Impact of Albumin-bilirubin (ALBI) score on the Prognostic Significance of Patients with Heart Failure:A Retrospective Cohort Study

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Abstract

Objectives Liver dysfunction is prevalent in heart failure (HF) patients and it can bring a poor prognosis. Presently, albumin-bilirubin (ALBI) score has been designed as an effective and convenient scoring system for assessing liver function, but the correlation linking ALBI and in-hospital mortality in HF patients remains unclear.

Methods and Results A total of 9749 patients with HF (from January 2013 to December 2018) was enrolled and retrospectively analyzed. The main outcome is in-hospital death. We examined and analyzed ALBI as a continuous variable as well as according to 3 categories. Following adjustment for multivariable, patients which occurred in-hospital death was remarkably elevated in Tertile 3 group (ALBI>-2.27) (OR=1.670, 95% CI: 1.231~2.265, p=0.001), relative to the other two groups (Tertile 1: <-2.59; Tertile 2: -2.59~-2.27). When ALBI was inspected as a continuous variable, the incidence of HF patients with in-hospital death will increase by 8.2%. (For ALBI score per 0.1 score increasing, OR=1.082, 95% CI: 1.052~1.113, p<0.001). ALBI score for estimating in-hospital mortality under C-statistic was 0.650 (95% CI: 0.641~0.660, p<0.001) and the cut-off value of ALBI score was -2.32 with a specificity of 0.630 and a sensitivity of 0.632. Moreover, ALBI score can enhance the estimation potential of NT-proBNP (NT-proBNP+ALBI vs NT-proBNP: C-statistic: z=1.990, p=0.0467; net reclassification improvement=0.4012, p<0.001; integrated discrimination improvement= 0.0082, p<0.001).

Conclusions In patients with HF, ALBI score was an independent prognosticator of in-hospital death. The predictive significance of NT-proBNP +ALBI was superior to NT-proBNP, and ALBI score can enhance the estimation potential of NT-proBNP.

Introduction

Heart failure (HF) patients usually surfer poor quality of life and dismal prognosis.[1] In China, the age of heart failure onset has increased year by year, but the mortality rate of heart failure has not decreased significantly. [2] Therefore, how to identify high-risk HF patients and actively improve their prognosis have become important issues in aging societies. It is growingly becoming clear that HF is not a single-organ disease; numerous organs other than the myocardium constituting the kidney, the lung, and gastrointestinal systems play a role and interact with each other. [3–5] Besides, it has been reported that liver dysfunction is prevalent in HF patients. This is the result of high metabolic activity associated with a high oxygen demand and anatomical location near the heart associated with a high central venous pressure.[6–7] Previous studies have confirmed that liver dysfunction can lead to a dismal prognosis in HF patients, but they mostly measured bilirubin, albumin, alanine aminotransferase, etc.[8] In addition to conventional measures of liver function, a new approach, the albumin-bilirubin (ALBI) score, was developed as an important strategy to examine liver function.[9] Previous studies have confirmed that the ALBI score is related to the patient fluid overload and adverse events after discharge from the hospital, but there are no related studies of in-hospital events.[10]

In our study, we inspected whether ALBI score is a significant clinical factor to estimate in-hospital mortality in patients with HF. We additionally verified whether ALBI score could enhance the prognostic significance of NT-proBNP.

Methods

Study design and setting

Our retrospective study population comprised 11556 consecutively patients aged > 18 years with HF as the main diagnosis on admission from ShengJing Hospital of China Medical University located in the northeastern part of China (from January 2013 to December 2018). HF was defined based on the modified Framingham criteria.[11] We used a uniform questionnaire to collect clinical, as well as the procedural data of all the subjects. We employed the ($\log_{10}$ bilirubin [umol/L] * 0.66) + (albumin [g/L] * -0.085) formula to compute the ALBI score according to the serum albumin and total bilirubin levels at baseline.[9] We collected samples of the venous blood from all the subjects on admission and kept them in standard tubes. Serum albumin and total bilirubin were assayed using completely automated enhanced immunone-phelometric assay on a Beckman AU 5800 analyzer (Beckman Coulter, USA). The standard ranges for baseline albumin and total bilirubin are 35–53 g/L and 3.4–20.5 umol/L, respectively. The primary endpoint is all-cause in-hospital death.

Exclusion criteria included (1) acute myocardial infarction (492 cases); (2) chronic alcoholism (113 cases); (3) chronic kidney failure with dialysis and diagnosed liver disease on admission (460 cases); (4) prior history of cardiac transplantation (28 cases); (5) no albumin, no total bilirubin, or no NT-proBNP data (714 cases). We finally enrolled 9749 HF subjects into the study. The mean hospitalization period was 9.8 ± 5.7 days. Figure 1 exhibits the flowchart of selecting the patients. We clustered the subjects into three study groups as per the tertile of ALBI score on hospital admission [Tertile 1: <-2.59 (n = 3250); Tertile 2: -2.59~-2.27 (n = 3250); Tertile 3: >-2.27 (n = 3249)]. This study accedes to the Helsinki Declaration. Moreover, this study was ratified by the Research Ethics Committee in the Shengjing Hospital of China Medical University. We formally obtained a written informed consent from all the subjects.

