Charlson Comorbidity Index is correlated with readmission within six months in patients with heart failure: A retrospective cohort study in China

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Research Article

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Abstract

Background Charlson Comorbidity Index (CCI) is positively associated with readmission in patients with heart failure (HF) in western countries. However, there is a scarcity of strong scientific evidence supporting the correlation in China. This study aimed at testing this hypothesis among patients with HF in China.

Methods We conducted an analysis of 2,003 patients with HF in Zigong Fourth People's Hospital in China between December 2016 to June 2019. Logistic regression models were used to study the hypotheses, with adjustments for the four regression models. We also explore the linear trend and possible nonlinear relationship between CCI and the endpoints. Additionally, CCI alone was used to predict the readmission within six months and areas under the curve (AUC), accuracy, sensitivity and specificity and were reported to evaluate the performance of the predicted model.

Results In the adjusted II model**,** CCI was an independent prognostic factor for readmission within six months in patients with HF (*OR* = 1.14, 95% *CI*: 1.03–1.26, *P* = 0.0127). Trend tests revealed that there was a significant linear trend for the association**.** A nonlinear association was identified between them and the inflection point of CCI was 1. ROC analysis indicated CCI alone were inadequate for prediction with low AUC, accuracy, sensitivity and specificity.

Conclusion CCI was independently positively correlated with readmission within six months in patients with HF in Chinese population. However, CCI alone has limited value on predicting readmission within six months in patients with HF.

Introduction

Heart failure (HF) is one of the most life-threatening conditions in cardiovascular patients in China. A recent national epidemiologic survey in 2012–2015 revealed that the number of patients with HF has reached 89 million in China [1, 2]. Despite significant developments in cardiovascular therapy, the high rehospitalization rate has not changed significantly for the last twenty years. It is estimated that 50% of patients are re-hospitalized within six months following a first hospitalization for HF [3].

It has become a consensus that cardiovascular and non-cardiovascular comorbidities are frequently observed in more than half of patients with HF[4], such as myocardial infarction, cerebrovascular disease, diabetes mellitus, complicating the therapeutic management and leading to poor prognosis[5, 6]. Consequently, the prompt recognition of associated comorbid conditions is of great significance to optimize the clinical management, the follow-up, and the treatment of patients with HF. To objectively assess comorbid status, we used the Charlson Comorbidity Index (CCI) as a well-established surrogate marker of comorbidity[7]. Substantial research has been performed in western countries to verify the independent correlation between CCI and short-term readmission in patients with HF [8, 9]. However, there is a scarcity of strong scientific evidence supporting the correlation in Chinese settings. The present study

was therefore aimed at investigating this correlation in Chinese population. The following hypothesis was proposed in this study: Hypothesis 1. CCI was positively independently associated with readmission within six months among patients with HF in Chinese population. Hypothesis 2. There may be a threshold effect or inflection point between them in Chinese population.

Methods

Study population

Pertinent data were obtained from an online open-source database of patients with HF in China, which is available in PhysioNet (https://physionet.org/content/heart-failure-zigong/1.2/)[10, 11]. The database consecutivelycollected electronic healthcare records of 2,008 patients with HF who had been admitted to Zigong Fourth People's Hospital between December 2016 to June 2019.The database included all types of HF including acute HF, chronic HF, left HF, right HF, or a mixture of all.Patients with HF were identified usingInternational Classification of Diseases (ICD)-9 code. HF was diagnosed according tothe 2016 European Society of Cardiology (ESC) criteria[12].In the present study, patients without missing CCI were retained. Thus, a total of 2,003 patients was included in the analysis.The flowchart of patient selection is presented in Fig 1.Databasecontentand construction involving human participants were in accordance with the ethical standards of ethics committee of Zigong Fourth People's Hospital (Approval Number: 2020-010)and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.Studyprotocol andall the methods in this study were approved by ethics committee of Zigong Fourth People's Hospital. Ethics committee of Zigong Fourth People's Hospital waived off the informed consentdue to the retrospective design of the study[13, 14].

