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Association of total bilirubin and prognosis in disorders of consciousness

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Accurate prediction of the recovery of Disorders of Consciousness (DoC) is of paramount significance for clinicians and families. Serum total bilirubin (TBIL) formed by activation of heme oxygenase 2, is associated with incidence and prognosis of cardiovascular and cerebrovascular diseases. However, studies that based TBIL and DoC are limited. The study attempted to examine the association between serum TBIL levels and prognosis in patients with DoC. One hundred and sixty-eight patients with DoC in the Second hospital of Shandong University from June 2021 to June 2023 were recruited. The clinical characteristics and venous blood samples were collected within 24 h after admission. The diagnosis of DoC was determined by two skilled investigators employing various behavioral evaluations along the coma recovery scale-revised (CRS-R) and the investigators conducted follow-up assessments of diagnosis at 1, 3, and 6 months after admission. For statistical analysis, we categorized patients with an improvement in clinical diagnosis from study entry as having a "good outcome". In total, 139 individuals enrolled in the study. The median TBIL level was 8.2 μmol/L. Good recovery of DoC at 1, 3, and 6 months occurred in 25 (18.0%), 41 (29.5%), and 56 (40.3%) patients, respectively. After full adjustment, a significant association was found between TBIL levels and the prognosis of DoC at 1, 3, and 6 months. When TBIL levels were analyzed as categorical variables, an increasing trend in the tertiles of TBIL levels demonstrated a significant positive association with the recovery of DoC at 1, 3, and 6 months. Stratified analysis revealed that the association between serum TBIL levels and the recovery of DoC remained consistent across different sub-populations. A high serum TBIL level is associated with an improved likelihood of recovery of DoC. Additional research is required to elucidate the underlying pathophysiological causal association between TBIL levels and DoC.

Keywords Disorders of consciousness, Total bilirubin, Prognosis, Unresponsive wakefulness syndrome, Minimally conscious state

Abbreviations

DoC	Disorders of consciousness
ABI	Acquired brain injury
UWS	Unresponsive wakefulness syndrome
MCS	Minimally conscious state
TBI	Traumatic brain injury
TBIL	Total bilirubin
CRS-R	The coma recovery scale-revised
ORs	Odds ratios
CI	Confidence interval
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ALB	Albumin
BUN	Blood urea nitrogen
Cr	Creatinine
HIE	Hypoxic-ischemic encephalopathy

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GCS	Glasgow coma scale
DM	Diabetes mellitus
CHD	Coronary heart disease
TSH	Thyroid stimulating hormone

Disorders of consciousness (DoC) are altered states of consciousness that affected by acquired brain injuries (ABI), resulting in dysfunction in vigilance, awareness, and behavior[1,2]. DoC can manifest as coma, unresponsive wakefulness syndrome (UWS), or minimally conscious state (MCS)[3]. ABIs mainly include cerebral infarction, cerebral hemorrhage, and traumatic brain injury (TBI)[4,5]. DoC has catastrophic consequences for both families and society. Therefore, accurate prediction of the outcome of DoC is of paramount significance for clinicians and families[6,7].

Many previous studies have applied neurophysiological and neuroimaging techniques to predict prognosis in patients with DoC[8,9]. However, the clinical application and dissemination of these techniques remain difficult due to equipment and technology limitations. In this field, blood serum biomarkers offer several advantages because they can be easily measured in daily routine practice. One such biomarker is serum total bilirubin (TBIL), which is a lipophilic, linear tetrapyrrole molecule formed by the breakdown of heme, largely obtained from hemoglobin in red blood cells[10,11]. Bilirubin was traditionally assumed to have limited functions in biology[12,13]. However, recent studies have confirmed the association between TBIL with certain diseases, such as the incidence and prognosis of stroke[11], the severity and outcomes of intracerebral hemorrhages[14], and all-cause and cardiovascular mortality[15]. The association can be characterized by its anti-oxidative, anti-inflammatory, and anti-adipogenic functions, making it a potential therapeutic target[16].

Currently, there is no documentation available regarding the association between serum TBIL levels and DoC. Consequently, this investigation was conducted to evaluate the role of serum total bilirubin levels as a potential biomarker for the prognosis of patients with DoC caused by ABI.