Statistical analysis

The normal distributed quantitative variables were indicated as mean ± SD and compared using the Student's t test. However, the quantitative variables without normal distribution were indicated as median (IQR) and employed the Kruskal-Wallis H-test to compare them. The differences between categorical variables were compared by χ^2 test. When the number of variables was lower than 5, Fisher’s exact test was used to detect the differences. we performed the logistic univariate assessments to examine the prognosticators of in-hospital mortality (online supplementary appendices S1), and then enter into the multivariate logistic regression model to uncover the independent prognosticators of in-hospital mortality. We entered the variables in the univariate evaluations with $p < 0.05$ in a multivariate assessment. ALBI score was tested in the form of continuous variable and categorical variable. The output results were

presented by ORs with correlated 95% CIs. The prognostic potential of ALBI, NT-proBNP, and NT-proBNP + ALBI was inspected using the discrimination indices as below:(1) A receiver operating characteristic (ROC) curve and the area under the curve (AUC) in connection with the in-hospital mortality were determined by MedCalc statistical software (version 18.1.1).[12] (2) We got individual risk of in-hospital mortality by entering each model into a logistic regression model. The Nagelkerke-R2, as well as the Hosmer-Lemeshow (HL) test from the regression model were employed as indices of goodness-of-fit of each risk model and to examine their calibration potential.[13] We additionally computed the Brier scores of ALBI score, NT-proBNP, and NT-proBNP + ALBI score. Lower Brier scores exhibited improved precision.[14] (3) The absolute integrated discrimination improvement (IDI), as well as the category-free net reclassification improvement (NRI) were used to examine enhancements in risk estimation quantization of ALBI score and NT-proBNP + ALBI.[15] All the statistical tests were two-sided, and the statistical significance was marked by $p < 0.05$. We employed the Statistical Analysis Software (SAS Institute Inc, Cary, NC) V.9.4 to conduct all the statistical analysis.

Results

General characteristics

The flowchart of patient selection was shown in Fig. 1. We finally enrolled a study cohort of 9749 HF patients. The general characteristics were indicated in Table 1. The group of tertile 3 group had markedly higher percentage proportion of males, NYHA grading IV, relative to the other two groups. The tertile 3 group additionally had an inclination towards intensifying heart rate, serum glutamate-pyruvate transaminase (SGPT), serum glutamic oxaloacetic transaminase (SGOT), cTNI, total bilirubin, creatinine, and NT-proBNP on admission. There was a distinct pattern of diminishing systolic blood pressure, albumin, low density lipoprotein (LDL), fasting blood glucose(FBG), left ventricular ejection fraction (LVEF) in the Tertile 3 group. The proportion percentage of coronary heart disease (CHD), Hypertension, atrial fibrillation (AF) and diabetes mellitus (DM) were markedly lower in the group of tertile 3. Moreover, the tertile 3 group depicted the inclination of an elevated in-hospital mortality (6.1% vs 2.1% and 2.4%, $p < 0.001$) (Table 1).

Table 1
Baseline characteristics of the population by tertile of ALBI, median (IQR), or N (%), or means ± SD

Variable	Overall (n = 9749)	Tertile1 ALBI<-2.59 (n = 3250)	Tertile2 ALBI −2.59~-2.27 (n = 3250)	Tertile3 ALBI>-2.27 (n = 3249)	P value
Age (years)	69.1 ± 13.6	67.9 ± 12.8	70.2 ± 13.1	69.4 ± 14.6	< 0.001
Male [*n* (%)]	5158(52.9)	1650(50.8)	1731(53.3)	1777(54.7)	0.006
NYHA grading [*n* (%)]					< 0.001
	1954(20.0)	988(30.4)	637(19.6)	329(10.1)	
	4207(43.2)	1434(44.1)	1428(43.9)	1345(41.4)	
	3588(36.8)	828(25.5)	1185(36.5)	1575(48.5)	
Heart rate on admission, bpm	87.7 ± 22.3	85.0 ± 21.0	87.6 ± 22.4	90.5 ± 23.2	< 0.001
SBP on admission, mmHg	135.2 ± 22.7	136.1 ± 21.0	135.9 ± 22.7	133.5 ± 24.1	< 0.001
SGPT, U/L	25.5 ± 11.9	25.5 ± 11.0	25.2 ± 11.9	26.0 ± 12.7	0.046
SGOT, U/L	31 (26,35)	34 (23,34)	31 (24,35)	33 (28,37)	< 0.001
Albumin, g/L	37.1 ± 4.5	41.3 ± 2.5	37.4 ± 2.0	32.6 ± 3.5	< 0.001
TBIL, umol/L	16.2 ± 12.1	12.7 ± 6.8	15.2 ± 8.7	20.6 ± 16.9	< 0.001
LDL, mmol/L	2.52 ± 0.91	2.70 ± 0.94	2.52 ± 0.85	2.36 ± 0.92	< 0.001
Creatinine, mg/dl	1.07 ± 0.51	1.01 ± 0.45	1.06 ± 0.50	1.16 ± 0.56	< 0.001
Haemoglobin, g/L	127.6 ± 21.9	132.0 ± 19.6	128.1 ± 21.0	122.8 ± 24.1	< 0.001
Serum Na, mmol/L	138.9 ± 3.9	139.5 ± 3.3	139.2 ± 3.6	137.9 ± 4.5	< 0.001
FBG, mmol/L	6.5 ± 1.6	6.6 ± 1.7	6.5 ± 1.4	6.4 ± 1.6	< 0.001