<FIGURE 1>

Data collection

CCI was calculated by summing all comorbidity points describedin the database[11]. Demographic and clinical data, including age, gender, body mass index (BMI), occupation, admission ward, admission way, discharge day, body temperature, pulse, respiration, systolic blood pressure (SBP), diastolic blood pressure (DBP),NewYorkHeartAssociation (NYHA)cardiac function classification, Killip grade, type of HF, type II respiratory failure and Glasgow Coma Scale (GCS) were collected on admission. Also, a total of eight HF-related indicators of laboratory examination and cardiac ultrasound on admission were included in the present study. The indicators were as follow:glomerular filtration rate (GFR),cystatin,white blood cell (WBC), hemoglobin (HGB), high sensitivity troponin T (hs-TnT), brain natriuretic peptide (BNP), high sensitivity C reactive protein (hs-CRP), albumin (ALB) and left ventricular ejection fractions (LVEF).Detailsondata collection are provided intheoriginalpublications [11].

Study endpoints

The study endpoint was readmission within six months calculated from the date ofindex hospital admission.

Statistical analysis

Data were analyzed usingRversion4.1.0 (http://www.R-project.org,The R Foundation). All statistical inferences were made of two-sided test, and a value of $P < 0.05$ was considered to be statistically significant.Continuous variables that approximated thenormal distribution were expressed as means±SD, anddatawith a skeweddistributionwereexpressedasmedians (1stquartile-3rdquartile, Q1–Q3). Forcategoricalvariables, we reportfrequenciesandpercentages.Comparisons of the groups were examined by independent t-test for normally distributed data, MannWhitney U test for nonparametric data and Chi square (χ 2) test for categorical variables.

Afterward, univariate and multivariate logistic regression analyses were performed.Based on the Strengthening the Reporting of Observational studies in Epidemiology(STROBE)guideline[15],we displayed the results of multiple models, including non-adjusted, adjusted I, adjustedIIand fully-adjusted models. Non-adjustedmodel was not adjusted for any confounding factors. Adjusted I model was adjustedfor age and sex. Adjusted model was adjustedfor covariates using change-in-estimate (CIE) and directed acyclic graph (DAG) based onage and sex[16, 17]. Fully-adjusted model wasadjusted for all mentioned 25 covariates. Then patientswere grouped according tocategory of CCI as follows: lessthanorequalto1, 2, and greater orequalto2. We performed linear trend test by entering the median value of each category of CCI as a continuous variable in the four regression models[18]. We also explored whether there was a possible nonlinear relationship between the CCI and the endpoints (the threshold effect). We applied piece-wise regression that used a separate line segment to fit each interval. Log-likelihood ratio test(LRT)comparing one-line (non-segmented) model to segmented regression model was used to determine whether threshold exists. The inflection point that connecting the segments was based on the model gives maximum likelihood, and it was determined using two steps recursive method [19, 20].

There were cases with incomplete data for some covariates.Covariates with large amounts of missing data (hs-CRP and LVEF) were addressed using the dummy variable, with a category for each variable used to indicate “missing” status[21]. Then we used multiple imputations (MI) based on five replications and the chained equation approach to account for missing data forcystatin, occupation, GFR, WBC, HGB,hs-TnT, BNP and ALB (The proportion of missing value was less than 20%). Then the *OR*, 95% *CI*, and *P* value of logistic regression of the five replications were combined according to Rubin’s rule[20]. Additionally, we explored the potential unmeasured confounding between the CCIand the endpoints using an E-value calculator(https://www.evalue-calculator.com/)[22]. The E-value quantifies the magnitude of an unmeasured confounder that could negate the observed correlation between CCIand the endpoints[23]. Finally, receiver-operating characteristic (ROC) curve analysis was conducted, and areas under the curve (AUC), accuracy, sensitivity and specificity and were reported to evaluate the performance of CCI alone predicting the readmission within six months.

