Review Article



Readmission Risk Prediction Model for Patients with Chronic Heart Failure: A Systematic Review and Meta-Analysis

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Abstract

Background: The present systematic review and meta-analysis aimed to systematically evaluate a risk prediction model for the readmission of patients with CHF.

Methods: The search was carried out in databases including PubMed, Embase, EBSCO, Web of Science, Cochrane Library and also domestic databases including Chinese Biomedical Literature Database, Chinese Academic Journal Full Text Database, Wanfang Database, and Vipu Chinese Journal Service Platform. All the original studies published by July 2021. Two researchers identified previous studies involving readmission risk prediction models that met our selection criteria. The quality of the included studies was evaluated based on the CHARMS checklist, and the prediction models were systematically evaluated.

Results: Of the overall 4787 studies retrieved, nine studies—two prospective, seven retrospective—met our selection criteria. The area under the receiver operating characteristic curve exceeded 0.63 (0.63-0.80) for all the studies. The most common predictors in the model were B-type natriuretic peptide (BNP) or N-terminal probrain BNP (Odds Ratio 4.35; 95% confidence interval (CI) 2.53–7.49; P<0.001), renal insufficiency (Odds Ratio 1.60; 95%CI 1.24–2.08; P<0.001), comorbidities, and a history of hospitalization.

Conclusion: The use of non-parametric statistical methods and assessment of large samples of electronic data improve the predictive abilities of the risk assessment models. It is necessary to calibrate and verify such models and promote the combined use of parametric and non-parametric methods to establish precise predictive models for clinical use.

Keywords: Chronic heart failure; Re-admission; Prediction model; Systematic review

Introduction

Chronic heart failure (CHF) is the final stage of cardiovascular disease and is the main reason behind the hospitalization of elderly individuals (age>65 yr) (1). Readmission refers to the patient being readmitted to the hospital within a short

period of discharge (2). The American Heart Association (3) reports that 83% of CHF patients have been hospitalized at least once, and 43% were hospitalized at least four times (4). Identifying patients at high risk of readmission, and plan-



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ning appropriate interventions for such patients may significantly improve their prognosis as well as optimize the use of medical resources (5).

A risk prediction model can identify the characteristics of individuals at higher risk for a specific event, and has a high potential for predicting the risk of readmission (6). Risk prediction models can help medical staff identify potential problems at an early stage, appropriately modify clinical management, and develop personalized care plans for patients with CHF who are at a high risk of readmission (7).

Currently, several researchers have developed risk prediction models using prospective or retrospective methods in single or multiple centers to predict the risk of readmission for patients with CHF (8-11). However, previously published systematic reviews and meta-analyses (12) that assessed predictive models for this group (13, 14) focused mainly on combinations of end-point outcomes (such as readmission and death). The predictive models regarding death as the outcome are relatively mature, with a high level of model effectiveness and consensus on the most predictive factors. However, the predictive models that assess readmission as the only outcome have not been sufficiently validated (15). The performance of most predictive models was considered "moderate", the most effectively predictive factors for readmission are yet to be established. In order to improve the patients' quality of life and reduce the waste of medical resources, it is particularly important to accurately find the predictive factors so as to reduce the rate of patient readmission. Therefore, it is crucial to design a model that specifically predicts the risk of readmission for CHF patients.

We aimed to comprehensively search for studies on readmission risk prediction models for patients with CHF by systematically reviewing, summarizing, and comparing many variables to better predict the readmission risk for patients with CHF. The construction and application of the model will provide a theoretical basis for modulating the incidence of readmission of patients with CHF.

Methods

Ethical Approval

Ethical approval for this study was obtained from the research ethics committee of Qilu Hospital of Shandong University (KYLL-202107-031).

Literature search strategy

Four Chinese medical databases (Chinese Biomedical Literature Database, Chinese Academic Journal Full Text Database, Wanfang Database, and Vipu Chinese Journal Service Platform) and five English medical databases (PubMed, Embase, EBSCO, Web of Science, and Cochrane Library) were systematically searched. A search string was developed to identify prediction model of readmission in patients with CHF using terms including "Heart failure", "chronic heart failure", "Readmission", "Rehospitalization", "Prediction model", "prediction", "model", and "risk factor". MeSH terms and free-text words were used in combination. We also used the Boolean operators "OR" and "AND". The search time frame was all set as building the library until July 2021. No restrictions were imposed on language. Titles and abstracts were reviewed by two authors, and full-text papers were reviewed by at least two of the authors. Further, references of the included studies were retrospectively reviewed. In this study, the search strategy and the screening and selection of the data were based on the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.

