ORIGINAL ARTICLE

Association of Serum Bilirubin with Stroke Severity and Clinical Outcomes

Tian Xu, Jintao Zhang, Tan Xu, Wenqing Liu, Yan Kong, Yonghong Zhang

ABSTRACT: ***Objective:*** The aim of the study is to explore the association of serum bilirubin levels with admission severity and short term clinical outcomes among acute ischemic stroke patients. ***Methods:*** Data were collected from 2361 acute ischemic stroke patients in four hospitals of Shangdong Province during January 2006 and December 2008. National Institutes of Health Stroke Scale (NIHSS) was used to assess admission and discharge severity. NIHSS≥10 at discharge or in-hospital death was defined as short-term clinical outcomes. Logistic regression and trend test were used to examine the association of serum bilirubin levels with admission severity and short term clinical outcomes. ***Results:*** Serum bilirubin levels were significantly and positively associated with admission severity (P for trend <0.05). The age-sex adjusted odds ratios (95% confidential intervals) of NIHSS≥10 associated with the second, third and fourth quartile of total bilirubin/direct bilirubin were 1.245 (0.873, 1.777)/1.276 (0.895, 1.818), 1.484 (1.048, 2.102)/1.628 (1.158, 2.289) and 2.869 (2.076, 3.966)/2.765 (1.996, 3.828), respectively, compared with the lowest quartile; the multivariate adjusted odds ratios of NIHSS≥10 associated with the second, third and fourth quartile of total bilirubin/direct bilirubin were 1.088(0.711, 1.665)/1.436(0.94, 2.193), 1.328(0.877, 2.011)/1.647(1.092, 2.485) and 2.336(1.579, 3.458)/3.079 (2.049, 4.623), respectively, compared with the lowest quartile. However, no association between serum bilirubin levels and short-term clinical outcomes was observed in our study. ***Conclusion:*** Serum bilirubin levels were associated with initial stroke severity closely. Nevertheless, there is no significant relationship between serum bilirubin levels and short-term clinical outcomes among acute ischemic stroke patients.

RÉSUMÉ: Association du taux de bilirubine sérique avec la sévérité de l'accident vasculaire cérébral et l'issue clinique. ***Objectif :*** Le but de l'étude était d'examiner l'association entre le niveau de bilirubine sérique et la sévérité clinique au moment de l'arrivée à l'hôpital ainsi que l'issue clinique à court terme chez des patients atteints d'un accident vasculaire cérébral ischémique aigu (AVCIA). ***Méthode :*** Les données de 2 361 patients atteints d'un AVCIA ont été recueillies dans quatre hôpitaux de la province de Shangdong de janvier 2006 à décembre 2008. L'échelle National Institutes of Health Stroke Scale (NIHSS) a été utilisée pour évaluer la sévérité de l'AVC au moment de l'entrée et du congé hospitalier. L'issue clinique à court terme était définie comme étant un score ≥ 10 à la NIHSS au moment du congé hospitalier ou le décès en milieu hospitalier. L'analyse de régression logistique et l'analyse de tendance ont été utilisées pour examiner l'association entre le niveau de bilirubine sérique et la sévérité au moment de l'entrée à l'hôpital ainsi que l'issue clinique à court terme. ***Résultats :*** Le taux de bilirubine sérique était significativement et positivement associé à la sévérité au moment de l'arrivée à l'hôpital (tendance P < 0,05). Le rapport de cotes ajusté pour le sexe (intervalle de confiance à 95%) d'un score ≥ 10 à la NIHSS associé au deuxième, troisième et quatrième quartiles de bilirubine totale/bilirubine directe étaient 1,245 (0,873 à 1,777)/1,276 (0,895 à 1,818), 1,484 (1,048 à 2,102)/1,628 (1,158 à 2,289) et 2,869 (2,076 à 3,066)/2,765 (1,996 à 3,828) respectivement par rapport au quartile le plus bas. Les rapports de cotes avec ajustement multivarié d'un score ≥ 10 à la NIHSS associé au deuxième, troisième et quatrième quartile de bilirubine totale/bilirubine directe étaient 1.088 (0,711 à 1,665)/1,436 (0,94 à 2,193), 1,328 (0,877 à 2,011)/1,647 (1,092 à 2,485) et 2,336 (1,579 à 3,458)/3,079 (2,049 à 4,623) respectivement par rapport au quartile le plus bas. Cependant, nous n'avons pas observé d'association entre le niveau de bilirubine sérique et l'issue clinique à court terme dans notre étude. ***Conclusion :*** Le niveau de bilirubine sérique était étroitement associé à la sévérité initiale de l'AVC. Néanmoins, il n'existe pas de relation significative entre le niveau de bilirubine sérique et l'issue clinique à court terme chez les patients atteints d'un AVCIA.