*SBP, systolic blood pressure; SGPT, serum glutamate-pyruvate transaminase; SGOT, serum glutamic oxaloacetic transaminase; TBIL, total bilirubin; LDL, Low Density Lipoprotein; FBG, fasting blood glucose; cTNI, cardiac troponin I; LVEF, left ventricular ejection fraction; CHD, coronary heart disease; AF, atrial fibrillation; DM, diabetes mellitus

Variable	Overall (n = 9749)	Tertile1 ALBI<-2.59 (n = 3250)	Tertile2 ALBI −2.59~-2.27 (n = 3250)	Tertile3 ALBI>-2.27 (n = 3249)	P value
cTNI, ng/ml	0.04 (0.01, 0.28)	0.03 (0.01, 0.15)	0.04 (0.01, 0.31)	0.06 (0.02, 0.35)	< 0.001
NT-proBNP, pg/ml	2538(986, 5850)	1376(570, 3284)	2492(1066, 5419)	5186(1987, 9085)	< 0.001
LVEF, %	48.7 ± 11.3	50.4 ± 11.0	48.9 ± 11.3	46.9 ± 11.3	< 0.001
Accompanies, *n (%)*					
CHD	6282(64.4)	2184(67.2)	2129(65.5)	1969(60.6)	< 0.001
Hypertension	5948(61.0)	2149(63.8)	2129(63.4)	1860(55.8)	< 0.001
AF	3086(31.7)	1091(33.6)	1094(33.7)	901(27.7)	< 0.001
DM	3118(32.0)	1070(32.9)	1023(31.5)	1025(31.5)	0.371
Smoking [n (%)]	2664(27.3)	919(28.3)	855(26.3)	890(27.4)	0.203
In-hospital mortality	343(3.5)	67(2.1)	78(2.4)	198(6.1)	< 0.001

*SBP, systolic blood pressure; SGPT, serum glutamate-pyruvate transaminase; SGOT, serum glutamic oxaloacetic transaminase; TBIL, total bilirubin; LDL, Low Density Lipoprotein; FBG, fasting blood glucose; cTNI, cardiac troponin I; LVEF, left ventricular ejection fraction; CHD, coronary heart disease; AF, atrial fibrillation; DM, diabetes mellitus

Ability of ALBI score in prognosis estimation

Numerous variables had remarkable influences on in-hospital mortality through the univariate assessment supplemented online in Appendix S1: ALBI score, age, NYHA grading, heart rate on admission, systolic blood pressure on admission, SGPT, SGOT, creatinine, haemoglobin, Serum Na, FBG, cTNI, NT-proBNP, LVEF, and the history of CHD, hypertension, AF, DM (online supplementary appendices S1).

The univariate assessment indicated that the ALBI score was linked to the in-hospital mortality (OR = 1.135, 95%CI:1.108 ~ 1.163, p < 0.001, for per 0.1 score increase) (Table 2). Following covariate adjustments, the association remained present: the risk of in-hospital mortality increased by 8.2% for per 0.1 increase in ALBI score (OR = 1.082, 95% CI:1.052 ~ 1.113, p < 0.001) (Table 2).

Table 2
Effects of multiple variables on clinical outcomes in univariate and multivariate analysis

	Univariate analysis			*Multivariate analysis*		
	OR	95% CI	P value	OR	95% CI	P value
NT-proBNP per 100 pg/ml increase	**1.007**	**1.006 to 1.008**	**< 0.001**			
ALBI as a continuous variable						
ALBI, per 0.1 score increase	**1.135**	**1.108 to 1.163**	**< 0.001**	**1.082**	**1.052–1.113**	**< 0.001**
ALBI as a categories variable						
Tertile 1	**Reference**			**Reference**		
Tertile 2	**1.167**	**0.839 to 1.624**	**0.358**	**0.862**	**0.613 to 1.214**	**0.397**
Tertile 3	**3.082**	**2.326 to 4.084**	**< 0.001**	**1.670**	**1.231 to 2.265**	**0.001**
*Adjusted for age, NYHA grading, heart rate on admission, SBP on admission, SGPT, SGOT, creatinine, haemoglobin, serum Na, FBG, cTNI, LVEF, CHD, hypertension, AF, DM, smoking						

Upon categorization into 3 groups, the ALBI score still significantly predicated incidence of in-hospital death (Table 2). Under the univariate assessments, the Tertile 3 group exhibited a markedly elevated risk of in-hospital mortality contrasted with the Tertile 1 and 2 groups (OR = 3.082, 95%CI 2.326 ~ 4.084, p < .001) (Table 2). After adjusting for covariates, the group with the highest incidence of in-hospital mortality was still the Tertile 3 (OR = 1.670, 95% CI:1.231 ~ 2.265, p = 0.001) (Table 2).