Materials and methods

Subjects

Subjects who were hospitalized for their first visit at the department of rehabilitation in the Second Hospital of Shandong University from June 2021 to June 2023 were recruited in the study. The diagnosis of DoC was determined by two skilled investigators (LZ and DM G) using multiple behavioral assessments with the the coma recovery Scale-Revised (CRS-R). To obtain the most accurate CRS-R score, evaluations were conducted twice in the first week[17,18]. The clinical diagnosis was determined according to the best CRS-R scores to counterbalance the impacts of variable consciousness levels[19]. Eligibility criteria included: (1) age ≥ 18 years; (2) clinical diagnosis of prolonged DoC secondary to ABI; (3) post-injury time ranging from 28 days to 6 months; Exclusion criteria: (1) the subjects diagnosed with lock-in syndrome and hypersomnia; (2) subjects with preexisting liver diseases, such as liver disease, cholestatic liver illnesses, hemorrhagic sickness, and liver metastatic cancer. The study protocol received approval from the independent ethics committee of the Second Hospital of Shandong University (KYLL2024009). Written informed consent was obtained from the legal guardians of the subjects.

Data collection flow

A variety of demographic information including age, sex, marital status, tobacco use, and drinking habits, was gathered within 24 h of admission. Information about medical history and clinical details, including etiology, time since brain injury, muscle tone of the affected limbs, and clinical complications, was also gathered. Venous blood samples were taken at admission or the following morning and analyzed immediately in the core laboratory of the Second Hospital of Shandong University. These examinations included blood biochemistry tests as well as assessments of liver and renal function indicators. The detection of TBIL was performed using a total nitrogen method test kit, and the normal range of total bilirubin was 0–21 μmol/L.

Outcome definition

Clinically, the same investigators conducted follow-up assessments for diagnosis at 1, 3, and 6 months after admission. Face-to-face assessments were preferred, but when not possible, structured telephone interviews were proved effective and used instead[20,21]. The face-to-face assessment was conducted using CRS-R, while the telephone interviews involved caregivers or relatives completing a questionnaire based on five key items from CRS-R as recommended by Wannez et al. [22]. These items included fixation, visual pursuit, reproducible response to command, automatic motor response, and localization to harmful stimuli. The five key items accurately detected 99% of patients with MCS, rendering them especially suitable for clinicians aiming to conduct swift and precise assessments [22–24]. During the interviews, caregivers or relatives provided information about the subjects' current condition. In cases where the subject had passed away, the relatives were interviewed about the patients' last cognitive and medical state using the same questionnaire.

For statistical analysis, we categorized subjects with an improvement in clinical diagnosis from study entry (from UWS to MCS-, from UWS to MCS+ , from MCS- to MCS+ , or full recovery of consciousness) as having a "good outcome". Subjects with a clinical diagnosis that worsened or remained in UWS/MCS, or who passed away, were categorized as having a "poor outcome"[17].

Statistical analyses

Continuous variables that conform to a normal distribution were displayed as mean ± SD and assessed by a one-way analysis of variance. The median with interquartile range was utilized to display skewed continuous data distributions, while the Kruskal–Wallis H test was employed to assess the outcomes. Categorical or

dichotomous variables were displayed as absolute values (percentages) and analyzed using chi-squared statistics. Concentrations and distributions of TBIL were collected and assessed.

To assess the serum TBIL associated with the prognosis of DoC, we determined odds ratios (ORs) and confidence Intervals (CIs) with a confidence interval of 95% by logistic regression analysis. Participants were divided into three groups based on TBIL tertile amounts: Q1 (≤6.8 μmol/L; n = 45), Q2 (6.8–9.6 μmol/L; n = 47), Q3 (≥9.6 μmol/L; n = 47), with the lowest quartile serving as the reference group. We performed a logistic regression analysis utilizing TBIL as both continuous and categorical variables. Model 1 was adjusted for age as well as sex. Model 2 was additionally modified to account for alcohol use, smoking status, and etiology. Model 3 was further adjusted for alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin (ALB), blood urea nitrogen (BUN), creatinine (Cr). Moreover, logistic regression models were employed to perform interaction and subgroup assessments based on the fully adjusted model.

Considering the sample size was estimated solely based on the available data, no a priori estimate of statistical power was undertaken. The analyses were carried out using the statistical software programs R 4.3.0 and Free Statistics software version 1.7. A descriptive study was undertaken on all individuals. A significance level was set $p < 0.05$ using two-tailed testing.