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Stroke now ranks second to ischemic heart disease as a cause of death and is a leading cause of long-term disability worldwide[1]. Over two-thirds of stroke deaths worldwide are in developing countries[2]. In China, stroke is an enormous health issue as the second most common cause of death, accounting for nearly 20% of all deaths in both rural and urban settings[3]. Although the incidence and proportion of hemorrhagic stroke is higher in the Chinese population than in Western populations, ischemic stroke is still the dominant subtype of stroke in China[4].

Bilirubin, the end product of heme catabolism in mammals, is generally regarded as a potentially cytotoxic, lipid-soluble waste product that needs to be excreted[5]. However, recent data indicated that bilirubin exhibits potent antioxidant properties with substantial positive clinical consequences[6]. Some studies suggested that bilirubin plays an important role in the progress of various diseases associated with oxidative stress including ischemic stroke[7-10].

There are currently few data on the relationship between serum bilirubin levels and acute ischemic stroke in the Chinese population. In the present study, we aimed to examine the

From the Department of Epidemiology (TiX, TaX, YZ), School of Public Health, Medical College of Soochow University, Suzhou, Jiangsu Province; Department of Neurology (JZ, WL, YK), The 88th Hospital of PLA, Tai'an, Shandong Province, China.

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Correspondence to: Yonghong Zhang, Department of Epidemiology, School of Public Health, Medical College of Soochow University, 199 Renai Road, Industrial Park District, Suzhou, Jiangsu Province, China, 215123. Email: yhzhang@suda.edu.cn.

association of serum bilirubin levels with admission severity and short term clinical outcomes among acute ischemic stroke patients.

Methods

Study participants

This cross-sectional and follow-up study was conducted between 1 January 2006 and 31 December 2008 in four hospitals of Shandong Province, China. Two thousand, six hundred and seventy five acute ischemic patients, confirmed by a computed tomography (CT) scan or magnetic resonance imaging (MRI), were investigated. Three hundred and fourteen patients were excluded for missing data of bilirubin or other covariates. Stroke patients who were not admitted into the four hospitals including those who died outside of hospitals were not included in this analysis. This study was approved by Soochow University School of Public Health Ethics Committee.

Data collection

Baseline data were collected within the first 24 hours of hospital admission by in-person interview with patients or their family members (if patients were not able to communicate). Data on demographic characteristics, life-style risk factors, medical history, clinical laboratory tests, and imaging data (CT and MRI) were obtained using a standard questionnaire administered by trained staff. Cigarette smokers were defined as having smoked at least one cigarette per day for one year or more. Data on the amount and type of alcohol consumed during the past year were collected. Alcohol consumption was defined as consuming one or more alcoholic drinks per day during the last year. Blood pressure measurements were taken within 30 minutes of admission and in the first 72 hours (one measurement every eight hours) after admission while the study participants were in the supine position using a standard mercury sphygmomanometer according to a standard protocol[11].

