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ORIGINAL ARTICLE

Effect of conjugated bilirubin on clinical outcomes in infective endocarditis

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Abstract

Liver dysfunction is associated with adverse events in infective endocarditis (IE). However, few studies have explored the predictive value of conjugated bilirubin (CB) in IE. We aimed to investigate the nature of the link between CB and adverse prognosis in patients with IE. Consecutive patients with IE between January 2009 and July 2015 were enrolled. Multivariate analysis was performed to confirm whether CB was an independent risk factor for adverse outcomes. In all, 1010 patients were included and divided into two groups according to admission CB level (μmol/L): normal (≤ 7.0, $n = 820$) and elevated (> 7.0, $n = 190$) CB groups. In-hospital mortality (5.0% vs. 22.1%, $p < 0.001$) and major adverse cardiac events (16.8% vs. 36.3%, $p < 0.001$) were significantly higher in patients with increased CB. A possible J-shaped relationship was found between CB and in-hospital events. Further, CB had more predictive power than total bilirubin in predicting in-hospital death (AUC 0.715 vs. 0.674, $p = 0.010$). Elevated CB was an independent predictor of in-hospital death (adjusted OR = 2.62, 95%CI 1.40–4.91, $p = 0.003$). Moreover, CB (increment 1 μmol/L) was independently associated with higher long-term mortality. Kaplan–Meier curves indicated that patients with elevated CB were associated with higher cumulative rate of long-term death (log-rank = 21.47, $p < 0.001$). CB, a biomarker of liver function, was a relatively powerful predictor of in-hospital and long-term adverse prognosis of IE and could likely comprise a novel risk evaluation strategy.

Keywords Bilirubin · Infective endocarditis · Prognosis

Introduction

Infective endocarditis (IE) refers to inflammation of the endocardium, which is a serious and life-threatening condition despite early and intense diagnostic and therapeutic intervention [1]. Epidemiological data have revealed that the incidence of early death in IE is an estimated 10% [2]. Moreover, the mortality rate continues to rise during the follow-up period [3]. Early identification of patients with IE who are at a high risk of complications or death may allow for improved prognosis.

Bilirubin—a breakdown product of heme catabolism—is considered a true marker of liver function [4]. Hyperbilirubinemia or jaundice is a common complication in bacterial infections. A study showed that 20% of jaundice cases in a community hospital setting were due to sepsis and bacterial infection [5]. Although bilirubin has been proven to possess anti-oxidant and anti-inflammatory properties [6, 7], some studies reported that high bilirubin levels portended poor prognosis, especially in patients with sepsis and infection [8, 9]. In a recent study, Diab et al. found that perioperative liver dysfunction defined by total bilirubin (TB) was independently associated with short- and long-term mortality in IE [10]. However, their small sample size limited the prognostic evidence of bilirubin in IE and, hence, the predictive value of conjugated bilirubin (CB) remains unclear. Therefore, we designed the present study with a large sample size to explore the relationship between CB and adverse outcomes in patients with IE.

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Materials and methods

Study population

This observational study was performed at Guangdong Provincial People's Hospital, China. Between January 2009 and July 2015, 1293 consecutive patients with IE were admitted to our hospital. Diagnosis of IE was based on the modified Duke criteria, including pathologic and clinical criteria [11]. Only the first hospitalization was considered for patients who underwent multiple hospitalizations; other admissions were used for follow-up analysis. Accordingly, repeated hospital records were excluded ($n = 120$). Other exclusion criteria included the following: age less than 18 years ($n = 108$), diagnosis of IE after valve replacement surgery during hospitalization ($n = 2$), and missing serum bilirubin tests at admission ($n = 53$). The patient inclusion flow diagram is presented in Fig. 1. Finally, 1010 patients were included; all patients provided written informed consent before inclusion. This research was approved by our hospital's ethics committee.

Laboratory investigations

Circulating bilirubin and other blood variables were tested under fasted condition on the morning of the day after admission. Our laboratory's reference ranges for TB and CB are 7.0–19.0 μmol/L and 2.0–7.0 μmol/L, respectively. Venous blood samples were collected from three different venipuncture sites for blood cultures. The results of blood cultures from other hospitals were also accepted. Left ventricular ejection fraction (LVEF) was obtained using the Simpson's biplane method within 24 h after admission. We calculated estimated glomerular filtration rate (eGFR) using the four-variable Modification of Diet in Renal Disease equation for Chinese patients [12].