The prediction significance of ALBI, NT-proBNP, and NT-proBNP + ALBI was assessed by C-statistic, which result were 0.650 (95% CI: 0.641 ~ 0.660), 0.652 (95% CI:0.642 ~ 0.661), and 0.681 (95% CI:0.672 ~ 0.690) (Fig. 2 and Table 3), separately. The cut-off value for ALBI score was − 2.32 with a sensitivity of 0.632 and a specificity of 0.630.

Table 3
NT-proBNP, NT-proBNP + ALBI and ALBI performance for the prognosis prediction

NT-proBNP	Discrimination				Calibration		Precision
	C-statistic	SE	P value	95% CI	HL p value	R^2	Brier score
	0.652	0.0157	< 0.001	0.642 to 0.661	0.007	0.033	0.0336
NT-proBNP + ALBI	0.681	0.0157	< 0.001	0.672 to 0.690	< 0.001	0.039	0.0334
ALBI	0.650	0.0162	< 0.001	0.641 to 0.660	0.012	0.038	0.0335

Improvement of the prognostic significance of ALBI + NT-proBNP

The HL p value, Nagelkerke-R2, as well as Brier score the of ALBI + NT-proBNP were Significantly better than the other two groups (Table 3). The novel model in which the NT-proBNP was incorporated with ALBI can enhance the estimation significance. The prognostic value of NT-proBNP + ALBI was superior to that of NT-proBNP (C- statistic: z = 1.990, p = 0.0467; IDI = 0.0082, p < 0.001; NRI = 0.4012, p < 0.001) (Table 4).

Table 4
Comparisons of the predictive performance of NT-proBNP, NT-proBNP + ALBI and ALBI for the prognosis prediction

ALBI vs NT-proBNP	z for C-statistic	P for C-statistic	NRI	P for NRI	IDI	P for IDI
	0.0938	0.9253	0.0518	0.3461	0.0018	0.4204
ALBI + NT-proBNP vs NT-proBNP	1.990	0.0467	0.4012	< 0.001	0.0082	< 0.001
ALBI + NT-proBNP vs ALBI	4.362	< 0.001	0.4054	< 0.001	0.0063	0.0001

Discussion

The present study inspected the correlation linking the ALBI score and in-hospital mortality in HF patients. We elucidated that: (1) the ALBI score is an independent prognosticator of in-hospital death; (2) the predictive significance of NT-proBNP + ALBI is superior to NT-proBNP, and ALBI score can enhance the estimation potential of the initial NT-proBNP model in patients with HF.

Various studies have assessed the prognostic clinical significance using distinct liver function test (LFT) indices in HF patients. Post-hoc evaluation of the EVEREST study posited that the low baseline albumin and increased bilirubin, were associated with clinical outcome.[16] PROTECT study found the escalating AST and ALT on day 3, and diminishing albumin on day 4 are independent predictors of 180-day

outcomes of HF patients.[17] More and more studies have realized that the reserve of liver function is not only a single parameter, but also other factors with joint variables exist, so at present, the joint scoring system is mostly used to judge the liver function reserve of patients, including Child-Pugh classification(CP), MELD score and ALBI score.[9,18,19] The CP constitutes some weaknesses, such as subjective parameters (ascites and encephalopathy), and interrelated indices (serum albumin and ascites), and it was not statistically established.[20] MELD score system is an independent prediction index of adverse outcomes in HF patients.[21–25] However, for the ALBI score, there is limited research. To our best knowledge, no study has explored the prediction value of the ALBI score for the in-hospital mortality in HF patients. In our study, we elucidated that the ALBI score was correlated with in-hospital mortality for HF patients. With ALBI score as a continuous variable, we established that the risk of in-hospital mortality increased by 8.2% per 0.1 score increase in ALBI (OR = 1.082, 95% CI:1.052 ~ 1.113, p < 0.001). As illustrated in Table 2, ALBI score was still associated with in-hospital mortality when treated as a categorical variable (OR = 1.670, 95% CI:1.231 ~ 2.265, p = 0.001). Previous reports have verified that NT-proBNP is linked to adverse events in HF patients, whether in hospital or discharged.[26–27] NT-proBNP is excreted by the kidney, and its circulating concentrations must be interpreted based on renal clearance.[28] The patients with HF usually suffer a renal dysfunction,[3–5] NT-proBNP may be abnormally elevated in this group of patients, which limits its clinical utility in this setting. [28–29] The ALBI score has no such restrictions, compared to the classic indicator NT-proBNP, ALBI score has not less than its predictive value (C- statistic: z = 0.0938, p = 0.9253). Furthermore, ALBI score can enhance the predictive significance of NT-proBNP (C- statistic: z = 1.990, p = .0467; IDI = 0.0082, p < 0.001; NRI = 0.4012, p < 0.001).