Results

Study population

A total of 168 subjects suspected of having DoC completed the interview. Among them, 14 subjects who were diagnosed with locked-in syndrome and hypersomnia were excluded from the study. Additionally, 6 subjects with missing TBIL level data and 9 subjects with missing data on 1, 3, and 6month prognosis of DoC were also excluded. Ultimately, the analysis included 139 subjects in this case–control study. Please refer to Fig. 1 for a detailed explanation of the inclusion and exclusion process.

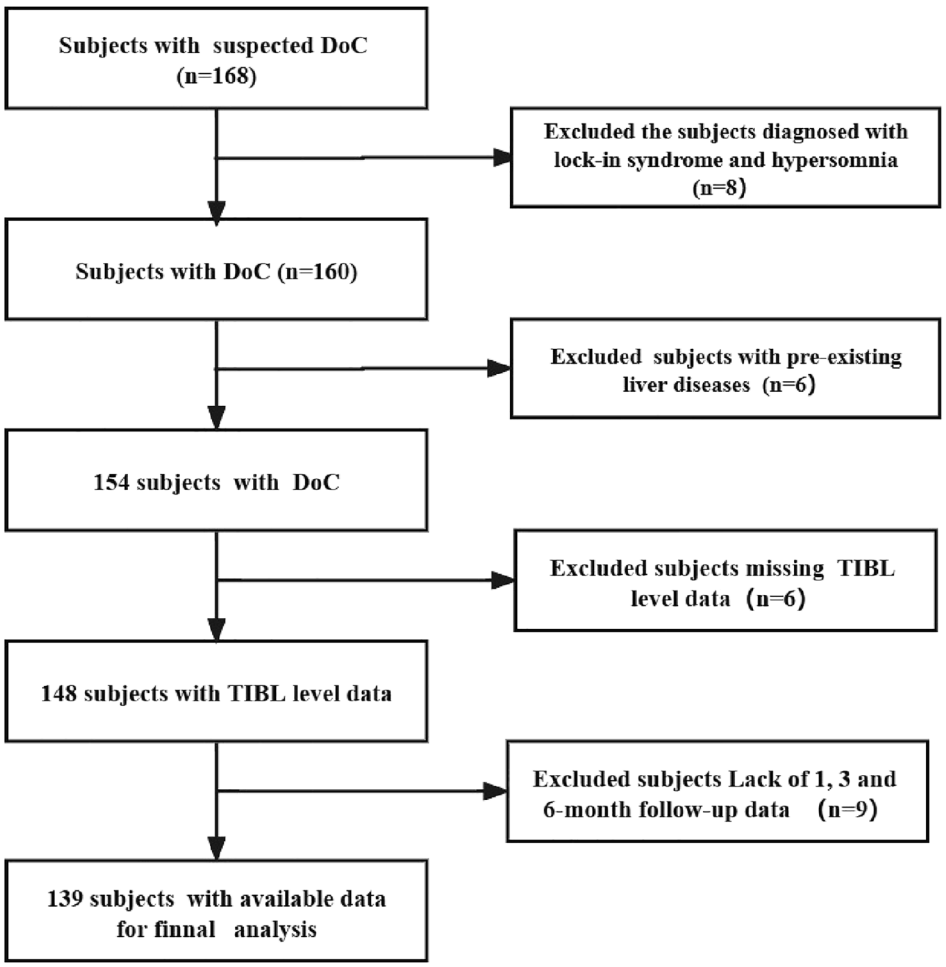

Fig. 1. The flow chart of the study. The flowchart illustrates initially enrolled patients, sequentially excluded patients, and ultimately included patients in the study.

Baseline characteristics

The baseline characteristics of all subjects according to TBIL are illustrated in Table 1. A total of 139 subjects with available data on TBIL and the prognosis of DoC were included in the analysis. The median TBIL level was 8.2 μmol/L. "Good outcome" of DoC at 1, 3, and 6 months occurred in 25 (18.0%), 41 (29.5%), and 56 (40.3%) subjects, respectively.

The mean age of the subjects was 62.1 ± 15.6 years, and 83 (59.7%) were men, most of whom were married or had a partner (111, 79.9%). At baseline, the time since brain injury was 40.1 days. The main etiology of DoC was cerebral hemorrhage (93, 66.9%), followed by ischemic stroke (52, 37.4%), TBI (21, 15.1%), and HIE (8, 5.8%). The mean scores of GCS and CRS-R were 6.3 ± 2.0 and 4.0 ± 2.0, respectively. Subjects with lower TBIL levels were more likely to have hypertonia in the affected limbs. There was no difference in smoking status, drinking habits, hypertension, diabetes mellitus (DM), coronary heart disease (CHD), ALT, AST, ALB, BUN, and Cr among different TBIL tertiles.