Eligibility criteria

Studies that met the following inclusion criteria were analyzed: 1) Patients with CHF whose symptoms were categorized under functional class II, III, or IV per the New York Heart Association (NYHA) criteria; 2) a predictive model constructed for the readmission of patients with CHF; 3) a detailed description for the statistical methods used in the establishment and verification of the model; 4) the internal or external verification performed after modeling. Patients' readmission was the only end-point outcome. Our exclusion criteria were: 1) analyses only for the risk factors but not modeling; 2) original data or quantitative endpoint data was insufficient not extracted; 3) failure to describe the modeling method or process; 4) low effectiveness of the final model; 5) results contained multiple endpoint outcomes; and 6) reviews, conference papers, or animal studies.

Data extraction

After retrieving the literature, two researchers independently reviewed the studies and made selections according to the inclusion and exclusion criteria. Differences were resolved through discussions, and if necessary, a third-party consultation. As the included literature was determined, the full text of each article was read to extract the following data: the first author, publication year, country or region, research type and object, modeling method and sample size, verification method and sample size, modeling the incidence of readmission, modeling or model verification area under receiver operating characteristic curve (AUROC), and predictive factors.

Quality assessment

The included studies were evaluated according to the bias risk assessment tool of the CHARMS checklist (16). The methodological quality evaluations for all included studies were independently performed by two investigators. Disagreements were discussed and resolved through consultations. If disagreements persisted, a third investigator would resolve them via arbitration.

Analysis

The extracted data were then organized according to the requirements of the meta-analysis. RevMan 5.3 software was used to conduct the meta-analysis on the predictive value of the variables in the model. For different types of data, odds ratio (OR) or risk ratio (HR) and the 95% confidence intervals (CI) were calculated. The OR Q test was used to assess the heterogeneity among the studies, and if the difference in heterogeneity among independent studies was not significant (P>0.100, I²<50%), the fixed effects model was used for analysis; otherwise, the random effects model was used, and sensitivity analysis was performed.

Results

Literature screening and results

Overall, 4,787 documents were obtained during the initial inspection, and nine were included after the tiered screening (Fig. 1). This study included nine (8-11, 17-21) CHF readmission prediction models, including two prospective studies (17, 18), and seven retrospective studies (8-11, 18, 20, 21). Of the included studies, four (8, 9, 11, 18) used the logistic regression method, two (19, 20) employed the Cox proportional hazards model, and the remaining three (10, 17, 21) used a competitive risk model, ensemble learning, and Bayesian model, with sample size of 246-27,714 cases for modeling. The sample size of the verification model was 105-8,531 cases, among which five studies (9, 11, 18, 19, 21) were verified internally, three (10, 17, 20) externally, and one study (8) was verified both internally and externally. The readmission rate varied greatly due to the sample size and time cut-off point, ranging from 3.10% to 36.30%. All included studies reported AUROC values, varying from 0.70 to 0.73, and model verification AUROC values were from 0.68 to 0.80. The basic characteristics and results of the risk of bias evaluation are presented in Tables 1 and 2, respectively.



Fig. 1: Literature screening process chart

Table 1: Basic characteristics of	f the included studies
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Included studies	coun- try	Type of study	model- ing methods	Model- Validation sample size	Validation model methods	AUC (modeling/ Validation	Main Out- come	Read- mission rate
)		
Zachary L et al (2018)(8)	Amer- ican	Retro- spective study	Logistic regression	1454-243	Internal / External validation	0.72/- (Internal)/0.63(Exte rnal)	1 month	23.00%
Bo-yu Tan et al (2019)(11)	China	Retro- spective study	Logistic regression	246-105	Internal val- idation	-/0.73	3 month	36.30%
Mahajan et al (2019)(10)	Amer- ican	Retro- spective study	Ensemble Machine Learning	27714-8531	External validation	0.70/-	1 month	35.70%
Leong et al (2017)(9)	Singa- pore	Retro- spective study	Logistic regression	888-587	Internal val- idation	-/0.76	1 month	9.90%
Hummel et al (2013)(20)	Amer- ican	Retro- spective study	Cox's propor- tional hazards model	1536-445	External validation	0.71/0.68	6 month	18.00%
Álvarez et al (2015)(17)	Span- ish	prospec- tive study	compet- ing risk	2507-992	External validation	0.72/0.73	1 month	3.10%

			method- ology				1 year	
Shameer et al (2017)(21)	Amer- ican	Retro- spective study	Bayes model	748-320	Internal val- idation	-/0.78	1 month	16.66%
Ying Tabak et al (2010)(18)	Amer- ican	Retro- spective study	Logistic regression	1029-343	Internal val- idation	0.73/0.69	1 month	24.10%
Betihavas et al (2015)(19)	Aus- tralia	prospec- tive study	Cox's propor- tional hazards model	280-50 ¹⁾	Internal val- idation	-/0.80	1 month 1 year	13.00%

 1° : The study adopted the bootstrap method in the internal verification process of the predictive model, randomly selected 50 sub-samples and repeated 200-times.