Although the detailed pathophysiological correlation linking liver dysfunction to HF requires detailed assessments, numerous likely mechanisms can be postulated. Severe congestive HF is linked to two different kinds of liver conditions: acute hepatocellular necrosis that is caused by compromised blood supply as well as jaundice, which is correlated with the passive congestion.[30] Compromised blood supply due to diminished cardiac output has a connection with acute hepatocellular necrosis with distinct escalations in serum aminotransferases.[31] The passive hepatic congestion is associated with the elevated central venous pressure, resulting in increments in the levels of liver enzymes, as well as indirect and direct circulating bilirubin. Kato et al studied liver metabolism of HF in a rat model and established that congestive HF is linked to atypical metabolism in tissues adjacent to the heart.[32] In the congestive HF rats, hepatic protein blood concentrations, including albumin, transferrin, retinol-binding protein, and transthyretin were reduced and correlated with elevated levels of circulatory proinflammatory cytokines (TNF-α and IL-1β). Because of heart which has poor capacity of energy storage, and it need a continuous energy supply, all the above studies support the possibility that liver dysfunction may lead to impaired cardiac energy supply, which may lead to a poor prognosis.[32,33] The ALBI score was initially created from Japanese hepatocellular carcinoma (HCC) patients to estimate the extent of liver dysfunction.[9] However, it has also been widely used in patients without HCC. [33–36]Notably, one study posited that the ALBI score was related to liver function as assayed by the indocyanine green injection test. [37] These results support that the ALBI score can reflect residual liver function reserve, even in patients without HCC.

Our findings have some clinical significance. First, observing ALBI in HF patients may be significant in establishing HF patients with elevated risk of in-hospital adverse events. Moreover, the predictive significance of ALBI score is as good as that achieved by NT-proBNP. If the patient is combined with kidney dysfunction, which NT-proBNP is limited for clinical utility, ALBI score may be useful for this setting. At last, if we consider the patient's cardiac function and liver dysfunction together, it may bring some help to clinicians.

The current study has several limitations. First, it constituted a retrospective and observational design; therefore, possible confounders and selection bias were not absolutely adjusted. Secondly, we did not examine all the LFTs individually, as some biosignatures were missing in our dataset. For example, in the FINRISK study, moderate to high levels of serum γ-glutamyltransferase were markedly correlated with incident HF among 38076 people.[38] In addition, higher alkaline phosphatase was linked to a dismal prognosis in patients with AHF.[39] Thirdly, the study population constituted part of the Asians, therefore, the results of the study may need to be further serious in other populations.

Conclusion

In patients with HF, ALBI score was an independent prognosticator of in-hospital death. The predictive significance of NT-proBNP + ALBI was superior to NT-proBNP, and ALBI score can enhance the estimation potential of NT-proBNP.

Declarations

Ethics approval and consent to participate: IRB information: Shengjing Hospital of China Medical University□2019PS594K

Consent for publication: Not applicable

Availability of data and materials: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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Authors' contributions: SH designed of the work and and was a major contributor in writing the manuscript. CHW, FT, YL collected and applied of statistical techniques to analyze study data. ZCL, ZQS managed activities to annotate (produce metadata), scrub data and maintain research data for initial use and later reuse. ZJS formulated of overarching research goals and aims, reviewed and edited the manuscript. All authors read and approved the final manuscript.