Table 1 shows the baseline characteristics of 139 subjects according to TBIL tertiles.

Relationship between TBIL level and 1month prognosis of DoC

Results based on the multivariate logistic regression analysis for the association between serum TBIL levels and the 1-month prognosis of DoC subjects are presented in Table 2 and Fig. 2. The median TBIL level was 10.8 μmol/L in "good outcome" and 7.7 μmol/L in "poor outcome" of DoC at 1 month; When TBIL was examined as a continuous variable, a significant independent positive association was found between TBIL and the 1-month "good outcome" of DoC in the unadjusted model (OR 1.13, 95% CI 1.03–1.24, $p = 0.014$). After adjusting for sex and age in Model 1, a significant association between TBIL levels and the 1-month prognosis of DoC was observed (OR 1.14, 95% CI 1.03–1.27, $p = 0.013$). Similar results were observed in Model 2, where adjustments were made for alcohol consumption, smoking, and etiology, a significant association between TBIL and the 1-month prognosis of DoC was found (OR 1.16, 95% CI 1.03–1.29, $p = 0.012$). Model 3 further adjusted for ALT, AST, ALB, BUN, and Cr. In the fully adjusted model, the association between TBIL and the 1-month "good outcome" of DoC was not found to be significant (OR 1.13, 95% CI 1–1.27, $p = 0.05$).

When TBIL levels were analyzed using tertiles, a significant positive association between TBIL and the 1-month "good outcome" of DoC was observed after adjusting for potential confounders. After full adjustment in Model 3, compared to individuals with lower TBIL levels in Q1 (≤ 6.8 μmol/L), the adjusted OR values for

Characteristics	Total	TBIL, μmol/L			*p*-value
		Q1 (≤ 6.8)	Q2(6.9–9.6)	Q3 (≥ 9.6)	
Participants, No	139	45	47	47	
TBIL (μmol/L), Median (IQR)	8.2 (6.4, 11.2)	5.4 (4.7, 6.4)	8.2 (7.5, 9.0)	13.3 (11.2, 15.1)	< 0.001
Male, n (%)	83 (59.7)	24 (53.3)	30 (63.8)	29 (61.7)	0.557
Age, (SD)	62.1 (15.6)	59.6 (15.4)	65.3 (15.3)	61.5 (16.1)	0.205
Married or with partner, n (%)	111 (79.9)	37 (82.2)	40 (85.1)	34 (72.3)	0.378
Time since brain injury (day), (SD)	40.1(31.0)	47.6 (31.3)	37.3 (28.8)	36.9(32.4)	0.307
Etiology					
Ischemic stroke, n (%)	52 (37.4)	13 (28.9)	17 (36.2)	22 (46.8)	0.202
Cerebral hemorrhage, n (%)	93 (66.9)	33 (73.3)	30 (63.8)	30 (63.8)	0.538
TBI, n (%)	21 (15.1)	7 (15.6)	8 (17)	6 (12.8)	0.843
HIE, n (%)	8 (5.8)	3 (6.7)	5 (10.6)	0 (0)	0.065
GCS, (SD)	6.3 (2.0)	6.5 (1.9)	6.3 (1.9)	6.0 (2.1)	0.441
CRS-R (SD)	4.0 (2.0)	4.2 (1.9)	4.0 (1.9)	3.8 (2.2)	0.53
Hypertonia on the affected limbs, n (%)	61 (43.9)	25 (55.6)	24 (51.1)	12 (25.5)	0.007
Smoking status, n (%)	32 (23.0)	11 (24.4)	12 (25.5)	9 (19.1)	0.735
Drinking using, n (%)	35 (25.2)	8 (17.8)	15 (31.9)	12 (25.5)	0.295
Hypertension, n (%)	84 (60.4)	27 (60)	25 (53.2)	32 (68.1)	0.335
DM, n (%)	38 (27.3)	9 (20)	15 (31.9)	14 (29.8)	0.395
CHD, n (%)	12 (8.6)	4 (8.9)	2 (4.3)	6 (12.8)	0.337
ALT, (U/L), Median (IQR)	22.0 (12.8, 39.0)	19.0 (13.0, 32.0)	17.5 (12.0, 30.8)	35.0 (13.5, 72.0)	0.025
AST, (U/L), Median (IQR)	25.0 (16.0, 37.0)	21.0 (15.0, 34.0)	24.0 (18.0, 32.2)	32.0 (18.5, 52.0)	0.035
ALB, (g/L), Median (IQR)	36.7 (34.0, 40.0)	36.7 (34.8, 39.7)	37.2 (34.3, 40.4)	35.8 (32.9, 40.6)	0.519
BUN, (mmol/L), Median (IQR)	5.2 (3.6, 7.4)	4.6 (3.6, 6.6)	4.9 (3.4, 7.0)	6.5 (4.0, 9.5)	0.077
Cr, (umol/L), Median (IQR)	48.5 (38.0, 59.0)	47.0 (39.0, 66.0)	48.0 (34.5, 58.5)	50.0 (38.2, 55.8)	0.6
1 month "Good outcome" of DoC, n (%)	25 (18.0)	2 (4.4)	9 (19.1)	14 (29.8)	0.006
3 month "Good outcome" of DoC, n (%)	41 (29.5)	7 (15.6)	14 (29.8)	20 (42.6)	0.018
6 month "Good outcome" of DoC, n (%)	56 (40.3)	10 (22.2)	19 (40.4)	27 (57.4)	0.003