Table 2: Evaluation results of the risk of bias of the included studies (CHARMS checklist)

Included studies	Source of Da- ta(risk of bias)	Partic- ipants (risk of bias)	Out- come to be pre- dicted (risk of bias)	Candi- date predic- tors(ris k of bias)	Sam- ple size(ri sk of bias)	Miss- ing da- ta(tisk of bias)	Model devel- op- ment(r isk of bias)	Model per- for- manc e(risk of bias)	Model evalua- tion (risk of bias)	Re- sults(risk of bias)	Inter- preta- tion and Dis- cussio n(risk of bias)
Zachary L et al (2018)(8)	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
Bo-yu Tan et al (2019)(11)	Low	Low	Low	Low	High	Un- clear	Low	Low	Low	Low	Low
Mahajan et al (2019)(10)	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
Leong et al (2017)(9)	Low	Low	Low	Low	Low	Un- clear	Low	Low	Low	High	Low
Hummel et al (2013)(20)	Low	Low	Low	Low	Low	Un- clear	Low	Low	Low	Low	Low
Álvarez et al (2015)(17)	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
Shameer et al (2017)(21)	Low	Low	Low	High	Low	Un- clear	Low	Low	Low	Low	Low
Ying Tabak et al (2010)(18)	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
Betihavas et al (2015)(19)	Low	Low	Low	Low	High	Un- clear	Low	Low	Low	Low	Low

Modeling methods included in the study

The modeling methods of the included studies were analyzed. Four studies (8, 9, 11, 18) used logistic regression to screen the predictive factors of readmission for CHF patients. Logistic regression model is a generalized Linear model, which solves the problem that the dependent variable is dichotomous. Two (19, 20) employed the Cox proportional hazards model to build prediction model. Cox proportional hazards model is the most widely used and classic modeling method in survival analysis. The Naive Bayes model was employed in one study (21) to predict patients' readmission risk based on Bayes' theorem and independent assumptions of characteristic conditions. For specific training samples, the feature attributes were first determined and then divided. Subsequently, a classifier was generated using an algorithm. Finally, the classifier was used to classify the new data and output the results of readmission risk. The ensemble learning method for modeling was adopted in one research (10), which integrated 10 basic learning models, and applied the prediction results with the best AU-ROC to the final integrated model, called the meta-learner. Four studies (9, 17, 19, 20) used the factor scoring method, and one (19) used a nomogram to calculated the final readmission risk probability. The remaining three studies (9, 17, 20) calculated the sum of the scores for each factor according to their weights of the OR or HR, then calculated to predict the risk of readmission for CHF patients. Simultaneously, the scores were divided, and the specific method of risk stratification was reported. Among the three studies, two (9, 17) divided the readmission rate into three levels according to the sum of factor scores, while one (20) divided it into four levels based on the factor scores.

Predictors included in the model

Of the nine included prediction models for the readmission of CHF patients, the most included predictors were 105 (21), while the least included predictors were three (11, 17). B-type natriuretic peptide (BNP) or N-terminal pro-brain natriuretic peptide (NT-proBNP) were the most common predictors, followed by renal insufficiency (including diagnoses of nephritis, abnormal glomerular filtration rate, renal failure, or dialysis), comorbidities, and previous hospitalization history. Some of the models included variables that may be amenable to intervention, such as sedentary lifestyle (19), drug abuse history (cocaine, etc.)(19) and treatment compliance (18). Such predictors revealed a higher OR or HR value in models, indicating that appropriate targeted and personalized interventions could be provided to patients. The specific conditions of the included predictors are presented in Table 3.

Meta-analysis results

BNP or NT-proBNP and renal insufficiency, as the common factors in the prediction model on the readmission of CHF patients, were assessed in the meta-analysis. Comorbidities and a history of admission were included in the model in four (8, 11, 19, 20) and three studies (8, 9, 20), respectively. However, meta-analysis could not be performed because of the different evaluation and classification methods, and time cut-off points used in the study. Two studies on machine learning (10, 21) were excluded due to the inability to extract relevant data.