Blood specimens were collected from all subjects within 24 hours of hospital admissionafter fasting (at least eight hours). Total bilirubin (Tbil) was measured by the 2,5-dichlorophenyl-diazonium (DPD) method[12] and direct bilirubin (Dbil) was measured by the method of Jendrassik et al[13]. Modified hexokinase enzymatic method was applied to test plasma glucose levels[14]. Total cholesterol, high-density lipoprotein (HDL)-cholesterol, and triglycerides were analyzed enzymatically on a Beckman Synchron CX5 Delta Clinical System (Beckman Coulter, Inc., Fullerton, California, USA) using commercial reagents[15]. Low-density lipoprotein (LDL)-cholesterol levels were calculated using Friedewald equation[16].

A comprehensive clinical evaluation with National Institutes of Health stroke scale (NIHSS) was conducted at admission and discharge. If a patient died in the hospital, a study staff member recorded the death on the event form and obtained the death certificate. In admission, NIHSS≥10 was considered as higher severity (primary outcome) in the cross-sectional analysis. NIHSS≥10 at discharge or in-hospital death was defined as short term clinical outcomes (secondary outcome) in the follow-up analysis[17].

Statistical analysis

The unadjusted means and standard deviations (SD) of normally-distributed continuous variables, mean ranks of ordinal variables and prevalence of categorical variables were calculated for baseline characteristics according to different admission severity and discharge status. Analysis of variance was used to calculate P values for difference in the means of continuous variables. Rank sum test was used to calculate P values for difference in mean ranks of ordinal variables. χ^2 test or Fisher exact test was used to calculate P values for difference in the prevalence of categorical variables. We used dichotomous variable as an outcome based on NIHSS≥10/death or NIHSS<10 and used Tbil and Dbil as exposures, which were quartile in the logistic regression model adjusted for age, sex, and other confounders and potential confounders in order to get unbiased parameter estimates. We also carefully examined collinearity between exposure and other confounders in the model and found there is no severe collinearity since all variance inflation factors (VIFs) between bilirubin and confounders were under 2.5. We did linear trend tests using Tbil and Dbil as continuous variables in the logistic regression. All P values were two-tailed and a significance level of 0.05 was used. Statistical analysis was conducted using SAS statistical software (version 9.13; SAS Institute Inc, Cary, North Carolina, USA).

Results

A total of 2361 acute ischemic stroke patients were included in our analysis. Table 1 presents the demographic and clinical characteristics by admission NIHSS. Those with higher admission NIHSS were more likely to be male and older, have higher alcohol consumption, systolic blood pressure (BP) levels, plasma glucose, serum Tbil, serum Dbil and lower triglycerides, have higher rates of histories of stroke, atrial fibrillation and rheumatic heart disease. Statistically significant differences were found in the mean of age, alcohol consumption, blood pressure, plasma glucose, serum Tbil, serum Dbil, triglycerides and the proportion of men, in-hospital complications, histories of diabetes and atrial fibrillation among three groups divided by discharge status (Table 2).

Age and sex-adjusted and multivariable-adjusted odds ratios of admission severity by the quartiles of Tbil and Dbil are presented in Table 3. The age and sex-adjusted odds ratios of severity were significantly higher in the third and top quartiles of Tbil and Dbil. The multivariable-adjusted odds ratios of severity were significantly higher in the top quartile of Tbil and the third and top quartiles of Dbil. There was a dose–response relationship between Tbil/Dbil levels and admission severity (all P values for linear trend were less than 0.05). However, serum Tbil/Dbil levels were not significantly associated with short clinical outcomes including discharge NIHSS≥10 or death in-hospital after confounding factors adjusted.

Discussion

The primary findings of this study are that elevated levels of serum Tbil and Dbil are associated with increased odds of admission severity in acute ischemic stroke patients. In contrast, both serum levels of Tbil and Dbil are poor prognostic factors for acute ischemic stroke in a short term.