Table 1. Characteristics of the study population based on TBIL.

Prognosis in DOC	Crude		Model 1		Model 2		Model 3	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
1-Month								
Continuous	1.13 (1.03–1.24)	0.014	1.14 (1.03–1.27)	0.013	1.16 (1.03–1.29)	0.012	1.13 (1–1.27)	0.05
Tertile								
Q1 (≤6.8 μmol/L)	1(Ref)		1(Ref)		1(Ref)		1(Ref)	
Q2 (6.9–9.6 μmol/L)	5.09 (1.04–25.04)	0.045	6.52 (1.29–33.06)	0.023	8.29 (1.53–44.99)	0.014	11.06 (1.96–62.57)	0.007
Q3 (≥9.6 μmol/L)	9.12 (1.94–42.95)	0.005	10.64 (2.21–51.21)	0.003	13.82 (2.65–72)	0.002	10.76 (1.96–59.03)	0.006
P for trend	2.59 (1.39–4.81)	0.003	2.69 (1.45–5.01)	0.002	3.04 (1.56–5.91)	0.001	2.65 (1.33–5.29)	0.006
3-Month								
Continuous	1.16 (1.06–1.27)	0.002	1.18 (1.07–1.31)	0.001	1.19 (1.07–1.33)	0.001	1.16 (1.04–1.3)	0.007
Tertile								
Q1 (≤6.8 μmol/L)	1(Ref)		1(Ref)		1(Ref)		1(Ref)	
Q2 (6.9–9.6 μmol/L)	2.3 (0.83–6.39)	0.109	2.76 (0.96–7.9)	0.058	3.32 (1.09–10.09)	0.035	4.06 (1.27–13.04)	0.018
Q3 (≥9.6 μmol/L)	4.02 (1.49–10.84)	0.006	4.55 (1.65–12.58)	0.003	5.27 (1.77–15.68)	0.003	4.06 (1.29–12.72)	0.016
P for trend	1.97 (1.22–3.19)	0.006	2.07 (1.27–3.36)	0.003	2.2 (1.31–3.7)	0.003	1.92 (1.12–3.29)	0.018
6-Month								
Continuous	1.19 (1.08–1.31)	0.001	1.2 (1.09–1.33)	< 0.001	1.21 (1.09–1.34)	< 0.001	1.18 (1.05–1.31)	0.004
Tertile								
Q1 (≤6.8 μmol/L)	1(Ref)		1(Ref)		1(Ref)		1(Ref)	
Q2 (6.9–9.6 μmol/L)	2.37 (0.95–5.92)	0.063	2.65 (1.04–6.77)	0.041	3.12 (1.16–8.42)	0.025	3.78 (1.33–10.72)	0.012
Q3 (≥9.6 μmol/L)	4.72 (1.9–11.74)	0.001	5.07 (2.01–12.81)	0.001	5.86 (2.16–15.89)	0.001	4.82 (1.69–13.76)	0.003
P for trend	2.16 (1.38–3.39)	0.001	2.22 (1.41–3.5)	0.001	2.38 (1.46–3.88)	0.001	2.16 (1.29–3.61)	0.003

Table 2. Associations between TBIL and Prognosis in DOC using multiple regression models.