Four studies (9, 11, 17, 20) (5,177 patients) reported the efficacy of BNP or NT-proBNP in predicting the readmission of HF patients. The heterogeneity among independent studies was statistically significant (P<0.0001, I²=88%). The difference was also significant using the random effects model for analysis (Z=2.41, P=0.020), and the combined OR was 2.28 (1.17-4.45). The forest diagram is illustrated in Fig. 2.

Four studies (8, 9, 17, 20) (4849 patients) reported the effectiveness of renal insufficiency in predicting re-hospitalization in HF patients. The heterogeneity test results confirmed the heterogeneity among the independent studies (P=0.005, $I^2=77\%$). The random effects model was used for analysis (Z=1.85, P>0.050), but the resulting difference was not statistically significant, and the combined OR was 1.39 (0.98-1.96) (Fig. 3).

Included studies	Num ber of pre- dic- tors	Predictors
Zachary L et al (2018)(8)	23	Age; gender; race;Socioeconomic Status(SES)vulnerability ;distance from home to hospital; comorbidi- ties (Renal Failure; Other Gastrointestinal Disorders; Major Psychiatric Disorders;Diabetes Mellitus or Diabetic Complications; Other Urinary Tract Disorders; Chronic Obstructive Pulmonary Disease; His- tory of Coronary Artery Bypass Graft Surgery; Peptic Ulcer, Hemorrhage, Other Specified Gastrointes- tinal Disorders; Fibrosis of Lung or Other Chronic Lung Disorders; Cancer, History of coronary angio- plasty of stenting, Dementia/Alzheimer's disease) ;Blood Urea Nitrogen(BUN)>40 mg/dL (1mg/dL=88.4 μmol/l) or Serum creatinine>2.5 mg/dL; Index Admission Serum Sodium; BMI; glucose>200 mg/dL; Index Hospital Admission Presentation(Emergent;Urgent;Elective);Number Hospital Admissions with Emergent Presentation in past 12 months.
Bo-yu Tan et al (2019)(11)	3	NT-proBNP; red cell volume distribution width (RDW-CV); Charlson Comorbidity Index (CCI).
Leong et al (2017)(9)	7	Number of preceding admissions for heart failure in preceding 1 year; Length of Stay (days); Serum creatinine>125umol/L; NT-proBNP>6000 pg/m; Electrocardiograph QRS duration (msec);Number of Medical Social Service indications for referral; βblocker upon discharge.
Hummel et al (2013)(20)	7	BUN; log BNP; NYHA class; Hospitalization within:1 month, 2-6 month; Atrial fibrillation/flutter; Diabetes mellitus.
Álvarez et al (2015)(17)	3	Framingham left HF signs; eGFR< 60 mL/min/1.73 m ² ; BNP>150 pg/mL or NT-proBNP>1000 pg/mL.
Ying Tabak et al (2010)(18)	11	History of depression or anxiety; Single; Male; Medicare; Number of home address changes; Residence census tract in lowest socioeconomic quintile; History of cocaine use; History of missed clinic visit; Used a health system pharmacy; No. prior inpatient admissions; Presented to emergency department 6 AM–6 PM for index admission.
Betihavas et al (2015)(19)	6	Age; Women versus men; Lives alone; Sedentary; No. of comorbid conditions; Number of years with CHF
PS:Two studies [effective	tablished models for machine learning methods, not described in the table. Because the machine learning information for prediction through the interaction between variables, it is impossible to extract specific

Table 3:	Predictors	of included	studies
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				Odds Ratio	Odds Ratio
Study or Subgroup log	g[Odds Ratio]	SE	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Bo-yu Tan et al.(2019)	1.5213	0.3415	23.5%	4.58 [2.34, 8.94]	
Hummel et al.(2013)	0.1398	0.0464	30.5%	1.15 [1.05, 1.26]	•
Leong et al.(2017)	0.5933	0.2359	26.8%	1.81 [1.14, 2.87]	- -
Álvarez et al.(2015)	1.3737	0.474	19.3%	3.95 [1.56, 10.00]	
Total (95% CI)			100.0%	2.28 [1.17, 4.45]	◆
Heterogeneity: Tau ² = 0.3 Test for overall effect: Z =	•		o < 0.000	1); I ² = 88%	0.01 0.1 1 10 100 Favours [experimental] Favours [control]