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Figures

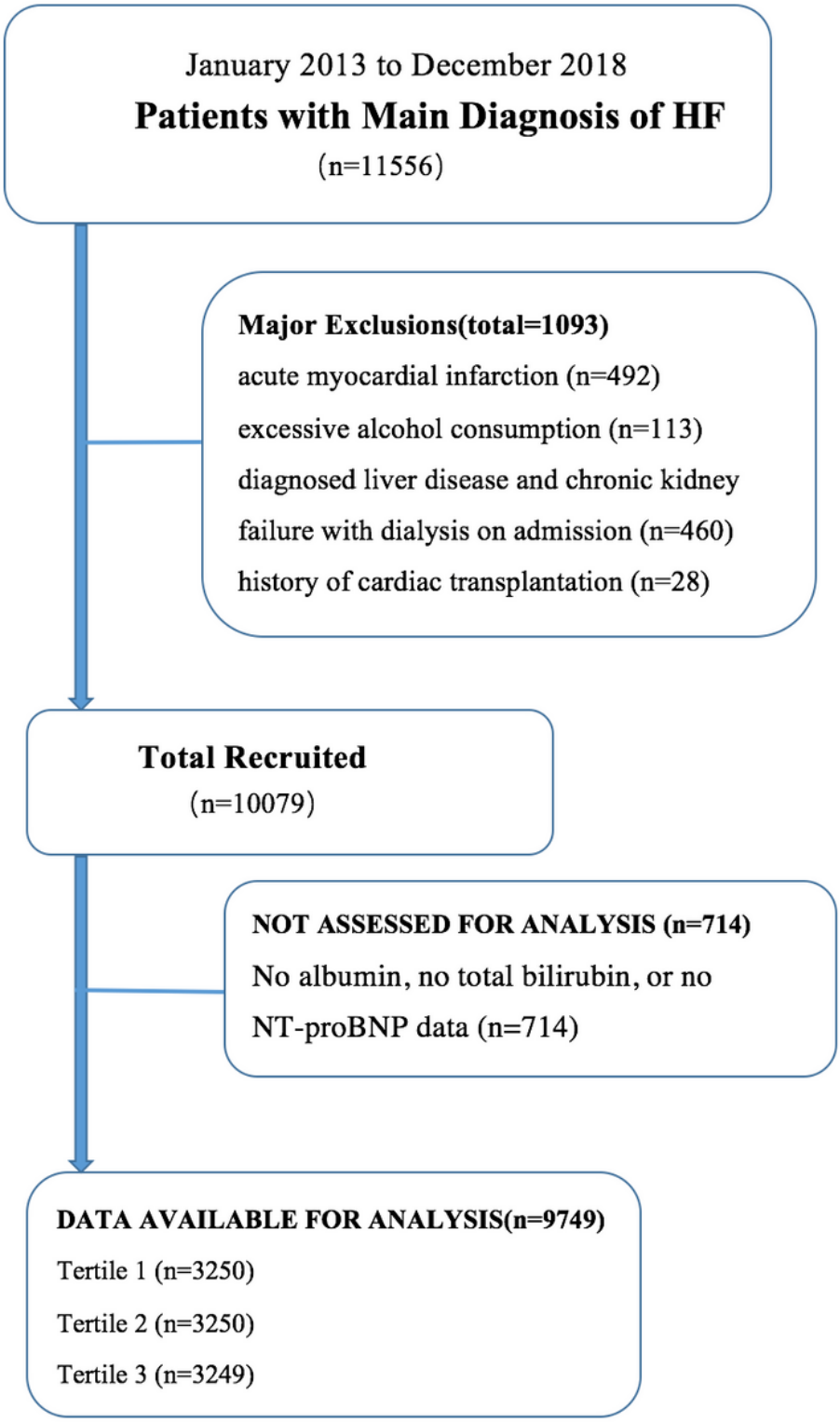
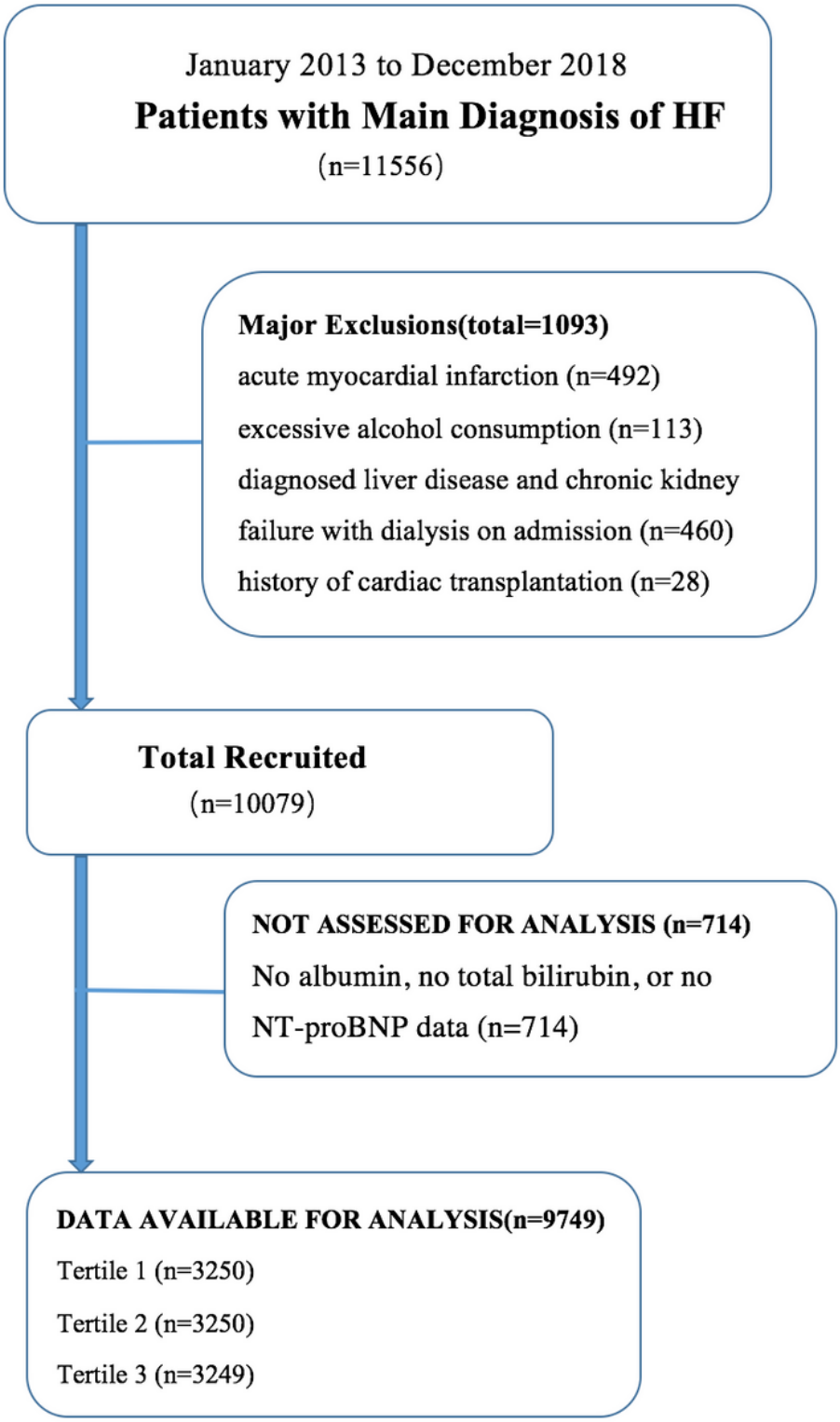