Results

Baseline characteristics

A total of 2,003 patients with HF were included in the study. The percentage of readmission within six months were 38.49%. The proportion of < 60 years, ≥ 60 and < 90 years, and ≥ 90 and < 110 years of patients were 8.86%, 53.93% and 37.21%, respectively. The proportion of male was 42.08%. There were no significant differences in age, gender, BMI, admission way, body temperature, respiration, DBP, killip, type II respiratory failure, WBC, HGB, BNP, hs-CRP and LVEF between readmission and non-readmission groups. Compared with non-readmission group, CCI, proportion of urban resident, proportion of cardiology ward on admission, discharge day, proportion of grade of NYHA, proportion of both left and right HF, GCS, cystatin, hs-TnT and ALB in readmission group were higher than non-readmission group. Pulse, SBP and GFR were lower in readmission group as compared to the non-readmission group. The baseline characteristics of the patients are shown in Table 1.

<TABLE 1>

Univariate analysis between CCI levels and readmission within six months

In univariate analysis, CCI, occupation, admission ward, discharge day, pulse, SBP, NYHA, type of HF, type II respiratory failure, GCS, GFR, cystatin and ALB were associated with readmission within six months (P < 0.05). The results of the univariate analyses are presented in Supplementary Table S1.

Multivariate analysis between ALB levels and the endpoints

In non-adjusted model, CCI was positively correlated with readmission within six months (*OR* = 1.19, 95% *CI*: 1.08–1.30, *P* = 0.0003). In the adjusted I and II models, ORs of the positive association were listed as follows: *OR* =1.18, 95% *CI*: 1.08–1.30, *P* = 0.0005 and *OR* = 1.14, 95% *CI*: 1.03–1.26, *P* = 0.0127. In fully-adjusted model, CCI was also positively related with the endpoints (*OR* = 1.17, 95% *CI*: 1.04–1.31, *P* = 0.0073). Trend tests revealed that there was a linear trend for the association between CCI and readmission and the linear trend tests were significant in the four models (P for trend < 0.05).
Effect size for the difference between CCI <= 1 and CCI = 2 group appeared quite different from that between CCI = 2 and CCI > 2 group. This suggested a possible threshold effect in this relationship which becomes more noticeable when the threshold is exceeded. The results were shown in Table 2

<TABLE 2>

Non-linearity of the correlation between CCI and readmission with six months

This analysis revealed a threshold effect and the inflection point of CCI was 1 after adjusting covariates in adjusted II model (*P* for LRT = 0.0350 < 0.05). The correlation was not significant before the inflection (*OR* = 0.62, 95%*CI*: 0.35-1.09, *P* = 0.0984) while the correlation became significant after the inflection

(*OR* = 1.18, 95%*CI*: 1.06-1.32, *P* = 0.0022). As a result, we concluded that the correlation between CCI and readmission was nonlinear.

Multiple imputations of missing values

We found that some variables for hs-CRP and LVEF, cystatin, occupation, GFR, WBC, HGB, hs-TnT, BNP and ALB were missing in raw data and the numbers of missing were 1066, 1370, 41, 27, 63, 27, 28, 79, 35 and 102, respectively. Dummy variable and MI method were used to handle missing value. The results of the MI indicated that there was only a slight difference in estimates (ORs) between raw data and combined imputed data (the differences were less than 10%.). In other words, we concluded that the data for cystatin, occupation, GFR, WBC, HGB, hs-TnT, BNP and ALB appeared to be missing at random, which would not significantly alter the results of initial data. A summary of imputed data compared with the initial incomplete data is illustrated in Supplementary Table 2.

The ROC analysis and AUC for CCI predicting readmission with six months

The AUC for CCI alone predicting readmission with six months was 53.98% (95%*CI*: 51.49-56.46%). The sensitivity, specificity and accuracy of prediction model were 28.02%, 78.73% and 59.21%, respectively.