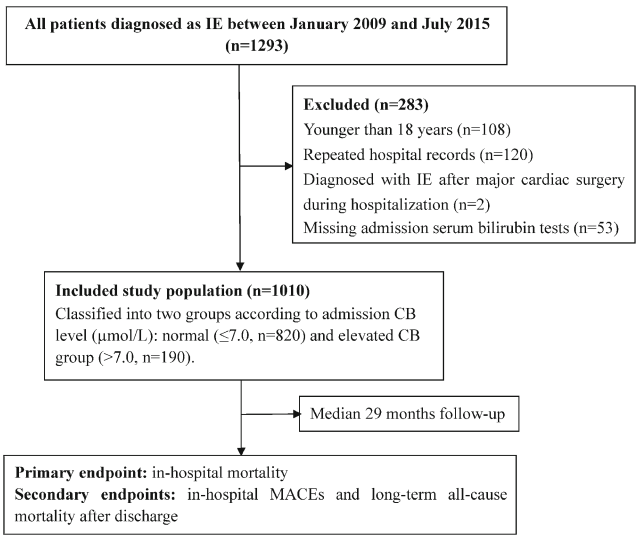

Fig. 1 Flow chart of the study population

Clinical outcomes

The primary end point of this study was all cause in-hospital mortality, and the secondary end points were long-term death after discharge and in-hospital major adverse clinical events (MACEs) including death, stroke, renal failure with dialysis, and acute heart failure at the time of hospitalization.

Statistical analysis

All analyses were conducted using SPSS software (version 22.0; SPSS Inc., Chicago, IL, USA). For continuous variables, the mean (± SD) or median (interquartile range) is described. Subsequently, independent sample t test or Wilcoxon rank sum test were performed. Logarithmic transformation was performed for variables with skewed distribution. The chi-square or Fisher's exact test was performed for categorical variables, represented as absolute values (percentages). Receiver operating characteristic (ROC) curves were plotted to evaluate the predictive power, and area under the curves (AUCs) were compared using nonparametric tests. Univariate and multivariate logistic regression analyses were conducted to identify the risk factors of in-hospital mortality. Variables whose p value was less than 0.01 in the univariate analysis were included in the multivariate analysis. The relationship between variables and survival was established using multivariate Cox proportional hazard analyses. The Kaplan–Meier curve was constructed to evaluate the cumulative long-term mortality rate among patients with different levels of serum bilirubin, and comparisons were performed using the log-rank test. Statistical significance was defined as $p < 0.05$.

Results

Basic clinical characteristics

In total, 1010 patients (69.9% men; mean age, 45 ± 15 years) were divided into two groups according to admission serum CB levels—normal (≤ 7.0, $n = 820$) and elevated (> 7.0, $n = 190$) CB groups. The demographic and clinical features of participants are shown in Table 1. Patients with elevated CB were more likely to have a history of rheumatic heart disease and valve replacement than those with normal CB levels. Elevated CB was associated with an increased number of patients with New York Heart Association (NYHA) functional class III or IV and those with an affected aortic valve. However, the rate of affected mitral valve decreased. The percentage of patients infected with *Staphylococcus* was higher in the elevated CB group, in whom infected with Streptococcus was lower. Patients with elevated CB had increased baseline levels of TB and CB, and increased levels of alanine transaminase (ALT) and C-reactive protein (CRP),