Figure 1

Flowchart of patient selection



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Flowchart of patient selection

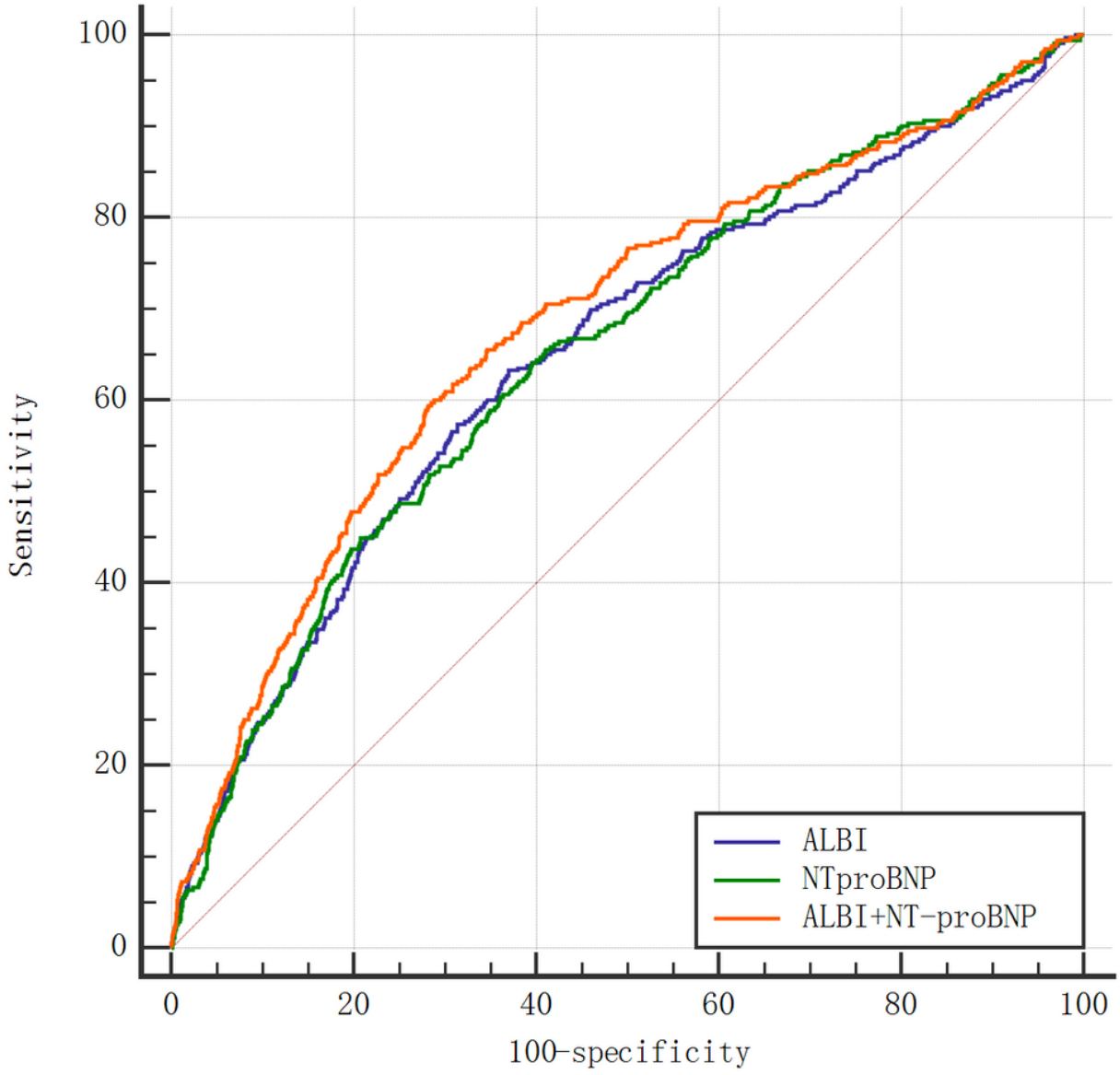

Figure 2

Receiver operating characteristic curves of ALBI, NT-proBNP and ALBI +NT-proBNP for in-hospital death prediction.