Discussion

Significant comorbidities are common in patients with severe HF, as we have experienced in clinical practice. As the CCI is the most widely known standardized comorbidity score, the present study evaluated the prognostic value of CCI for readmission with six months in HF for this purpose. In our study, CCI was identified as a significant and independent prognostic factor for readmission with six months. The patients with higher CCI had a greater likelihood of readmission with six months than those with a lower CCI in adjust II model (*OR* = 1.14, 95% *CI*: 1.03–1.26, *P* = 0.0127, *P* for trend = 0.0258). Furthermore, we found a curvilinear correlation between them (LRT P > 0.05) and the inflection of CCI was 1. However, it needs to be noted that CCI alone was inadequate for predicting readmission with six months in HF.

Previous studies have mainly confirmed the positive correlation between CCI and readmission in western countries. A national retrospective cohort study in the Netherlands reported that a higher CCI increased the risk of early readmission in patients ≥ 70 years with HF within 7, 30 and 42 days [8]. In a single-centered retrospective cohort study in the U.S., Daniel Keyes et.al confirmed that CCI were significantly lower for geriatric patients with HF in the > 30-day/non-readmitted subgroup compared to earlier readmission patients [9]. Our study further provided complementary evidence and corroborated the correlation between CCI and readmission in Chinese. Thus, current evidence points toward the existence of the association, no matter in western countries or in Chinese.

Compared with previous studies [8, 9], our study has a number of advantages. First of all, we proved that there was a significant linear trend relationship and threshold effect between CCI and readmission within

six months for the first time, which helped us study the correlation more accurately. Second strength of this study is the inclusion of more comprehensive confounding factors including demographic and clinical data and results of laboratory examination and ultrasound. In theory, at least, we believed that these advantages would make our results more credible.

We recognized some limitations of our study as well. First, this study represents a retrospective analysis, with inherent biases associated with this study design. Second, all subjects included were Chinses, and therefore our findings may not be extrapolated to other populations. Third, our cohort inevitably included a proportion of missing covariate data but it was addressed by dummy variables (covariates missing in large proportions) and multiple imputations (covariates missing in small proportions) in this study. We did not perform survival analysis due to immature survival data in follow-up time [11]. Fourth, as with any observational study, there is an unavoidable potential for residual confounding. However, based on E-value computations, changes to our results from unmeasured confounding would be unlikely (E-value = 1.34). E-values estimated in our study suggest that a confounder must have relative strong associations with both CCI and readmission within six months simultaneously (relative risk ≥ 1.34) to completely dilute the observed association [24].

Conclusion

In Chinese population, CCI was independently positively correlated with readmission within six months in patients with HF. However, CCI alone has limited value on predicting readmission within six months in patients with HF. As this study has several limitations, the principal conclusions of this paper need to be taken with caution.

Abbreviations

HF
heart failure
CCI
Charlson Comorbidity Index
ICD
International Classification of Diseases
ESC
European Society of Cardiology
BMI
body mass index
SBP
systolic blood pressure
DBP
diastolic blood pressure
NYHA

New York Heart Association

GCS

Glasgow Coma Scale

GFR

glomerular filtration rate

WBC

white blood cell

HGB

hemoglobin

hs-TnT

high sensitivity troponin

BNP

brain natriuretic peptide

hs-CRP

high sensitivity C reactive protein

ALB

albumin

LVEF

left ventricular ejection fractions

CI

Confidence Interval

Q1

1st quartile

Q3

3rd quartile

χ^2

chi-square

STROBE

Strengthening the Reporting of Observational studies in Epidemiology

CIE

change-in-estimate

DAG

directed acyclic graph

LRT

likelihood ratio test

MI

multiple imputations

ROC

receiver-operating characteristic

AUC

areas under the curve

Declarations

Ethical statement

Databasecontentand construction involving human participants were in accordance with the ethical standards of ethics committee of Zigong Fourth People's Hospital (Approval Number: 2020-010)and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.Studyprotocol andall the methods in this study were approved by ethics committee of Zigong Fourth People's Hospital. Ethics committee of Zigong Fourth People's Hospital waived off the informed consentdue to the retrospective design of the study.