Table 1 Demographic characteristics stratified by conjugated bilirubin values

	Normal CB ($n = 820$)	Elevated CB ($n = 190$)	P value
Age (years)	44.3 ± 15.2	45.6 ± 15.4	0.269
Sex, *n* (%)			
Male	563 (68.7)	143 (75.3)	0.074
Female	257 (31.3)	47 (24.7)	
Smoker, *n* (%)	132 (16.1)	36 (18.9)	0.342
Hypertension, *n* (%)	115 (14.0)	17 (8.9)	0.061
Previous diabetes	61 (7.4)	15 (7.9)	0.830
NYHA class III or IV, *n* (%)	254 (31.0)	104 (54.7)	< 0.001
Previous IE	57 (7.0)	7 (3.7)	0.096
Predisposing heart disease			
Rheumatic heart disease	171 (20.9)	54 (28.4)	0.024
Congenital heart disease	228 (27.8)	60 (31.6)	0.299
Prosthetic valves	48 (5.9)	24 (12.6)	0.001
C reactive protein (mg/L)	18.5 (5.6, 43.8)	30.9 (8.3, 91.0)	< 0.001
Hemoglobin (g/L)	110.4 ± 23.5	108.7 ± 27.4	0.433
eGFR (mL/min/1.73 m^2)	105.1 ± 41.0	84.0 ± 39.0	< 0.001
Liver function tests			
ALT (U/L)	21.0 (14.0, 30.0)	32.5 (20.0, 70.5)	< 0.001
Albumin (g/L)	31.5 ± 6.1	28.0 ± 6.5	< 0.001
Baseline TB, μmol/L	13.1 (9.8, 17.1)	31.2 (24.7, 40.0)	< 0.001
Baseline CB, μmol/L	4.1 (3.4, 5.1)	10.4 (8.4, 16.4)	< 0.001
LVEF (%)	64.8 ± 8.0	62.9 ± 9.9	0.014
Affected site, *n* (%)			
Aortic valve	339 (41.3)	93 (50.5)	0.021
Mitral valve	429 (52.3)	78 (41.1)	0.005
Aortic + mitral valve	64 (7.8)	15 (7.9)	0.967
Others	111 (13.5)	33 (17.4)	0.173
Microorganisms			
Streptococcus	169 (20.6)	22 (11.6)	0.004
Staphylococcus	62 (7.6)	32 (16.8)	< 0.001
Other microbes	74 (9.0)	15 (7.9)	0.621
Surgical treatment	592 (72.2)	105 (55.3)	< 0.001
In-hospital events			
Death	41 (5.0)	42 (22.1)	< 0.001
MACEs	138 (16.8)	69 (36.3)	< 0.001

NYHA New York Heart Association, *IE* infective endocarditis, *eGFR* estimated glomerular filtration rate, *ALT* alanine transaminase, *CB* conjugated bilirubin, *TB* total bilirubin, *LVEF* left ventricular ejection fraction, *MACEs* major adverse clinical events

along with lower eGFR, serum albumin, and LVEF than the normal CB group. A total of 697 (69.0%) patients underwent surgery, the rate of which was significantly lower in the elevated CB group (72.2% vs. 55.3%, $p < 0.001$).

During hospitalization, 83 (8.2%) patients died, 90 (8.9%) experienced acute heart failure, 64 (6.3%) received renal dialysis, and 77 (7.6%) had a stroke. In-hospital mortality (5.0% vs. 22.1%, $p < 0.001$) and MACEs (16.8% vs. 36.3%, $p < 0.001$) were significantly higher in patients with elevated CB. In the ROC analysis, CB > 5.8 μmol/L had a sensitivity and specificity of 66.3% and 73.8%, respectively, (AUC = 0.715, 95% confidence interval [CI], 0.649–0.782, $p < 0.001$); furthermore, CB showed better predictive power than TB (AUC 0.715 vs. 0.674, $p = 0.010$) in predicting in-hospital death (Fig. 2).

The optimal cutoff of CB for in-hospital death was 5.8 μmol/L, which was within the normal range. To gain a better understanding of the relationship between CB and adverse events, patients were classified into six groups based on admission serum CB levels: ≤ 3.0 ($n = 131$), 3.0–4.0 ($n = 259$), 4.0–5.0 ($n = 217$), 5.0–6.0 ($n = 127$), 6.0–7.0 ($n = 86$), and > 7.0 ($n = 190$). There was a possible J-shaped