Fig. 2: Forest plot of the effect of BNP or NT-proBNP on readmission of patients with chronic heart failure



Fig. 3: Forest plot of the effect of renal insufficiency on re-admission of patients with chronic heart failure

Sensitivity analysis results

Sensitivity analysis is required for BNP or NTproBNP and renal insufficiency. After excluding two studies (9, 20), there was no heterogeneity between studies (P=0.800, $I^2=0\%$). The fixedeffects model was used for analysis, and the combined OR value was 4.35 (2.53-7.49; Z=5.31; P<0.001). The possible reasons for this heterogeneity may be the difference in research areas, time limits, and predictive factor thresholds. One study conducted in Singapore (9) focused on the readmission risk within 30 d in CHF patients, and another study (20) in the United States focused on the readmission risk within 180 d. Moreover, the judgment thresholds on the BNP and NTproBNP levels were also different between the two studies. Refer to Fig. 4 for the forest diagram after the sensitivity analysis.



Fig. 4: Forest plot after sensitivity analysis of BNP or NT-proBNP

There was no heterogeneity between studies $(P=0.700, I^2=0\%)$ after eliminating one study (18) according to the sensitivity analysis of renal insufficiency, and a combined OR of 1.60 (1.24 -2.08; Z=3.57; P<0.001) was obtained through the fixed-effects model analysis. The heterogeneity

may be related to the different evaluation indicators for renal insufficiency used in the excluded study, where blood urea nitrogen threshold low can lead to deviations in predictive performance (Fig. 5).



Fig. 5: Forest plot after sensitivity analysis of renal insufficiency

Discussion

This systematic review included nine readmission risk prediction models for CHF patients, among which four (8, 10, 17, 18) were of high quality, and five (9, 11, 19-21) were of medium quality. The AUROC of all models in the modeling and verification methods was greater than 0.63, demonstrating an excellent model performance. The common predictors in the model were BNP or NT-proBNP, renal insufficiency, comorbidities, and admission history.

The reliability of a systematic review is closely related to the quality of the included studies (22). Two studies (11, 19) had low sample sizes, of which one (11) did not adopt special statistical methods for processing, which may have affected the accuracy of parameter estimation to an extent. Another article (19) used a bootstrap resampling method to achieve the small sample expansion, so that the obtained model was more stable. Four studies (8, 10, 17, 18) specifically reported the missing data. Among these, two (17, 18) used the multiple regression interpolation as a solution; one(8) used the mean filling method, and the remaining one(10) used the multiple filling method of the chain equation.

All prediction models included in this study were internally or externally verified, and most of the modeling or model verification AUROCs were greater than 0.70, indicating that the included models were of considerable utility in evaluating readmission risk of CHF patients. Most studies used logistic regression and Cox risk regression methods for modeling. Notably, two studies involving machine learning (10, 21) presented characteristics that were different from traditional studies in terms of predictive factors. Traditional statistical methods (logistic regression and Cox risk regression model) generally assume that the independent variable and the dependent variable are linear, and limit the number of independent variables. The organizational structure and mode of machine learning is more suitable for analyzing big datasets and multivariate data. It objectively requires more predictors to meet the requirements of machine autonomous learning. However, a larger number of predictors are conducive to the use of machine learning models for complex nonlinear interactions between multiple variables; to output more refined and detailed prediction results; and to improve the scope of discrimination and prediction of the outcomes of HF (23). The combination of parameterization and machine learning methods allows for better performance of the prediction model.

Among all predictive models in this study, the significantly overlapping predictors included BNP or NT-proBNP, renal insufficiency, comorbidities, and previous hospitalization history. Meta-analysis revealed that BNP or NT-proBNP levels and renal insufficiency were independent predictors of readmission in CHF patients. However, meta-analysis could not be conducted because of the different evaluation and classification methods, and cut-off time points used in the included studies. For some variables, a textual description analysis was performed.

It was observed that BNP or NT-proBNP and renal insufficiency were the most common predictors of readmission among the nine prediction models. BNP and NT-proBNP are mainly secreted by ventricular myocytes in the event of ventricular volume and pressure overload. Heart dysfunction, such as ventricular myocyte damage or HF, leads to elevated levels of BNP and NTproBNP in blood circulation (24, 25). Therefore, they are considered to potentially reflect the body's compensatory pathophysiological changes, and restore circulatory stability. The BNP in the AUROC close to 0.70 was the best biomarker for predicting the readmission of HF patients within 60 d (26). Renal insufficiency can manifest as renal failure, abnormal glomerular filtration rate, or high BUN or serum creatinine (27). In patients with CHF and renal insufficiency, the cardiovascular system encounters accelerated atherosclerosis, left ventricular hypertrophy, and remodeling. Furthermore, decreased kidney function can lead to the activation of inflammatory factors in the body, which aggravates already-damaged heart tissue, and further worsens the prognosis of HF patients (28). The deterioration of renal function

was a sensitive sign of reduced organ perfusion and an important independent predictor of the readmission risk in patients with CHF (29).

