


# Decreased Serum Total Bilirubin Level Predicts Early Neurological Deterioration in Patients with Acute Ischemic Stroke

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**Objective:** This study aimed to investigate the relationship between serum total bilirubin (TBil) level and early neurological deterioration (END) in patients with acute ischemic stroke of large artery atherosclerosis.

**Patients and Methods:** In this retrospective study, a total of 291 patients with acute ischemic stroke were enrolled. The demographic and laboratory data were collected. Stroke severity had been assessed using the National Institutes of Health Stroke Scale (NIHSS). Multivariable logistic regression was used to examine the independent association between TBil and END.

**Results:** Approximately 63 (21.6%) of the patients were diagnosed with END within the first seven days. The proportion of hypertension, diabetes mellitus (DM) and previous stroke/transient ischemic attack (TIA) was significantly greater in the lowest quartile ( $<9.8 \mu\text{mol/l}$ ) of TBil. The proportion of patients with an elevated TBil levels was significantly lower in the END group than in the non-END group. After controlling for covariates, the first quartiles ( $<9.8 \mu\text{mol/l}$ ) of TBil were still associated with END. In addition, an increased level of CRP and age were also associated with an increased risk of END.

**Conclusion:** The TBil levels in patients with acute cerebral infarction may be a useful biomarker for the prediction of END.

**Keywords:** acute ischemic stroke, early neurological deterioration, total bilirubin, predictor

## Introduction

Early neurological deterioration (END) has been defined as any new neurological symptoms/signs or any neurological worsening. END occurs in 13–38% of acute ischemic stroke cases and has been associated with reduced neurological function, increased fatality, and worse functional outcomes.<sup>1,2</sup> Many studies have reported some biological or clinical factors that can predict END.<sup>3</sup> However, many of these factors cannot explain the mechanisms of END.

Some studies have shown that bilirubin is a strong physiological antioxidant, and that low levels of bilirubin are closely related to atherosclerosis.<sup>4,5</sup> The level of serum bilirubin in patients with acute ischemic cerebral infarction is lower than that in normal subjects and is related to the severity of stroke.<sup>6–8</sup>

However, the relationship between bilirubin and END is still unclear. Therefore, this study investigated the relationship between serum bilirubin level and END in patients with acute ischemic stroke.

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## Patients and Methods

### Subjects

This study was a single-center retrospective study. The patients were aged  $\geq 18$  years and had developed acute ischemic stroke due to large artery atherosclerosis within 24 h of symptom onset presented to the stroke unit from January 2018 to June 2019. All patients underwent brain computed tomography (CT) scans to exclude cerebral or subarachnoid hemorrhage. Acute ischemic stroke was confirmed by brain magnetic resonance imaging (MRI) or brain CT within 24 h of admission. The main exclusion criteria were as follows: 1) probable stroke mimics, 2) some diseases might affected bilirubin excretion, such as infection, or inflammatory diseases, hematological diseases, hepatic and renal insufficiency. All patients received the best medical treatment. All patients or their legally authorized representatives provided written informed consent. This study was approved by the Ethical Committee of Suzhou Ninth People's Hospital (No. WJYY-201747).

### Data Collection

The demographic data of the patients in the study such as age, sex, and vascular risk factors including hypertension, diabetes mellitus (DM), dyslipidemia, previous stroke or transient ischemic attack (TIA), coronary artery disease and atrial fibrillation were collected. All patients' venous blood samples were collected and analyzed following overnight fasting for at least 12 h. Serum total bilirubin (TBil) and other biochemical dates were analyzed by a solid-phase chemiluminescent immunometric assay on Immulite 2000 (Siemens Healthineers, Erlangen, Germany) using the reagents provided by the manufacturer. The patients were divided into four groups based on the quartiles of serum TBil level.

### Neurological Severity and Early Neurological Deterioration

We assessed stroke severity using the National Institutes of Health Stroke Scale (NIHSS). END was defined as follows: 1) an increment in the NIHSS score (consciousness and motor score are excluded)  $\geq 2$  points; 2) an increment in the NIHSS consciousness score  $\geq 1$  point; 3) an increment in the NIHSS score on motor of 1 or more points; or 4) any new neurological deficit during the first 7 days after symptom onset.<sup>9</sup> We classified the patients into two groups according to the presence or absence of END.