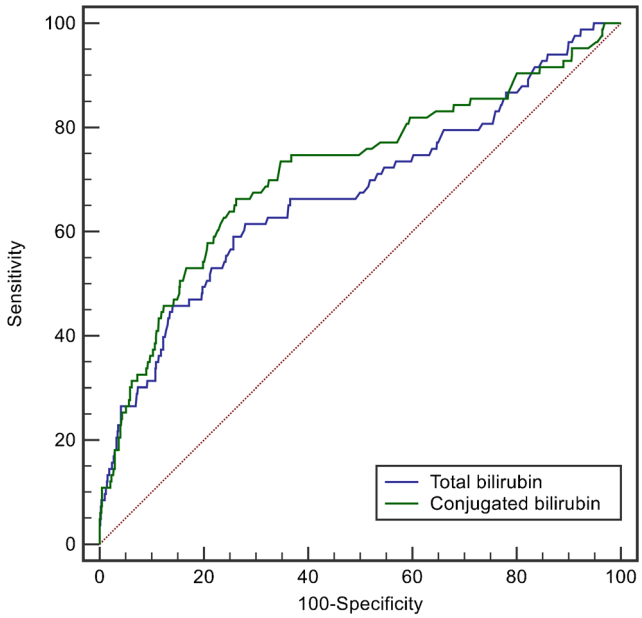

Fig. 2 ROC curve of bilirubin for in-hospital mortality

relationship between bilirubin levels and in-hospital death (5.3% vs. 3.1% vs. 2.8% vs. 7.9% vs. 11.6% vs. 22.1%, respectively, $p < 0.001$) and MACEs (16.8% vs. 12.0% vs. 15.7% vs. 21.3% vs. 27.9% vs. 36.4%, respectively, $p < 0.001$; Fig. 3). In Spearman analysis, CB positively correlated with in-hospital death ($r = 0.205$, $p < 0.001$) and MACEs ($r = 0.184$, $p < 0.001$).

Logistic regression analysis for in-hospital death

Results of the univariate and multivariate logistic regression analysis for in-hospital death are given in Table 2. Elevated CB was related to an increase in in-hospital deaths, and the unadjusted odds ratio (OR) was 5.39. Variables with $p < 0.01$ in the univariate analysis were included in multivariate logistic regression. Elevated CB remained significantly associated with in-hospital death, even after adjusting for potential risk factors (adjusted OR = 2.62, 95%CI 1.40–4.91, $p = 0.003$; Table 2).

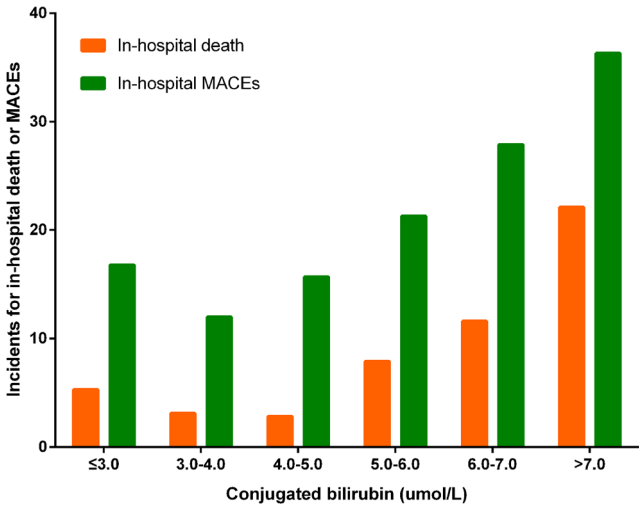

Fig. 3 The relationship between conjugated bilirubin and in-hospital events

CB and long-term mortality

All in-hospital patients who survived were routinely followed-up after discharge. In all, 87.2% (808/927) patients completed the median 29-month follow-up, during which time 61 patients died. Univariate survival analysis for long-term mortality indicated that the p values of age, rheumatic heart disease, prosthetic valves, anemia, eGFR < 90 mL/min/1.73 m^2, hypoalbuminemia, bilirubin levels, LVEF, and surgical treatment were < 0.05 (Table 3). These statistically significant variables were included in the multivariate Cox proportional hazard model to reveal that both CB (increment, 1 μmol/L) and TB (increment, 1 μmol/L) were independently associated with higher long-term mortality (Table 4). The Kaplan–Meier curves for long-term death among groups indicated that elevated CB or TB were associated with higher cumulative rate of long-term mortality after discharge (log-rank = 21.47, $p < 0.001$ or 13.02, $p < 0.001$; Fig. 4).