Four studies (8, 11, 19, 20) included comorbidities as predictive factors for analyses, but due to different evaluation forms and grading methods used, a meta-analysis could not be conducted. Two of the papers (8, 20) separately analyzed some of the diseases included in the comorbidities. The remaining two (11, 19) used the comorbidity index to represent the comorbidities, from which the data on renal insufficiency could be extracted for the meta-analysis. These four studies revealed that the comorbidity index or significant independent risk factors (such as renal insufficiency and diabetes) increase the risk of rehospitalization of CHF patients. This may be because diabetes and its related comorbidities exacerbate the progression of HF, making the patient's cardiovascular system more prone to imbalance (30).

Three studies (8, 9, 20) incorporated the history of admission as a predictor in the model for analysis, that is, whether the patient was admitted to the hospital (HF or all causes) within the specified time (1 month, 6 months, and 1 year) and the number of admissions were used as independent characteristic variables to predict the readmission risk for HF patients. Since the three studies did not use the same evaluation methods and cut-off time points, it was impossible to conduct meta-analysis. HF before admission or a history of emergency admissions can increase the readmission risk in patients with CHF. At least one HF admission or recorded history of HF within 1 year before admission is a significant predictor in the model (31).

The predictors included in the current prediction models for the re-hospitalization of chronic HF patients are inconsistent. The reasons include differences in the populations at baseline and different data sources. Moreover, some variables could not be included in the meta-analysis due to different evaluation and classification methods, and cut-off timepoints used. We could not obtain data-supported specific predictors of CHF readmission because meta-analyses were only performed on some well-known variables. Therefore, it is necessary and important to build a risk prediction model only for the readmissions of CHF patients.

According to The China Heart Failure Diagnosis and Treatment Guidelines, 2018 (32) and Guidelines for Rational Use of Medicines for Heart Failure (Second Edition) (33), measures such as exercise, weight control, and improvement of drug compliance can effectively improve the prognosis of patients with CHF. Additionally, there is evidence that water and sodium restriction, aerobic exercises (34), medication compliance (35), and psychological intervention (36) can reduce the readmission rate of patients with CHF (37). Nurse-led education interventions could effectively reduce the readmission rate (38). However, most prediction models focus on the predictive ability of the clinical parameters, while few studies concentrate on the preventable predictive factors concerning readmission. A sedentary lifestyle increases the risk of readmission in CHF patients, and it is difficult for the patients' admission clinical parameters and other indicators to provide direct guidance to the medical staff (21). Relative to these indicators, researches dedicated to finding adjustable and preventable indicators, such as exercise, diet, depression, and drug compliance, in order to reduce the incidence of readmission in CHF patients may provide more practical clinical significance for medical staff.

This study has certain limitations. First, like all meta-analyses, this work is limited by variations in the original studies, it was difficult to conduct a meta-analysis on some of the high-weightage predictors in this systematic review due to the different evaluation methods, classification methods, and cut-off time points, so that a detailed textual description analysis was performed. Second, studies on the readmission of CHF patients often take the readmission rate and mortality as a combined result. There are few models that consider readmission rate as a single result, thus the number of studies that could be included in the analysis was relatively insufficient, risk prediction models for readmission in patients with CHF should be increased in the future.

Conclusion

This systematic review included nine readmission risk prediction models for patients with CHF, exhibited good predictive performance, and can effectively screen high-risk readmitted patients. or NT-proBNP, renal insufficiency, BNP comorbidities, and previous hospitalization history are independent predictors of readmission risk in patients with CHF. The complexities of disease management and high readmission rates in CHF patients drive the need for the development of innovative risk prediction models. Through statistical methods such as machine learning, a large amount of electronic data can be used to design a prediction model, which may improve the model's efficacy and overcome the limitations of the traditional modeling methods. In the future, researchers should aim to combine traditional parametric and non-parametric modeling methods to build a prediction model that can better fit the characteristics of clinical work and the individualized characteristics of the target population. This will lead to the development of appropriate interventions for patients at different risk levels, and promote the fair distribution of medical resources, while reducing the readmissions of CHF patients.

Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Conflicts of interest

The authors declare that there is no conflict of interest.

References

- Adams KF, Jr., Fonarow GC, Emerman CL, et al (2005). Characteristics and outcomes of patients hospitalized for heart failure in the United States: rationale, design, and preliminary observations from the first 100,000 cases in the Acute Decompensated Heart Failure National Registry (ADHERE). *Am Heart J*, 149(2):209-16.
- Liu X LP, Guo Lh (2017). Research status of influencing factors and intervention measures for readmission of patients with heart failure. Chinese Nursing Management. *Chinese Nursing Management*, 17(6): 859-863.
- Writing Group M, Mozaffarian D, Benjamin EJ, et al (2016). Heart Disease and Stroke Statistics-2016 Update: A Report from the American Heart Association. *Circulation*, 133(4):e38-360.
- Harkness K, Spaling MA, Currie K, et al (2015). A systematic review of patient heart failure self-care strategies. J Cardiovasc Nurs, 30(2):121-35.
- Lu MX, Zhang YY, Jiang JF, et al (2016). Weight Management Belief is the Leading Influential Factor of Weight Monitoring Compliance in Congestive Heart Failure Patients. *Acta Cardiol Sin*, 32(6):708-15.
- Moons KGM, Kengne AP, Grobbee DE, et al (2012). Risk prediction models: II. External validation, model updating, and impact assessment. *Heart*, 98(9):691-8.
- Mizukawa M, Moriyama M, Yamamoto H, et al (2019). Nurse-Led Collaborative Management Using Telemonitoring Improves Quality of Life and Prevention of Rehospitalization in Patients with Heart Failure A Pilot Study. Int Heart J, 60(6):1293-302.
- 8. Cox ZL, Lai P, Lewis CM, et al (2018). Customizing national models for a medical center's population to rapidly identify patients at high risk of 30-day all-cause hospital

readmission following a heart failure hospitalization. *Heart Lung*, 47(4):290-6.

- Leong KTG, Wong LY, Aung KCY, et al (2017). Risk Stratification Model for 30-Day Heart Failure Readmission in a Multiethnic South East Asian Community. *Am J Cardiol*, 119(9):1428-32.
- 10. Mahajan SM, Ghani R(2019). Using Ensemble Machine Learning Methods for Predicting Risk of Readmission for Heart Failure. *Stud Health Technol Inform*, 264:243-7.
- Tan BY, Gu JY, Wei HY, et al (2019). Electronic medical record-based model to predict the risk of 90-day readmission for patients with heart failure. *BMC Med Inform Decis Mak*, 19(1):193.
- Saito M, Negishi K, Marwick TH(2016). Meta-Analysis of Risks for Short-Term Readmission in Patients With Heart Failure. *Am J Cardiol*, 117(4):626-32.
- 13. Betihavas V, Davidson PM, Newton PJ, et al (2012). What are the factors in risk prediction models for rehospitalisation for adults with chronic heart failure? *Aust Crit Care*, 25(1):31-40.
- Ouwerkerk W, Voors AA, Zwinderman AH (2014). Factors Influencing the Predictive Power of Models for Predicting Mortality and/or Heart Failure Hospitalization in Patients With Heart Failure. JACC Heart Fail, 2(5):429-36.
- Benjamin EJ, Blaha MJ, Chiuve SE, et al (2017). Heart Disease and Stroke Statistics-2017 Update: A Report From the American Heart Association. *Circulation*, 135(10):e146-e603.
- Moons KG, de Groot JA, Bouwmeester W, et al (2014). Critical appraisal and data extraction for systematic reviews of prediction modelling studies: the CHARMS checklist. *PLaS Med*, 11(10):e1001744.
- Alvarez-Garcia J, Ferrero-Gregori A, Puig T, et al (2015). A simple validated method for predicting the risk of hospitalization for worsening of heart failure in ambulatory patients: the Redin-SCORE. *Eur J Heart Fail*, 17(8):818-27.
- Amarasingham R, Moore BJ, Tabak YP, et al (2010). An Automated Model to Identify Heart Failure Patients at Risk for 30-Day Readmission or Death Using Electronic Medical Record Data. *Med Care*, 48(11):981-8.