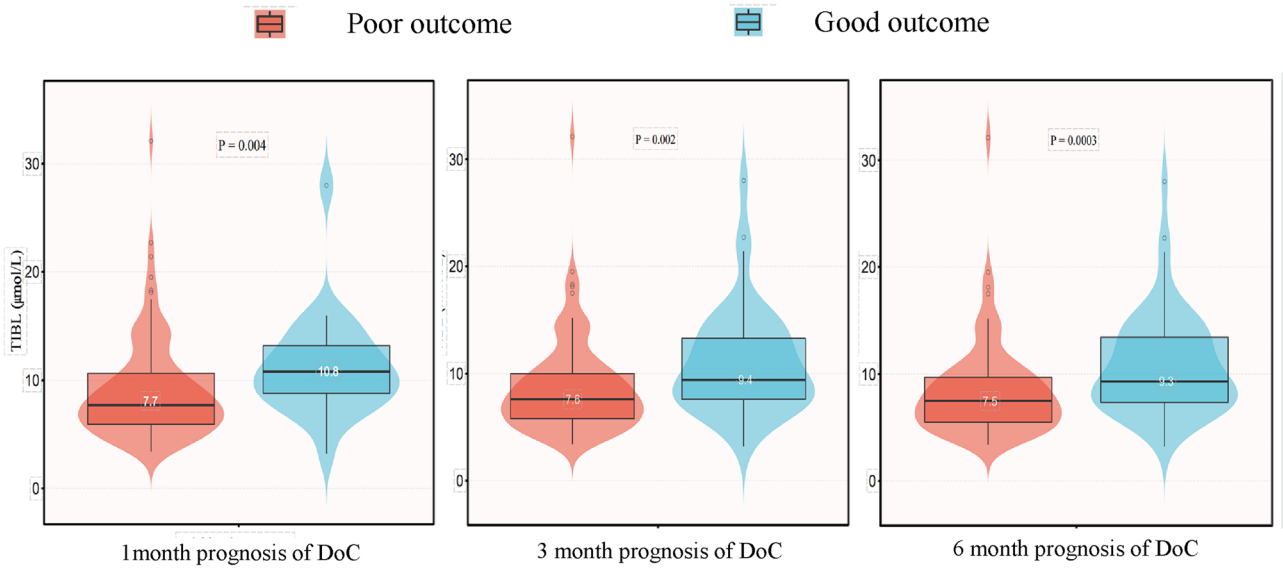

Fig. 2. The median TBIL level of different prognosis of DoC at 1, 3, and 6 month. Prognosis of DoC including "good outcome" and "poor outcome". "Good outcome" are indicated in red, while "Poor outcome" are indicated in blue. The median TBIL level was shown in each respective box plot.

TBIL and 1-month "good outcome" of DoC in Q2 (6.9–9.6 μmol/L) and Q3 (≥9.6 μmol/L) were 11.06 (95% CI 1.96–62.57, $p = 0.007$) and 10.76 (95% CI 1.96–59.03, $p = 0.006$), respectively (Table 2). As the tertiles of TBIL levels increased, the probability of a good outcome at 1 month increased.

Associations between TBIL levels and the prognosis of DoC at 3 and 6 months

The relationship between TBIL levels and the prognosis of patients with DoC at 3 and 6 months was presented in Table 2 and Fig. 2. The median TBIL levels were 9.4 and 9.3 μmol/L in "good outcome" and 7.6 and 7.5 μmol/L in "poor outcome" in DoC at 3 and 6 month, respectively; When TBIL was analyzed as a continuous variable, a

significant independent positive association was found between TBIL and the 3-month prognosis of DoC in the crude model (OR 1.16, 95% CI 1.06–1.27, $p = 0.002$). After full adjustment, the results remained consistent. The adjusted OR values for TBIL and 3-month "good outcome" of DoC was 1.16 (95% CI 1.04–1.3, $p = 0.007$). When TBIL was examined as categorical variables, after full adjustment in Model 3, compared to individuals with lower TBIL levels in Q1, the adjusted OR values for TBIL and the 3-month "good outcome" of DoC were 4.06 (95% CI 1.27–13.04, $p = 0.018$) in Q2 and 4.06 (95% CI 1.29–12.72, $p = 0.016$) in Q3 (Table 2).