Discussion

To our best knowledge, this is the first study to investigate the prognostic value of CB in IE. Our results showed the following: (1) There was a possible J-shaped relationship between CB and the rate of in-hospital adverse events in IE. (2) CB was a stronger predictor of in-hospital mortality than TB. (3) Elevated CB was an independent predictor of in-hospital and long-term mortality. (4) CB could be a novel risk evaluation strategy among patients with IE.

In a rat model of endotoxemia, bilirubin treatment improved survival and ameliorated liver injury in response to lipopolysaccharide infusion by suppressing inducible nitric oxide synthase expression and nitric oxide production [13]. Overhaus et al. [14] found that the administration of bilirubin could attenuate sepsis-induced inflammation in rats by decreasing mRNA expressions for inflammatory mediators. Additionally, bilirubin could inhibit vascular cell adhesion molecule-1-dependent leukocyte migration [15]. These anti-oxidant and anti-inflammatory features of bilirubin were a likely explanation for our findings, in that CB might decrease the risk of adverse prognosis to some extent in patients with IE and that excessively low CB level portended poor outcomes.

Table 2 Univariate and multivariate logistic regression analyses for in-hospital mortality

Clinical variables	Univariate analysis		Multivariate analysis		
	OR	*P*	OR	95% CI	*P*
Age	1.05	< 0.001	1.02	1.00, 1.04	0.034
Female sex	0.88	0.621			
Smoker	1.12	0.713			
Hypertension	1.67	0.083			
Previous diabetes	3.13	< 0.001	1.77	0.76, 4.13	0.190
NYHA class III/IV	4.05	< 0.001	3.51	1.90, 6.48	< 0.001
Previous IE	0.73	0.555			
Rheumatic heart disease	1.67	0.040			
Congenital heart disease	0.62	0.093			
Prosthetic valves	4.48	< 0.001	1.80	0.80, 4.07	0.158
lgCRP	3.77	< 0.001	1.95	1.05, 3.63	0.036
Anemia	1.85	0.018			
eGFR < 90 mL/min/1.73 m^2	3.83	< 0.001	1.80	0.94, 3.44	0.074
lgALT	2.85	< 0.001	1.57	0.78, 3.17	0.204
Hypoalbuminemia	4.87	< 0.001	1.17	0.42, 3.28	0.762
TB	1.04	< 0.001			
Elevated CB	5.39	< 0.001	2.62	1.40, 4.91	0.003
LVEF	0.97	0.033			
Aortic valve affected	1.81	0.010			
Mitral valve affected	0.67	0.081			
Infected with Streptococcus	0.94	0.839			
Infected with Staphylococcus	1.55	0.200			
Surgical treatment	0.13	< 0.001	0.16	0.08, 0.30	< 0.001

OR odds ratio, *CI* confidence interval, *NYHA* New York Heart Association, *IE* infective endocarditis, *CRP* C reactive protein, *eGFR* estimated glomerular filtration rate, *ALT* alanine transaminase, *CB* conjugated bilirubin, *TB* total bilirubin, *LVEF* left ventricular ejection fraction

On the other hand, high levels of CB can likely be a risk marker in IE. First, IE is frequently complicated by heart failure. Impaired perfusion and systemic congestion by hemodynamic changes would lead to acute cardiogenic liver injury (ACLI) [16]. Hepatocyte necrosis and cytolysis are common histological changes in this condition [17]. Further, bile-duct compression resulting from direct compression and congestion might block bile flow in turn increasing serum bilirubin level [18]. Patients with heart failure often have elevated bilirubin levels, which have been reported as a risk factor for poor prognosis [19, 20]. Besides ACLI, increased serum bilirubin level has been found in patients with sepsis, likely attributed to hepatic dysfunction, hemolysis, and cholestasis [21]. Hyperbilirubinemia—an important component of Multiple Organ Dysfunction Score (MODS) and Sequential Organ Failure Assessment (SOFA)—is a signal of hepatic insufficiency. MODS and SOFA are both reliable predictors of adverse outcomes in critically ill patients [22, 23]. We speculated that higher bilirubin levels might indicate the severity of IE-induced organ failure. Second, IE is a systemic inflammatory disease that triggers the secretion of proinflammatory and pro-oxidant cytokines, thereby resulting in tissue injury [24]. Elevated bilirubin is an adaptive physiological response [25]. An obvious increase in serum bilirubin might reflect higher levels of inflammation and oxidative stress. Third, in an animal model research by Lang et al., bilirubin stimulated Ca^{2+} entry and ceramide formation, which triggered suicidal erythrocyte death. This enhanced eryptosis fosters the development of anemia despite increased reticulocyte numbers [26]. The prognosis of IE worsens when complicated by anemia.