### Statistical Analysis

SPSS 19.0 (SPSS Inc., Chicago, IL, USA) was used for data analysis. Study participants were divided into four groups, based on quartiles of TBil levels. Continuous variables were expressed as mean  $\pm$  standard deviation (SD) or median (interquartile range [IQR]) and were compared using the analysis of variance, Kruskal–Wallis test, or Wilcoxon rank-sum test, where appropriate. Categorical variables were expressed as frequency (%) and compared using the chi-square test. Covariates with statistically significant differences ( $P < 0.05$ ) were investigated using univariate analysis, and those with clinically important factors, even if they were not statistically significant, were adjusted for multivariate analysis. We analyzed the relationship between the level of TBil and END using the restricted cubic spline function with 3 knots at 10th, 50th and 90th percentiles of TBil.  $P < 0.05$  was considered statistically significant.<sup>10</sup>

## Results

### Baseline Characteristics of the Study Subjects by Quartiles of Total Bilirubin

A total of 291 patients with acute ischemic stroke were enrolled in this study. Their mean age was  $69.4 \pm 12.6$  years, 160 (55%) were male, and 63 (21.6%) were diagnosed with END within the first 7 days (Table 1). The median TBil level was  $12.3 \mu\text{mol/L}$ , and the quartile levels were as follows: quartile 1 ( $< 9.8 \mu\text{mol/L}$ ), quartile 2 ( $9.8 \mu\text{mol/L} - 12.3 \mu\text{mol/L}$ ), quartile 3 ( $12.4 \mu\text{mol/L} - 16.4 \mu\text{mol/L}$ ), and quartile 4 ( $> 16.4 \mu\text{mol/L}$ ). The proportion of hypertension, DM, and previous stroke/TIA was significant greater in the lowest quartile of TBil ( $P = 0.034$ ,  $0.039$ , and  $0.033$  respectively; Table 1). Compared with the quartile 4, the level of C-reaction protein (CRP), total cholesterol (TC), and low density lipoprotein (LDL) were significant higher in patients with the quartile 1 ( $P = 0.036$ ,  $0.026$ , and  $0.002$  respectively; Table 1). There was no significant difference in age, sex, smoking, history of cardiovascular diseases (CVD), initial NIHSS scores, levels of triglyceride (TG), or high density lipoprotein (HDL) among the four groups ( $P > 0.05$ ). Approximately 63 (21.6%) of the patients were diagnosed with END within the first 7 days after stroke onset. The proportion of END was significant higher in the lowest quartile of TBil ( $P = 0.005$ , Table 1).

**Table 1** Baseline Characteristics of the Study Subjects by Quartiles of Total Bilirubin

|                              | Total<br>(n=291) | Quartile 1 <9.8<br>n=74 | Quartile 2 9.8–12.3<br>n=72 | Quartile 3 12.4–16.4<br>n=73 | Quartile 4 >16.4<br>n=72 | <i>P</i> <sup>a</sup><br>value | <i>P</i> <sup>b</sup><br>value |
|------------------------------|------------------|-------------------------|-----------------------------|------------------------------|--------------------------|--------------------------------|--------------------------------|
| Age, (mean±SD), years        | 69.4±12.6        | 67.7±12.4               | 68.9±13.3                   | 69.8±11.8                    | 71.4±12.7                | 0.43                           |                                |
| Male, n (%)                  | 160 (55.0)       | 38 (51.4)               | 40 (55.6)                   | 41 (56.2)                    | 41 (56.9)                | 0.91                           |                                |
| Hypertension, n (%)          | 195 (67.0)       | 58 (78.4)               | 51 (70.8)                   | 43 (58.9)                    | 43 (59.7)                | 0.034                          | 0.024                          |
| DM, n (%)                    | 66 (22.7)        | 23 (31.1)               | 19 (26.4)                   | 15 (20.5)                    | 9 (12.5)                 | 0.039                          | 0.012                          |
| Smoking, n (%)               | 55 (18.9)        | 13 (17.6)               | 16 (22.2)                   | 15 (20.5)                    | 11 (15.3)                | 0.72                           |                                |
| Previous stroke/TIA, n (%)   | 51 (17.5)        | 19 (25.7)               | 16 (22.2)                   | 8 (11.0)                     | 8 (11.1)                 | 0.033                          | 0.40                           |
| CHD, n (%)                   | 14 (4.8)         | 5 (6.8)                 | 4 (5.6)                     | 2 (2.7)                      | 3 (4.2)                  | 0.74                           |                                |
| Initial NIHSS (median [IQR]) | 3 [2–5]          | 4 [1–8]                 | 3 [1–6]                     | 2 [2–5]                      | 2 [1–5]                  | 0.23                           |                                |
| END, n (%)                   | 63 (21.6)        | 23 (31.1)               | 18 (25.0)                   | 12 (16.4)                    | 10 (13.9)                | 0.005                          | 0.022                          |
| CRP (ug/l)                   | 7.7±10.3         | 12.5±13.3               | 8.4±14.1                    | 6.1±11.4                     | 3.5±10.3                 | 0.036                          | 0.009                          |
| TC (mmol/l)                  | 4.93±3.11        | 6.14±4.33               | 5.21±5.27                   | 4.31±4.71                    | 3.87±5.21                | 0.026                          | 0.011                          |
| TG (mmol/l)                  | 1.53±1.71        | 1.98±2.53               | 1.63±2.12                   | 1.31±2.26                    | 1.17±2.35                | 0.11                           |                                |
| HDL (mmol/l)                 | 1.16±0.41        | 1.24±0.77               | 1.17±0.58                   | 1.04±0.63                    | 1.10±0.49                | 0.73                           |                                |
| LDL (mmol/l)                 | 2.85±0.82        | 3.44±1.76               | 3.11±1.63                   | 2.68±1.59                    | 2.44±1.66                | 0.002                          | 0.024                          |