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Conflict of interest

All the authors have declared no competing interest.

Authorcontributions

Song Sheng completed the statistical analysis and wrote the paper. Professor Feng-qin Xu designed the study and substantively revised it.

Data Availability Statement

Thedataused in this study are available online in PhysioNet (https://physionet.org/content/heart-failure-zigong/1.2/).

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Tables

Table 1. Baseline characteristics of the patients

readmission within six months	No	Yes	*P* value
N	1232	771	
CCI	1.80 ± 0.91	1.96 ± 1.03	<0.001
age (years)			0.463
<60	116 (9.42%)	61 (7.91%)	
60-89	656 (53.25%)	425 (55.12%)	
90-110	460 (37.34%)	285 (36.96%)	
gender			0.388
female	724 (58.77%)	438 (56.81%)	
Male	508 (41.23%)	333 (43.19%)	
BMI (kg/m^2)	21.86 ± 13.24	21.68 ± 14.32	0.776
occupation			<0.001
urban resident	1002 (82.06%)	663 (87.81%)	
farmer	150 (12.29%)	48 (6.36%)	
others	69 (5.65%)	44 (5.83%)	
admission ward			0.005
cardiology ward	926 (75.16%)	617 (80.03%)	
general ward	165 (13.39%)	99 (12.84%)	
others	141 (11.44%)	55 (7.13%)	
admission way			0.911
emergency	588 (47.73%)	366 (47.47%)	
non-emergency	644 (52.27%)	405 (52.53%)	
discharge day	7.00 (5.00-10.00)	8.00 (6.00-11.00)	<0.001
body temperature (℃)	36.43 ± 0.44	36.39 ± 0.43	0.070
pulse (bpm)	86.03 ± 22.19	83.96 ± 20.45	0.036
respiration (bpm)	19.10 ± 1.80	19.06 ± 1.63	0.650
SBP (mmHg)	132.57 ± 24.77	128.49 ± 24.48	<0.001
DBP (mmHg)	77.03 ± 14.44	75.85 ± 14.49	0.073
NYHA			<0.001

II	249 (20.21%)	103 (13.36%)	
III	643 (52.19%)	394 (51.10%)	
IV	340 (27.60%)	274 (35.54%)	
Killip			0.289
I	328 (26.62%)	199 (25.81%)	
II	618 (50.16%)	408 (52.92%)	
III	253 (20.54%)	137 (17.77%)	
IV	33 (2.68%)	27 (3.50%)	
type of heart failure			<0.001
left	347 (28.17%)	130 (16.86%)	
right	33 (2.68%)	18 (2.33%)	
both	852 (69.16%)	623 (80.80%)	
type II respiratory failure			0.333
no	1157 (93.91%)	732 (94.94%)	
yes	75 (6.09%)	39 (5.06%)	
GCS	14.78 ± 1.39	14.91 ± 0.73	0.021
GFR (ml/min)	69.00 (44.34-93.67)	57.72 (39.13-82.29)	<0.001
cystatin (mg/l)	1.80 ± 0.96	1.91 ± 0.92	0.014
WBC (10^9/l)	7.40 ± 3.58	7.16 ± 3.30	0.133
HGB (g/l)	115.93 ± 24.19	113.72 ± 25.02	0.052
Hs-TnT (pg/ml)	0.05 (0.02-0.12)	0.06 (0.03-0.12)	0.002
BNP (pg/ml)	726.77 (301.63-1684.99)	861.39 (312.25-1883.15)	0.157
Hs-CRP (mg/l)			0.057
<=5	196 (15.91%)	113 (14.66%)	
>5	406 (32.95%)	222 (28.79%)	
missing	630 (51.14%)	436 (56.55%)	
ALB (g/l)	36.35 ± 4.98	36.85 ± 4.94	0.035
LVEF (%)			0.649
<45	123 (9.98%)	83 (10.77%)	