Our study also showed that CB was a more powerful predictor of in-hospital mortality than TB. First, hepatic bilirubin metabolism mainly includes hepatocyte uptake, microsomal conjugation, and biliary secretion; the last step is the rate-limiting step in this metabolic pathway [27]. Second, atrophy, necrosis, or both are common in the central third of the hepatic lobule during ACLI. TB consists of CB and unconjugated bilirubin (UCB); the latter can be up taken by non-damaged hepatocytes and transformed into CB. However, CB can flow into the blood circulation through necrotic hepatocytes. Furthermore, swollen hepatocytes, damaged portal

Table 3 Univariate Cox proportional hazard analysis for long-term mortality

Clinical variables	HR	95% CI	*P* value
Age	1.05	1.04, 1.07	< 0.001
Female sex	1.19	0.70, 2.12	0.522
Smoker	0.83	0.41, 1.69	0.615
Hypertension	1.15	0.57, 2.33	0.704
Previous diabetes	1.53	0.66, 3.54	0.327
NYHA class III/IV	1.58	0.95, 2.61	0.077
Previous IE	0.44	0.11, 1.78	0.248
Rheumatic heart disease	1.90	1.12, 3.22	0.018
Congenital heart disease	0.72	0.40, 1.31	0.284
Prosthetic valves	2.26	1.03, 4.96	0.043
lgCRP	1.51	0.93, 2.47	0.098
Anemia	1.87	1.06, 3.32	0.031
eGFR < 90 mL/min/1.73 m2	2.75	1.62, 4.65	< 0.001
lgALT	0.41	0.15, 1.07	0.069
Hypoalbuminemia	2.47	1.17, 5.20	0.018
TB (increment 1 μmol/L)	1.03	1.01, 1.04	< 0.001
Elevated TB	2.45	1.48, 4.04	< 0.001
CB (increment 1 μmol/L)	1.07	1.04, 1.10	< 0.001
Elevated CB	3.25	1.91, 5.51	< 0.001
LVEF	0.95	0.93, 0.98	< 0.001
Aortic valve affected	1.47	0.89, 2.43	0.134
Mitral valve affected	0.62	0.37, 1.04	0.072
Infected with Streptococcus	0.55	0.25, 1.20	0.131
Infected with Staphylococcus	0.54	0.17, 1.71	0.294
Surgical treatment	0.19	0.11, 0.32	< 0.001

HR hazard ratio, *CI* confidence interval, *NYHA* New York Heart Association, *IE* infective endocarditis, *CRP* C reactive protein, *eGFR* estimated glomerular filtration rate, *ALT* alanine transaminase, *CB* conjugated bilirubin, *TB* total bilirubin, *LVEF* left ventricular ejection fraction

area, or bile thrombi are known to block biliary secretion [17, 18]. Therefore, although serum CB increases, TB is not markedly elevated because of decreased UCB. Third, patients with mitral valve disease have a reduced capacity to eliminate CB, which is attributed to reduced liver flow [28]. The findings of these studies support our results showing that serum CB elevation precedes TB elevation as a marker of early disease.

