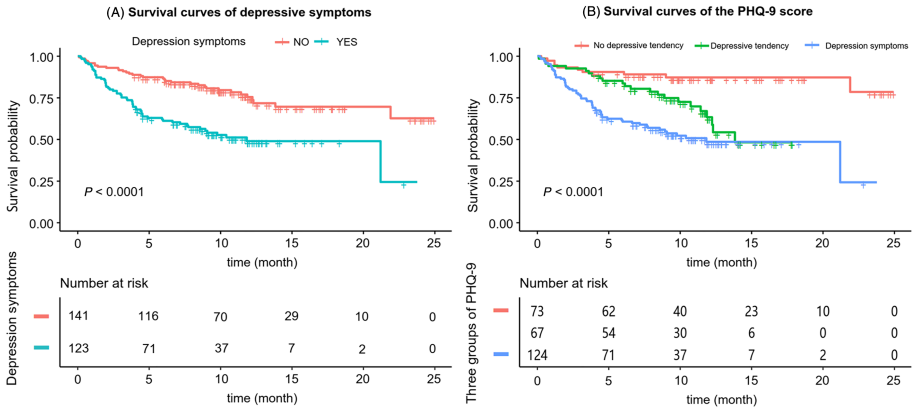


Table 2 Regression model of PHQ-9 score in the prognosis of hospitalized HF patients

Variable	Unadjusted (HR, 95% CI, *P*)	Adjusted I (HR, 95% CI, *P*)	Adjusted II (HR, 95% CI, *P*)
PHQ-9	1.12 (1.07, 1.16), <0.001	1.10 (1.05, 1.15), <0.001	1.11 (1.06, 1.16), <0.001
Three subgroups			
<5	Ref.	Ref.	Ref.
≥5, <10	3.10 (1.45, 6.64), 0.004	2.80 (1.29, 6.07), 0.009	2.80 (1.29, 6.11), 0.010
≥10	5.30 (2.66, 10.54), <0.001	4.79 (2.35, 9.76), <0.001	4.82 (2.35, 9.91), <0.001
P for trend	<0.001	<0.001	<0.001

Adjusted I: Age, NYHA class, NT-proBNP (lnNT-proBNP), diabetes mellitus, length of hospitalization, diuretics and PHQ-9 score; adjusted II: sex, age, NYHA class, NT-proBNP (lnNT-proBNP), diabetes mellitus, coronary artery disease, renal insufficiency, anaemia, length of hospitalization, CVD hospitalization history, blood pressure and standardized medications (diuretics, beta-blockers and ACEI/ARB/ARNI).

(OR = 0.76, 95% CI: 0.46–1.27, $P = 0.296$), it was still listed as a confounder in the multivariate logistic regression considering its association with depression.[17] The regression coefficients of univariate and multivariate logistic regression for risk prediction models are shown in the Supporting Information, *Table S3*. The results showed that obesity (OR = 0.27, 95% CI: 0.09–0.77, $P = 0.015$), increased NT-proBNP level (lnNT-proBNP: OR = 1.55, 95% CI: 1.20–2.01, $P < 0.001$) and RDW (OR = 1.26, 95% CI: 1.08–1.47, $P = 0.004$) were independently related to depressive symptoms in hospitalized patients with HF (Supporting Information, *Table S4*). The predictor variables were further optimized using LASSO (*Figure 2*). The final six predictor variables, including CVD hospitalization history, obesity, renal insufficiency, NT-proBNP (lnNT-proBNP), N (%) and RDW, were included in the prediction model for the risk of depression in hospitalized patients with HF (Supporting Information, *Figure S3*), and a nomogram was drawn with the prediction model parameters (*Figure 3*). The possible risk of comorbid depressive symptoms in different predictor subjects can be derived by calculating the total score corresponding to each of the different variables of the predictor subjects after summing up.

Evaluation of predictive model

The receiver operating characteristic (ROC) curve for the model in the original data is shown in *Figure 4A* with an AUC of 0.730, indicating that the model is highly discriminatory and has high predictive power for depressive symptoms in hospitalized patients with HF. The model was internally validated using Bootstrap. After 500 resamplings, the corrected C-statistic was 0.729, and the calibration curve was approximately distributed along the reference line (*Figure 4*), indicating that the predictive probability is highly consistent with the actual probability. In summary, the model has a high level of discrimination and calibration.