>=45	257 (20.86%)	170 (22.05%)
missing	852 (69.16%)	518 (67.19%)

Table 2. Results of the multivariate analysis and trend test between CCI and readmission

model	non-adjusted	adjust I	adjust II	fully-adjusted
N	2003	2003	1923	1736
CCI	1.19 (1.08, 1.30) 0.0003	1.18 (1.08, 1.30) 0.0005	1.14 (1.03, 1.26) 0.0127	1.17 (1.04, 1.31) 0.0073
CCI group				
<=1	Ref	Ref	Ref	Ref
2	1.08 (0.87, 1.33) 0.4802	1.07 (0.87, 1.32) 0.5141	1.05 (0.84, 1.31) 0.6703	1.02 (0.81, 1.30) 0.8421
>2	1.49 (1.19, 1.88) 0.0006	1.47 (1.17, 1.86) 0.0011	1.35 (1.05, 1.73) 0.0184	1.43 (1.08, 1.90) 0.0114
P for trend	0.0011	0.0019	0.0258	0.0196

Non-adjusted model adjusted for: None

Adjusted I model adjusted for: age, sex

Adjusted I model adjusted for: age, sex, type of HF, NYHA, GFR, cystatin, discharge day

Fully adjusted model adjusted for: all covariates.

Figures

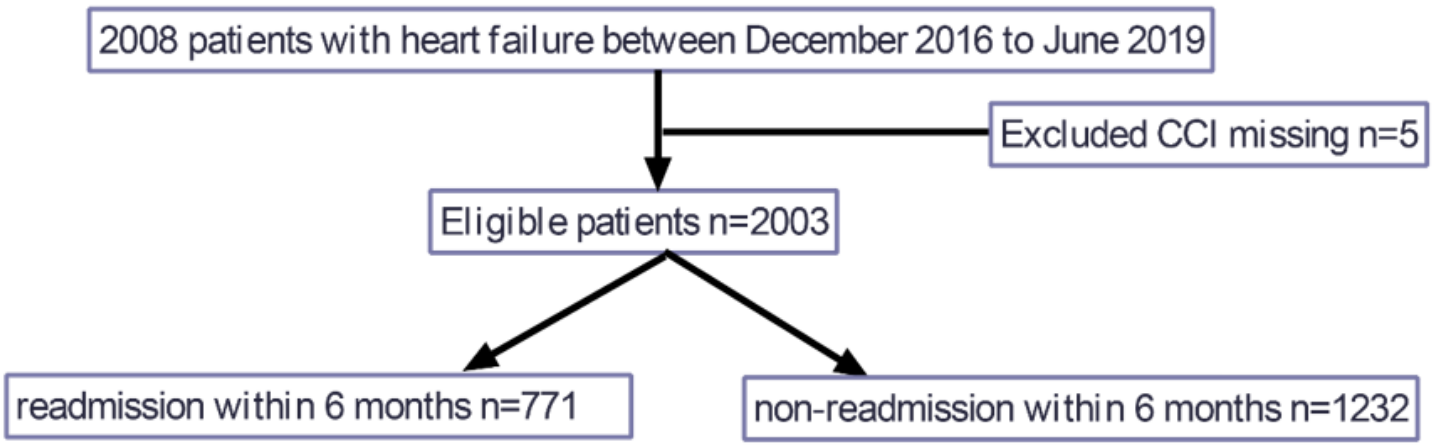

Figure 1

The flowchart of patient selection in this study

Supplementary Files

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- SupplementaryTable.xlsx