Similarly, there was a significant independent positive association between TBIL and the 6-month "good outcome" of DoC in the fully adjusted model (OR 1.18, 95% CI 1.05–1.31, $p = 0.004$). Compared to individuals with lower TBIL levels in Q1, the adjusted OR values for TBIL and the 6-month "good outcome" of DoC were 3.78 (95% CI 1.33–10.72, $p = 0.012$) in Q2 and 4.82 (95% CI 1.69–13.76, $p = 0.003$) in Q3 (Table 2). As TBIL levels increased, the likelihood of a good recover at 3 and 6 months also increased. Also, associations between other variables and prognosis in DoC were presented in Tables S1 and S2.

Table 2 shows the relationship between TBIL levels and the prognosis of patients with DoC at 1, 3 and 6 months. TBIL was analyzed as a continuous variable or categorical variables. Model 1 was adjusted for age as well as sex. Model 2 was additionally modified to account for alcohol use, smoking status, and etiology. Model 3 was further adjusted for ALT, AST, ALB, BUN, Cr.

Stratified analyses

Stratified analyses were performed to examine the robustness of the association between serum TBIL level and 1, 3, and 6 month prognosis of DoC, TBIL was examined as a continuous variable. In fully adjusted Model 3, the findings of the stratified analysis suggested that the association of serum TBIL and prognosis of DoC at1, 3, and 6 month was consistent across different sub-populations (all $p > 0.05$, as shown in Fig. 3).

Discussion

The study enrolled 139 subjects and evaluated the association between serum TBIL levels and the prognosis of subjects with DoC at 1, 3, and 6 months after admission. We defined a "good outcome" as an improvement in the clinical diagnosis compared to the time of study entry. To the best of our knowledge, this is the first study to explore the association between serum TBIL levels and the prognosis of DoC. After adjusting for potential confounding factors, high serum TBIL levels were independently associated with an improved likelihood of recovery for DoC subjects during the 1-, 3-, and 6-month follow-up after admission; meanwhile, as TBIL levels increased, the likelihood of a "good outcome" also increased. Furthermore, stratified analyses revealed that the association between serum TBIL and the prognosis of DoC remained consistent and reliable.

Blood biomarkers are emerging tools used to increase diagnostic and prediction accuracy for individuals with DoC[25]. Chiara et al. found lower initial thyroid stimulating hormone (TSH) levels and higher TSH increases after 6 months were linked with improved functional and cognitive results in patients with prolonged DoC, while the underlying processes remain to be explained[26]. Bernhard et al. found early blood levels of heart-fatty

Subgroup	1-m prognosis of DoC OR(95%CI)	3-m prognosis of DoC OR(95%CI)	6-m prognosis of DoC OR(95%CI)	*P* for interaction (1,3,6-m prognosisof DoC respectively)
Sex				
Female	1.24 (1.03~1.5)	1.13 (0.91~1.4)	1.13 (0.87~1.47)	0.23; 0.96; 0.91
Male	1.09 (0.95~1.25)	1.16 (1.01~1.33)	1.17 (1.01~1.36)	
Age				
age≤60	1.24 (1.06~1.46)	1.72 (1~2.94)	1.45 (1.03~2.02)	0.09; 0.10; 0.78
age>60	1.01 (0.86~1.18)	1.07 (0.91~1.24)	1.14(0.99~1.33)	
Muscle tone				
Normal or hypotonia	1.12 (1~1.25)	1.16 (0.99~1.35)	1.19 (1.01~1.4)	0.14; 0.57; 0.91
Hypertonia	1.15 (0.95~1.39)	1.46 (0.96~2.23)	1.22 (0.91~1.65)	
Ischemic stroke				
No	1.31 (1.08~1.59)	1.31 (1.08~1.59)	1.27 (1.07~1.5)	0.63; 0.20; 0.70
Yes	1.06 (0.86~1.31)	1.06 (0.86~1.31)	1.12 (0.9~1.38)	
Cerebral hemorrhage				
No	1.08 (0.87~1.33)	1.27 (1.07~1.5)	2.1 (1.06~4.16)	0.41; 0.70; 0.06
Yes	1.14 (1.02~1.28)	1.12 (0.9~1.38)	1.12 (0.99~1.27)	