Discussion

HF is becoming a more serious public health concern.[10] Even after standardized medication, patients with HF are still at high risk of readmission and mortality,[18] which burdens the financial and psychological stress of individuals with HF.[19] Thus, it is necessary to identify risk factors associated with the prognosis of patients with HF. Previous studies have shown that many HF clinical characteristics, including demographic information (gender, age, BMI, baseline blood pressure, etc.), HF-specific indicators (NYHA classification, NT-proBNP levels, LVEF, heart rate, etc.), comorbidities (diabetes, CAD, renal insufficiency, anaemia, etc.), HF medication regimens and laboratory test indicators, are all associated with the prognosis of hospitalized patients with HF.[20] In this study, researchers found that advanced age, longer hospitalization days, diabetes and depressive symptoms were all independent risk factors for poor prognosis (multivariate logistic regression $P < 0.05$). Remarkably, survival curves revealed that the depressive symptoms group had a significantly higher risk of endpoint events than the group of non-depressive symptoms ($P < 0.001$). In a retrospective study involving 3 500 570 patients with HF, Patel et al.[21] discovered that the presence of depression is associated with increased all-cause readmission within 30 and 90 days, driven primarily by psychiatric causes but not cardiac readmission, suggesting that standardized HF treatment failed to modify this portion of all-cause readmission, further demonstrating the importance of paying attention to depressive symptoms in patients with HF.

Figure 2 LASSO for risk factors associated with depressive symptoms in hospitalized HF patients. HF, heart failure; LASSO, least absolute shrinkage and selection operator.

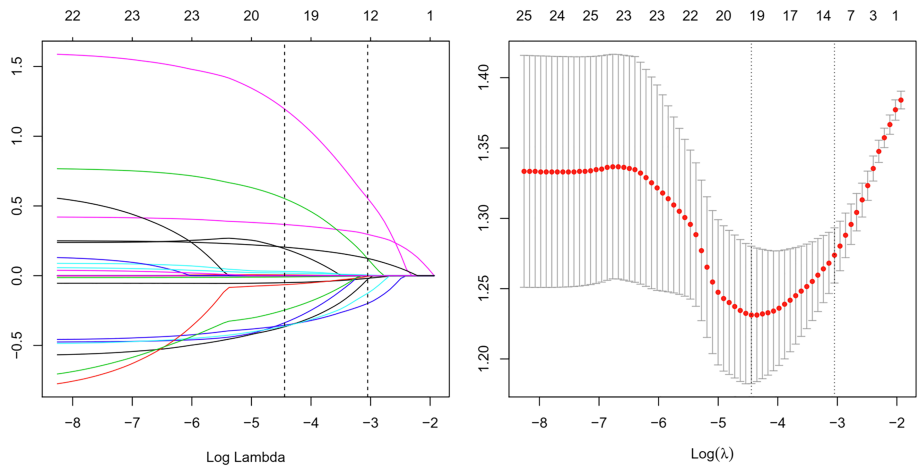


Figure 3 Nomogram of predictors of depression symptoms in hospitalized HF patients. CVDs, cardiovascular diseases; LnNT-proBNP, Napierian logarithm of *N*-terminal brain natriuretic peptide precursor; N (%), neutrophil ratio; RDW, red blood cell distribution width.