**Notes:** <sup>a</sup>Comparison between four groups; <sup>b</sup>Comparison between Quartile 1 and Quartile 4 if *P*<sup>2</sup><0.05. The data are shown as mean ± SD, median [Q1, Q3], or n (%).

**Abbreviations:** DM, diabetes mellitus; TIA, transient ischemic attack; CHD, coronary heart disease; NIHSS, National Institutes of Health Stroke Scale; IQR, interquartile range; END, early neurological deterioration; CRP, C-Reaction protein; TC, total cholesterol; TG, triglyceride; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; SD, standard deviation.

## Baseline Characteristics According to END

Compared to patients without END, patients with END were older (*P*=0.017), had a higher proportion of DM (*P*<0.001), and higher CRP and LDL levels (*P*=0.011

and 0.036, respectively). The proportion of patients with an elevated TBil level was significantly lower in the END group than in the control (patients without END) group (*P*=0.005; Table 2). There was no significant difference in sex, smoking, history of hypertension, previous stroke/

**Table 2** Baseline Characteristics According to Early Neurological Deterioration

|                              | END Group (n=63) | Control Group (n=228) | <i>aP</i> value |
|------------------------------|------------------|-----------------------|-----------------|
| Age, (mean±SD), years        | 73.5±14.7        | 68.1±10.2             | 0.017           |
| Male, n (%)                  | 30 (47.6)        | 130 (57.0)            | 0.18            |
| Hypertension, n (%)          | 47 (74.6)        | 148 (64.9)            | 0.15            |
| DM, n (%)                    | 26 (41.3)        | 40 (17.5)             | <0.001          |
| Smoking, n (%)               | 13 (20.6)        | 42 (18.4)             | 0.69            |
| Previous stroke/TIA, n (%)   | 12 (19.0)        | 39 (17.1)             | 0.72            |
| CHD, n (%)                   | 4 (6.3)          | 10 (4.4)              | 0.53            |
| Initial NIHSS (median [IQR]) | 3 [2–7]          | 3 [1–9]               | 0.64            |
| CRP (ug/l)                   | 9.8±5.1          | 7.1±1.94              | 0.011           |
| TC (mmol/l)                  | 5.13±4.22        | 4.87±2.98             | 0.33            |
| TG (mmol/l)                  | 1.56±2.76        | 1.52±1.12             | 0.87            |
| HDL (mmol/l)                 | 1.19±0.55        | 1.15±0.27             | 0.63            |
| LDL (mmol/l)                 | 3.18±1.46        | 2.76±0.64             | 0.036           |
| Quartiles of TBil, n(%)      |                  |                       | 0.005           |
| Quartile 1                   | 23 (36.5)        | 51 (22.4)             |                 |
| Quartile 2                   | 18 (28.6)        | 54 (23.7)             |                 |
| Quartile 3                   | 12 (19.0)        | 61 (26.8)             |                 |
| Quartile 4                   | 10 (15.9)        | 62 (23.1)             |                 |

**Notes:** <sup>a</sup>Comparison between control and END groups. The data are shown as mean ± SD, median [Q1, Q3], or n (%).