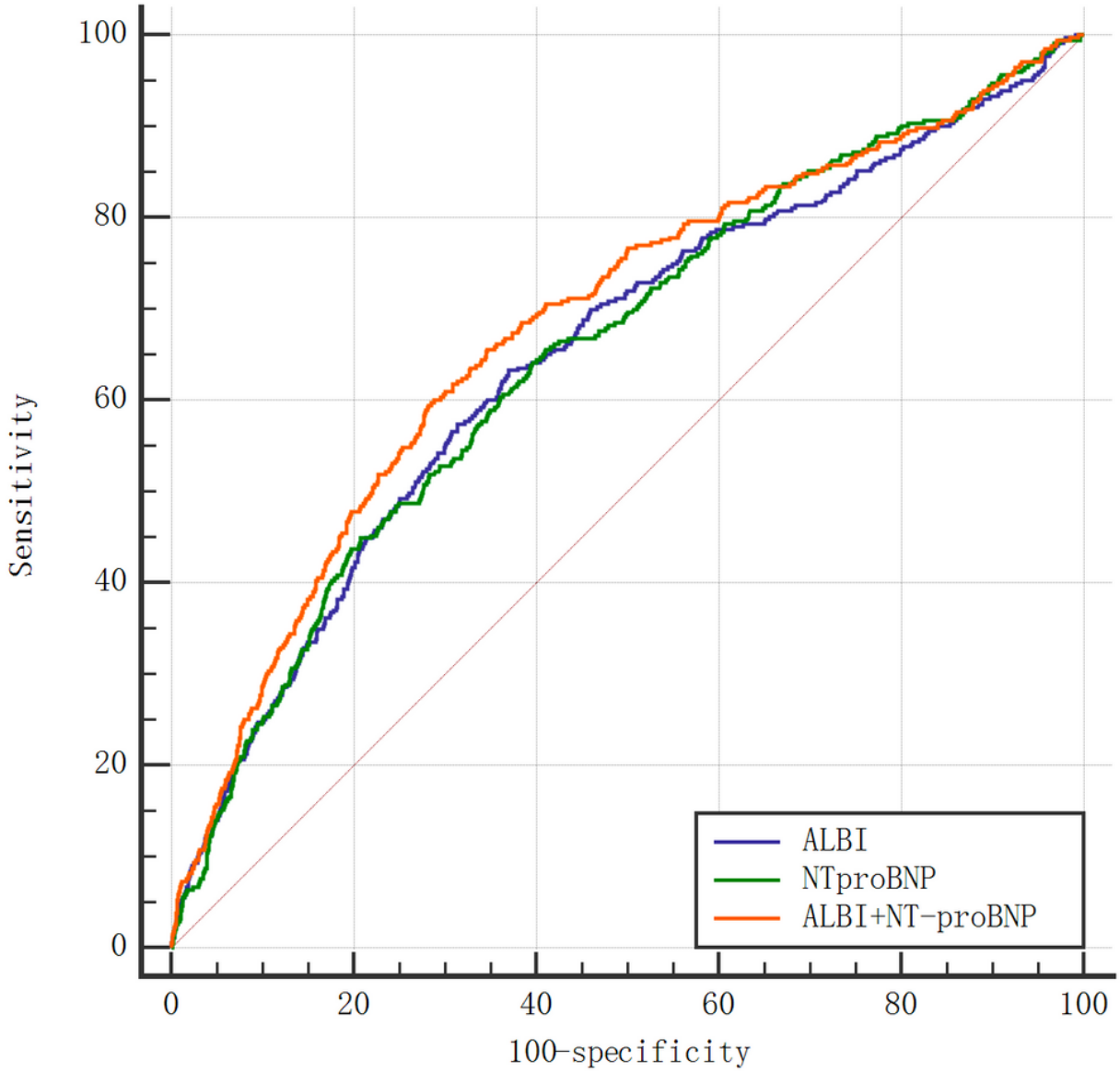

Figure 2

Receiver operating characteristic curves of ALBI, NT-proBNP and ALBI +NT-proBNP for in-hospital death prediction.

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