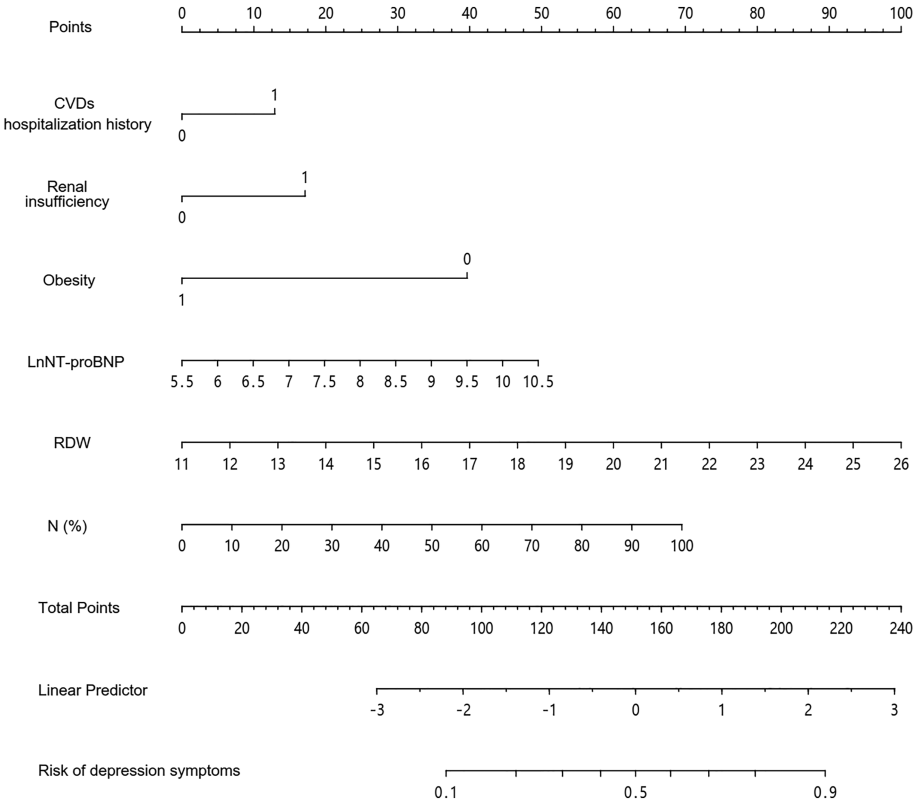
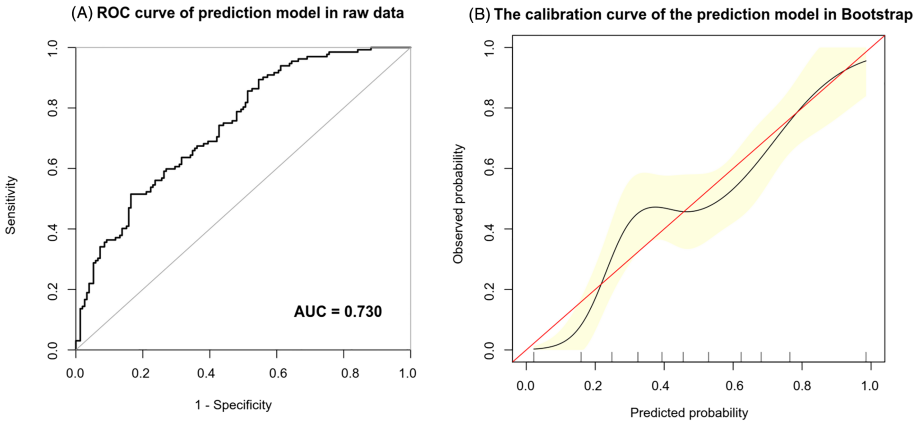


Figure 4 Internal validation of prediction model. AUC, area under the curve; ROC, receiver operating characteristic.



Depression is now widely recognized as an independent risk factor for poor prognosis in patients with HF.[9,22] In HF patients, moderate/severe depression increases the risk of readmission and all-cause mortality even more than mild depression.[8] Liu et al.[13] remarked that even mild symptoms can increase the risk of a poor prognosis. Mild depressive symptoms, on the other hand, have had a relatively uncommon prognostic impact in HF patients. The findings of this study suggest that the higher the propensity for depression symptoms, the higher the risk of endpoint events in hospitalized HF patients ($P < 0.001$). The relationship between the PHQ-9 score as a continuous variable and endpoint

events in hospitalized HF patients has also been investigated. A positive association between PHQ-9 score and endpoint events was found using univariate Cox regression. In a multivariate Cox regression, all potential risk factors for endpoint events in hospitalized patients with HF were included, and the PHQ-9 score was still found to be an independent risk factor for endpoint events, suggesting that even if patients do not meet the criteria for depression, their mild depressive symptoms may still increase the risk of endpoint events. Therefore, early identification of the risk of depression in hospitalized patients with HF and early intervention is necessary.