**Abbreviations:** END, early neurological deterioration; DM, diabetes mellitus; CHD, congestive heart failure; TIA, transient ischemic attack; NIHSS, National Institutes of Health Stroke Scale; IQR, interquartile range; CRP, C-Reaction protein; TC, total cholesterol; TG, triglyceride; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; TBil, total bilirubin; SD, standard deviation.

TIA, CVD, initial NIHSS scores, TC, TG, or HDL in the two groups ( $P>0.05$ ; Table 2). The risk of END increased with the level of TBil.

# Multivariate Analysis According to END TBil Levels

A decreased level of TBil was associated with an increased risk of END (odds ratio [OR]=2.93 and 1.98 in the first and second quartiles, respectively;  $P$  for trend, 0.017; Table 3). After controlling for age, sex, hypertension and DM, the first and second quartiles of TBil were still associated with END (OR=1.61 and 1.46, respectively; Model 1,  $P$  for trend, 0.033; Table 3). After controlling for age, sex, hypertension, DM, NIHSS score, CRP, TC, TG, and LDL, the first quartiles of TBil were still associated with END (OR=1.34; Model 2,  $P$  for trend, 0.044; Table 3). In addition, an increased level of CRP and age were also associated with an increased risk of END (OR=1.27 and 1.12 respectively; Table 3).

# Discussion

In this study, we investigated the impact of TBil on END in patients with acute ischemic stroke. We found that the lowest level of TBil was an independently associated with END, which demonstrated that TBil is important in acute ischemic stroke. Compared with patients with the highest level of TBil, the risk of END in patients in quartile 1 increased by 1.38 times. In addition, increased age and level of CRP may be independent predictors of END, independent of established conventional risk factors.

END in acute ischemic stroke is a common event that has been associated with reduced neurological function and an increase in the rate of disability and mortality.<sup>1</sup> Helleberg's study indicated that the prevalence of END was 13.9%. They defined END as a decrease  $\geq 2$  points in

any Scandinavian Stroke Scale item for consciousness, gaze, arm and leg motor power, or 3 points for speech.<sup>11</sup> In a Japanese study, 25% of acute stroke patients had END.<sup>12</sup> Our study demonstrated that the incidence of END was 21.6%. However, END was defined as an increase in the NIHSS score of  $\geq 2$  points during the first 7 days of symptom onset in our study.<sup>9</sup> Previous studies indicated that END prevalence varied from 13% to 38% after acute ischemic stroke, possibly due to the different study designs, definition, neurological function assessment methods and source of subjects.<sup>2</sup>

The mechanisms for END in patients with ischemic stroke are not yet completely understood. The occurrence of END is caused by multiple factors, such as age, diabetes, infection, inflammation, metabolic, hemodynamic causes, and seizures.<sup>13,14</sup> Previous studies suggested that reduced oxygen delivery and regional metabolic disturbances appeared to be the most common fundamental pathophysiological mechanism of END.<sup>15,16</sup> Bilirubin is the end metabolic production of heme and has been considered as one of the strongest endogenous antioxidant, anti-inflammatory, and neuroprotective molecules as a hormone in mammalian tissues whose actions have been mostly characterized in the high micromolar range.<sup>4,17</sup> Oda et al<sup>8</sup> reported that low TBil was associated with a higher prevalence of stroke in a Japanese health screening population. Another study suggested that higher serum TBil level is associated with improved stroke outcomes.<sup>6</sup> A meta-analysis of existing studies has confirmed that serum bilirubin concentrations are inversely related to CVD.<sup>18</sup> Bilirubin, as a hormone, was shown to reduce body weight by reshaping the peroxisome proliferator-activated receptor  $\alpha$  (PPAR $\alpha$ ) coregulator profile, remodeling white adipose tissue to improve metabolic function, and reducing plasma TGs, very LDL and fat accumulation which are directly linked to increased stroke.<sup>19,20</sup> However, the relationship between