Table 4 Adjusted HR and 95% CI for long-term mortality

	Model 1		Model 2		Model 3	
	Adjusted HR (95%CI)	P value	Adjusted HR (95%CI)	P value	Adjusted HR (95%CI)	P value
TB (increment 1 μmol/L)	1.02 (1.01, 1.04)	0.006	1.02 (1.01, 1.04)	0.011	1.02 (1.01, 1.04)	0.006
Elevated TB	2.27 (1.34, 3.85)	0.002	2.19 (1.29, 3.71)	0.004	2.37 (1.39, 4.06)	0.002
CB (increment 1 μmol/L)	1.05 (1.01, 1.09)	0.006	1.05 (1.01, 1.08)	0.007	1.05 (1.01, 1.08)	0.013
Elevated CB	2.52 (1.44, 4.41)	0.001	2.43 (1.39, 4.26)	0.002	2.34 (1.31, 4.18)	0.004

Model 1 adjusted for age, eGFR < 90 mL/min/1.73 m^2, LVEF, and surgery treatment

Model 2 adjusted for model 1 plus rheumatic heart disease and prosthetic valves

Model 3 adjusted for model 1 plus hypoalbuminemia and anemia

HR hazard ratio, CI confidence interval, NYHA New York Heart Association, CRP C reactive protein, eGFR estimated glomerular filtration rate, ALT alanine transaminase, CB conjugated bilirubin, TB total bilirubin, LVEF left ventricular ejection fraction

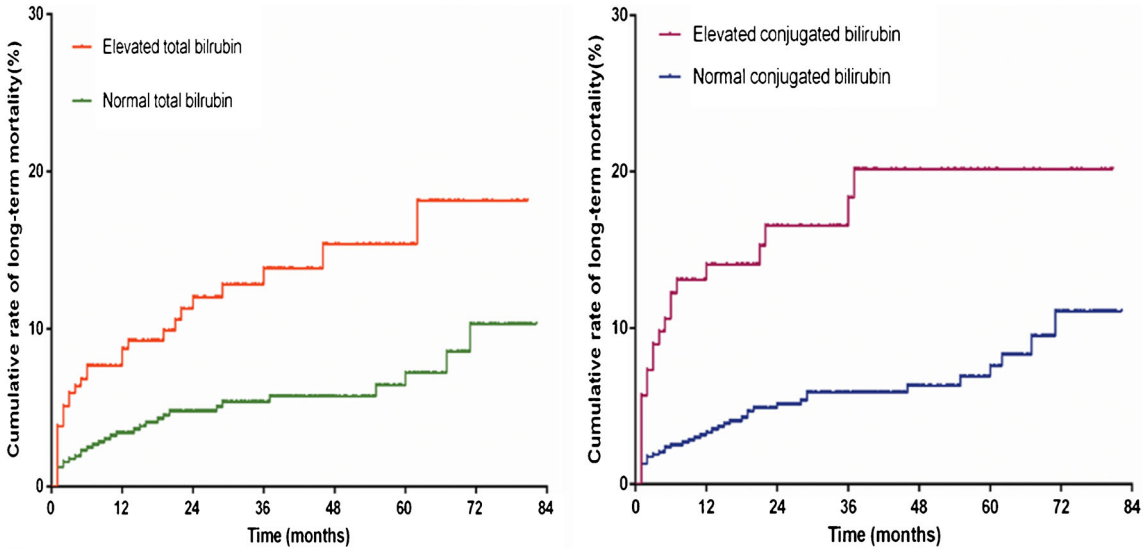

Fig. 4 Kaplan–Meier curve for cumulative rate of long-term mortality

Limitations

Our study has some limitations. First, although we found a possible J-shaped relationship between CB and in-hospital adverse events rate in IE, we were unable to confirm this correlation given the small sample size. Second, this was a retrospective analysis based on prospectively collected data. Although multivariate logistic regression analysis was performed, residual confounding factors possibly affected the mortality risk. Third, CB was not measured dynamically, and the prognostic value of change in CB level for adverse outcomes was unclear.

Conclusions

Elevated CB was independently associated with higher in-hospital and long-term death in patients with IE. There was a possible J-shaped relationship between CB and rate of in-hospital events in IE. CB was a stronger predictor of in-hospital mortality than TB. Thus, assessment of CB levels could be a novel approach for risk evaluation in IE and potentially helpful to identify those at high risk of adverse outcomes.

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Compliance with ethical standards

All patients provided written informed consent before inclusion. This research was approved by the ethics committee of Guangdong Provincial People's Hospital.

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Conflict of interest The authors declare that they have no conflict of interest.

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