A combination of biological, psychological and social factors contribute to depression. Female, advanced age (≥70 years), smoking, poor economic status, lack of social support and lower adherence are all potential risk factors for depression.[6] However, there are still no studies on clinical predictors of depressive symptoms in hospitalized patients with HF. Even though the European Society of Cardiology (ESC) and the American College of Cardiology/American Heart Association (ACC/AHA) HF guidelines recommend screening and treating depression in patients with HF,[14,23] clinicians have not paid enough attention to depressive symptoms in patients with HF. Another issue is that using depression scales to assess depressive symptoms in patients with HF is still subject to individual subjectivity and scale selection variability. Although we have previously made preliminary attempts to explore biomarkers of CVDs combined with depressive symptoms,[24] predictors of depressive symptoms in hospitalized patients with HF are still lacking. In this study, six predictor variables, including CVD hospitalization history, obesity, renal insufficiency, NT-proBNP (lnNT-proBNP), N (%) and RDW, were screened by multivariate Cox regression and LASSO to construct a prediction model for depression symptoms, which was internally validated by Bootstrap. The AUC and calibration curves indicated that the model had good discrimination and calibration. In particular, some hospitalized HF patients have severe cases, making it difficult to assess their depression using conventional scales. For these patients, the prediction model is extremely useful. This predictive model, on the other hand, is only recommended as one of the screening methods for the risk of depressive symptoms, and it aims to provide objective indicators of depressive symptoms to help clinicians better identify depressive symptoms and intervene early. Even though depression has a significant impact on the quality of life and long-term prognosis of patients with HF, antidepressants have yet to show significant efficacy in HF patients with depression. Commonly, pharmacological treatment of depression should be considered and prescribed in patients with major depression, chronic depression or relapse of depression, previous positive response to antidepressants and a family history of depression.[25] However, tricyclic antidepressants are contraindicated in patients with CVDs, given the risks of hypotension, arrhythmias and myocardial infarction.[26] Selective serotonin reuptake inhibitors failed to demonstrate pharmacologic benefits in improving depression in patients with heart failure.[27] Notably, in the SADHART study, sertraline improved depressive symptoms in patients with HF, although there was no significant difference in conventional treatment.[28] Similarly, escitalopram did not improve either depressive symptoms in patients with HF or the prognosis of these patients in the MOOD-HF study (HR = 0.99, 95% CI: 0.76–1.27, P = 0.02).[16] Furthermore, whereas recent studies have shown that antidepressants are safer in patients with CVDs, more research is needed to better understand the antidepressant's potential side effects in patients with HF.[29] Exercise training, cognitive-behavioural therapy and progressive nursing interventions may also be beneficial in heart failure patients with depression.

Limitations

First, this study was a single-centre, small sample size clinical study with a short follow-up period. To validate the findings of this study, larger multicentre studies with longer follow-ups are needed. Second, the PHQ-9 was only assessed at the time of initial hospitalization, and time-dependent data on the PHQ-9 score were lacking. Therefore, the impact of changes in PHQ-9 score during follow-up on their long-term prognosis may have been neglected. Third, the clinical prediction model of depressive symptoms in hospitalized patients with HF constructed in this study was only internally validated by Bootstrap and was not externally validated. Fourth, this study failed to assess other relevant psychiatric comorbidities, such as anxiety, and did not analyse residual confounding factors, such as income level, social support and marital status, which may be relevant for the study's purpose. Analysis of these factors has the potential to further optimize the predictive model. Finally, even though preventive measures have the potential to reduce the risk of depression,[30] this study has not yet intervened with preventive strategies for depressive symptoms in hospitalized patients with HF.

Conclusion

Depressive symptoms are an independent risk factor for the prognosis of hospitalized patients with HF, and even mild depressive symptoms may have a significant impact on their prognosis. The prediction model constructed with six predictor variables, including CVD hospitalization history, obesity, renal insufficiency, NT-proBNP (lnNT-proBNP), N (%) and RDW, can objectively identify the risk of depression in hospitalized patients with HF. Consequently, follow-up multicentre studies with a larger sample size are still needed to confirm the findings of this study.

Conflict of interest

The authors declare no conflicts of interest.

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Supporting information

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

Figure S1. Flowchart of the study. HF: heart failure; PHQ-9: Patient Health Questionnaire-9.
Figure S2. Classification of etiology of patients with heart failure.
Figure S3. Forest plot of predictors of depression symptoms in hospitalized patients with HF. CVDs: cardiovascular diseases; LnNT-proBNP: napierian logarithm of N-terminal brain natriuretic peptide precursor; N (%): neutrophil ratio; RDW: red blood cell distribution width.
Table S1. Clinical characteristics of HF patients with or without endpoint events.
Table S2. Correlation of depressive symptoms and clinical characteristics with endpoint events in hospitalized patients with HF.
Table S3. The regression coefficients of univariate and multivariate Logistic regression for risk prediction model.
Table S4. Correlation of clinical characteristics and depressive symptoms in hospitalized patients with HF.
Appendix S1. The introduction of Patient Health Questionnaire-9. The Patient Health Questionnaire (PHQ) is a multiple-choice self-report scale used to screen and diagnose mental health disorders such as anxiety and depression. PHQ-2 involves two questions, mainly asking patients whether they have the following problems in recent 2 weeks, (1) little interest or pleasure in doing things or (2) feeling down, depressed, or hopeless. The PHQ-9 is a screening tool that has been developed specifically for depression and is widely used in clinical screening and clinical research because of its high sensitivity and specificity.

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