**Table 3** Multivariate Analysis According to END

| TBil               | Unadjusted OR (95% CI) | P value            | Model 1          | P value            | Model 2          | P value            |
|--------------------|------------------------|--------------------|------------------|--------------------|------------------|--------------------|
| <i>P</i> for trend | 0.017                  | 0.033              | 0.044            |                    |                  |                    |
| Quartile 1         | 2.93 (1.24–5.77)       | 0.003 <sup>a</sup> | 1.61 (1.23–4.93) | 0.019 <sup>a</sup> | 1.34 (1.28–3.24) | 0.026 <sup>a</sup> |
| Quartile 2         | 1.98 (1.42–4.28)       | 0.021 <sup>a</sup> | 1.46 (1.25–3.17) | 0.035 <sup>a</sup> | 1.14 (0.88–2.46) | 0.150 <sup>a</sup> |
| Quartile 3         | 1.47 (0.86–2.71)       | 0.060 <sup>a</sup> | 1.13 (0.71–2.93) | 0.130 <sup>a</sup> | 1.05 (0.67–2.77) | 0.320 <sup>a</sup> |
| Quartile 4         | 1 (reference)          | 1                  | 1                |                    |                  |                    |
| Age                | 1.76 (1.16–4.71)       | 0.019              | 1.58 (1.33–4.44) | 0.027              | 1.27 (1.07–3.88) | 0.044              |
| CRP                | 1.53 (1.36–3.55)       | 0.012              | 1.36 (1.24–3.58) | 0.025              | 1.12 (1.05–3.49) | 0.040              |

**Notes:** <sup>a</sup>Compared with quartile 4. The data are shown as mean  $\pm$  SD. Model 1, adjusted for age, sex, hypertension, and DM. Model 2, adjusted for age, sex, hypertension, DM, NIHSS score, CRP, TC, TG, and LDL.  
**Abbreviations:** TBil, total bilirubin; CRP, C-Reaction protein; OR, odds ratio; CI, Confidence interval.

bilirubin level and END is still controversial, with only a few studies on this topic. One study reported that higher serum bilirubin was correlated with the higher NIHSS scores.<sup>7</sup> This study explained that severe strokes were associated with a higher bilirubin concentration, which can limit further neurologic damage and is the reason why higher bilirubin levels are associated with better stroke outcomes. Geng et al found that direct bilirubin level at admission, dose not indirect and total bilirubin, was significantly associated with END in acute ischemic stroke. The increase of direct bilirubin levels may be related to END.<sup>21</sup> Another study indicated that the level of indirect bilirubin was significantly decreased in the acute phase of stroke.<sup>22</sup> In our study, patients with END had a incidence of DM and higher level of LDL and CRP, which were negatively associated with the TBil level. After adjustment for potential variables, the first quartile of TBil was associated with END. These results suggested that the lowest level of TBil is a possible predictor for the development of END.

Oxidized LDL has been known to be involved in the process of atherosclerosis.<sup>23</sup> Numerous studies have shown a negative relationship between serum bilirubin levels and atherosclerosis.<sup>24–26</sup> A meta-analysis reported a close negative relationship was found between ordered serum bilirubin levels and severity of atherosclerosis.<sup>27</sup> Oda reported that bilirubin suppresses the oxidation of lipid in liposomes, which is regarded as the best antioxidant of lipid peroxidation.<sup>28</sup> In our study, compared with patients with the highest TBil levels, patients with the lowest TBil levels had significantly higher LDL levels. On the other hand, we found that patients with END had decreased TBil levels and increased LDL levels. Therefore, bilirubin may be able to inhibit oxidant damage related to atherosclerosis disease.

Inflammation plays a key role in the pathogenesis of stroke. CRP has been regarded as a non-specific marker of the acute response to inflammation, infection, and tissue injury, and is the most extensively used and established marker to date.<sup>29</sup> A recent study has shown that an increase in CRP is positively associated with an increased risk and severity of stroke.<sup>30</sup> Another previous study demonstrated that high concentrations of inflammatory markers in the blood are associated with END.<sup>31</sup> Growing evidence suggests that bilirubin could decrease inflammatory responses by preventing the migration of leukocytes.<sup>32</sup> Therefore, bilirubin may be able to inhibit neuroinflammation-related END.

There are some limitations to our study. First, this study was a retrospective single-center study with a small sample size, and the results needs further verification in a larger, prospective, multi-center study. Second, we measured bilirubin at admission and the level of bilirubin in patients had not been followed up. Third, different definition of END may have resulted in bias in the evaluation of END. Finally, stroke subtypes had not been classified. However, the bilirubin was not various with the Chinese ischemic stroke subclassification.<sup>12</sup>

## Conclusion

In conclusion, END after acute ischemic stroke is likely a multifactorial event. Our study shows a negative relationship between TBil levels at admission and END in patients with acute ischemic stroke. It suggest that TBil level in patients with acute cerebral infarction may be a useful biomarker for the prediction of END. In the future, prospective studies are needed to clarify the role of bilirubin in the END.

## Ethical Approval

The study was approved by the Ethical Committee of Suzhou Ninth People's Hospital (No. WJYY-201747) and conducted in accordance with the Declaration of Helsinki.

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## Disclosure

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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