- Betihavas V, Frost SA, Newton PJ, et al (2015). An Absolute Risk Prediction Model to Determine Unplanned Cardiovascular Readmissions for Adults with Chronic Heart Failure. *Heart Lung Circ*, 24(11):1068-73.
- Hummel SL, Ghalib HH, Ratz D, et al (2013). Risk stratification for death and all-cause hospitalization in heart failure clinic outpatients. *Am Heart J*, 166(5): 895-903.e1.
- Shameer K, Johnson KW, Yahi A, et al (2017). Predictive Modeling of Hospital Readmission Rates Using Electronic Medical Record-Wide Machine Learning: A Case-Study Using Mount Sinai Heart Failure Cohort. *Pac Symp Biocomput*, 22: 276-87.
- Li YI ZB, Liu Hm.(2014). Meta-analysis of the effect of the duration of low molecular weight heparin subcutaneous injection on adverse reactions. *Chinese Journal of Practical Nursing*, 30(18): 59-62.
- 23. Mortazavi BJ, Downing NS, Bucholz EM, et al (2016). Analysis of Machine Learning Techniques for Heart Failure Readmissions. *Circ Cardiovasc Qual Outcomes*, 9(6):629-640.
- 24. Tsutamoto T, Wada A, Maeda K, et al (1997). Attenuation of compensation of endogenous cardiac natriuretic peptide system in chronic heart failure - Prognostic role of plasma brain natriuretic peptide concentration in patients with chronic symptomatic left ventricular dysfunction. *Circulation*, 96(2):509-16.
- 25. McCallum W, Tighiouart H, Kiernan MS, et al (2020). Relation of Kidney Function Decline and NT-proBNP With Risk of Mortality and Readmission in Acute Decompensated Heart Failure. *Am J Med*, 133(1): 115-122.e2.
- Sudharshan S, Novak E, Hock K, et al (2017). Use of Biomarkers to Predict Readmission for Congestive Heart Failure. *Am J Cardiol*, 119(3):445-51.
- Tedeschi A, Agostoni P, Pezzuto B, et al (2020). Role of comorbidities in heart failure prognosis Part 2: Chronic kidney disease, elevated serum uric acid. *Eur J Prev Cardiol*, 27(2_suppl):35-45.
- Tang WHW, Kitai T(2016). Intrarenal Venous Flow A Window Into the Congestive Kidney Failure Phenotype of Heart Failure? JACC Heart Fail, 4(8):683-6.
- 29. Ruiz-Laiglesia FJ, Sanchez-Marteles M, Perez-Calvo JI, et al (2014). Comorbidity in heart

failure. Results of the Spanish RICA Registry. *QJM*, 107(12):989-94.

- 30. Thomas MC(2018). Perspective Review: Type 2 Diabetes and Readmission for Heart Failure. *Clin Med Insights Cardiol*, 12:1179546818779588.
- Krumholz HM, Chen YT, Wang Y, et al (2000). Predictors of readmission among elderly survivors of admission with heart failure. *Am Heart J*, 139(1 Pt 1):72-7.
- Heart Failure Group of Chinese Society of Cardiology of Chinese Medical Association; Chinese Heart Failure Association of Chinese Medical Doctor Association; Editorial Board of Chinese Journal of Cardiology (2018). [Chinese guidelines for the diagnosis and treatment of heart failure 2018]. *Zhonghua Xin Xue Guan Bing Za Zhi*, 46(10):760-789.
- Expert Committee of Rational Drug Use of National Health and Family Planning Commission CPA (2019). Guidelines for rational drug use in heart failure (2nd edition).
- 34. Zhao X WW, Zhao Xj (2020). Summary of the best evidence for the management of patients

with chronic heart failure. *Chinese Journal of* Nursing, 2020, 55(3): 456-461.

- 35. Ruppar TM, Cooper PS, Mehr DR, et al (2016). Medication Adherence Interventions Improve Heart Failure Mortality and Readmission Rates: Systematic Review and Meta-Analysis of Controlled Trials. J Am Heart Assoc, 5(6):e002606.
- Calvillo-King L, Arnold D, Eubank KJ, et al (2013). Impact of Social Factors on Risk of Readmission or Mortality in Pneumonia and Heart Failure: Systematic Review. J Gen Intern Med, 28(2):269-82.
- 37. Lim NK, Lee SE, Lee HY, et al (2019). Risk prediction for 30-day heart failure-specific readmission or death after discharge: Data from the Korean Acute Heart Failure (KorAHF) registry. J Cardiol, 73(2):108-13.
- Rice H, Say R, Betihavas V (2018). The effect of nurse-led education on hospitalisation, readmission, quality of life and cost in adults with heart failure. A systematic review. *Patient Educ Couns*, 101(3):363-74.