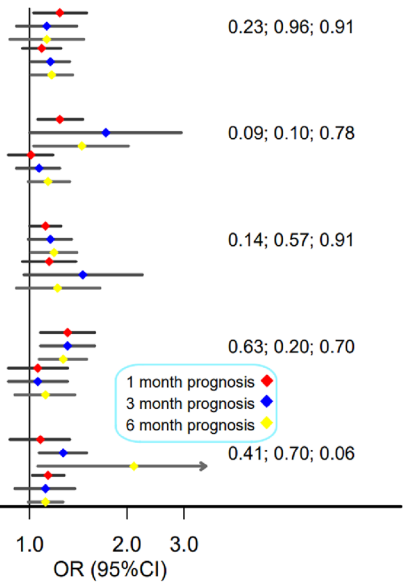

Fig. 3. Forest plot of serum TBIL on prognosis of DoC. The stratified analysis was adjusted in Model 3, and different sub-populations were conducted to examine the robustness of the association between serum TBIL level and 1,3, and 6month prognosis of DoC. The effect of TBIL on prognosis of DoC in different sub-populations was displayed in the forest plot.

acidic binding protein following TBI have predictive value for survival and impairment[27]. To date, we found little evidence of associations between serum TBIL levels and the prognosis of DoC. However, TBIL as prognosis biomarker have been discussed in certain diseases.

The association between TBIL and diseases related to DoC has been extensively studied, however, the conclusions are not entirely consistent: (1) elevated bilirubin levels were linked to an increased stroke risk and higher mortality from TBIL[28,29]; (2) there was no significant relationship between serum bilirubin levels and the risk or clinical outcomes of ischemic stroke[30–32]; (3) elevated bilirubin levels were associated with a reduced risk of stroke and improved stroke outcomes[33–38]. TBIL is an important biochemical marker for predicting stroke risk and prognosis. In line with our research, as the tertiles of TBIL levels increased, the probability of a "good outcome" also increased at the 1-month, 3-month, and 6-month follow-up after admission.

Inasmuch, the primary etiology of DoC was toxic-metabolic insults and structural lesions of brain (4). Emerging evidence suggests that the inflammatory signal and oxidative stress play pivotal role in ABIs[39,40] and the accumulation of harmful byproducts of metabolism lipid species that might otherwise harm the integrity of mitochondria and advocate cell death[41]. The relationship between bilirubin and oxidative stress[16,42], inflammatory mediator[43] and lipid metabolism[16,44], in brain injuries was widely studied. Our result documented that high serum TBIL level was independently associated with an improved likelihood of recovery for DoC. The protective nature of bilirubin can be addressed due to its anti-oxidative, anti-inflammatory, and anti-adipogenic activities, making it an intriguing prognostic biomarker.

There are some limitations need to be considered. Firstly, this study is a single-center study conducted at a regional hospital over a 2-years period, resulting in a relatively small sample size, especially, the proportion of patients with DoC caused by HIE and TBI was relatively small, which limits the effectiveness of stratified analysis. Secondly, the conclusions drawn are based solely on data from the hospital in China, and further investigation is needed to assess their applicability more broadly. Thirdly, data on TBIL was gathered only once at the beginning, and it seems uncertain whether deviations in TBIL levels as time passed might influence the prognosis of DoC. Fourthly, due to limitations in data structure and research design, this study did not conduct multiple comparison correction analysis, which affected the accurate assessment of statistical significance. In the future, more rigorous statistical analysis methods will be adopted to ensure the reliability and validity of research results.

Conclusion

A high serum TBIL level is associated with an increased likelihood of recovery for subjects with DoC. Generally, serum TBIL may serve as an intriguing indicator for the regular evaluation of the prognosis of subjects with DoC. More studies will be required to establish the underlying pathophysiological causal association between serum TBIL level and DoC.

Data availability

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

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Author contributions

BJ C and LG H contributed to the study concept and design. LG H, LZ, and DM G contributed to the data acquisition. MS and WH A performed the statistical analysis. LG H and BJ C drafted the manuscript. QS S and FS Z reviewed and revised the manuscript. All authors contributed to the analysis and interpretation of the data and critically revised the manuscript. All authors have approved the final version of the manuscript. The authors unanimously agreed to publish the manuscript. What this study did was not covered by previous studies. This manuscript will not be published elsewhere.

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Competing interests

The authors declare no competing interests.

Ethical approval and consent to participate

The study protocol was approved by the Ethics Committee of The Second Hospital of Shandong University. This study was performed in line with the principles of the Declaration of Helsinki.

Additional information

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