Table 1: Characteristics of 2361 ischemic stroke patients according to admission NIHSS

variables	admission NIHSS≥10	admission NIHSS<10	p values
No. of participants	347	2014	
Men, no. (%)	200 (57.6)	1293 (64.2)	0.019
Age, mean (SD) (years)	65.418 (11.52)	63.745 (11.792)	0.0144
Cigarette smoking, no. (%)	93 (26.8)	529 (26.3)	0.834
Alcohol consumption (mean rank)	6.93	1.15	0.028*
Admission systolic pressure mean(SD) (mmHg)	148 (26)	145 (21)	0.0252
Admission diastolic pressure mean(SD) (mmHg)	89 (15)	88 (13)	0.1356
plasma glucose mean(SD) (mmol/L)	7.321 (3.74)	6.333 (2.594)	<0.0001
Total cholesterol mean(SD) (mmol/L)	4.93 (1.231)	5.026 (1.167)	0.1396
Triglycerides mean(SD) (mmol/L)	1.3715 (0.8594)	1.5693 (1.1454)	<0.0001
HDL cholesterol mean(SD) (mmol/l)	1.2789 (0.3736)	1.2629 (0.3483)	0.486
LDL cholesterol mean(SD) (mmol/l)	2.921 (0.9174)	3.0096 (0.872)	0.1223
serum level of Tbil mean(SD) (umol/l)	17.97 (9.559)	14.385 (6.926)	<0.0001
serum level of Dbil mean(SD) (umol/l)	4.616 (3.583)	3.343 (2.424)	<0.0001
History of hypertension no. (%)	204 (58.8)	1254 (62.3)	0.219
History of diabetes no. (%)	48 (13.8)	297 (14.7)	0.656
History of coronary heart disease, no. (%)	55 (15.9)	318 (15.8)	0.977
History of atrial fibrillation, no. (%)	33 (9.5)	41 (2.0)	0.000
History of stroke, no. (%)	128 (36.9)	616 (30.6)	0.02
History of rheumatic heart disease, no. (%)	12 (3.5)	10 (0.5)	0.000
history of dyslipidemia no. (%)	130 (37.5)	766 (38)	0.84
Family history of stroke no. (%)	27 (7.8)	128 (6.4)	0.322
Family history of hypertension no. (%)	22 (6.3)	129 (6.4)	0.963
Family history of diabetes no. (%)	3 (0.9)	14 (0.7)	0.999

* We categorize alcohol consumption as four ordinal levels (high: 4, medium: 3, low: 2, none: 1).
SD=standard deviation; Tbil=total bilirubin; Dbil=direct bilirubin; HDL=high-density lipoprotein; LDL=low-density lipoprotein

Table 2: Characteristics of 2361 ischemic stroke patients according to discharge status

variables	Discharge NIHSS<10	discharge NIHSS≥10	death	p values
No. of participants	2192	152	17	
Men, no. (%)	1389 (63.4)	89 (58.6)	15 (88.2)	0.049
Age, mean (SD) (years)	63.86 (11.77)	65.05 (11.53)	71.94 (11.24)	0.0096
Cigarette smoking, no. (%)	579 (26.4)	40 (26.3)	3 (17.6)	0.716
Alcohol consumption (mean rank)	1.06	15.77	180.28	0.009**
Mean DBP(SD) in first three days following admission in	88 (13)	91 (16)	84 (14)	0.0257
Mean SBP (SD)in first three days following admission in	145 (21)	150 (27)	150 (32)	0.041
In-hospital complication, no. (%)	30 (1.4)	5 (3.3)	4 (23.5)	0.000*
plasma glucose mean(SD) (mmol/L)	6.40 (2.73)	7.33 (3.36)	9.25 (4.75)	<0.0001
Total cholesterol mean(SD) (mmol/L)	5.01(1.158)	5.022(1.428)	5.214(1.497)	0.7292
Triglycerides mean(SD) (mmol/L)	1.515(1.095)	1.326(0.894)	1.466(1.609)	0.0469
HDL cholesterol mean(SD) (mmol/l)	1.283(0.365)	1.289(0.354)	1.282(0.247)	0.9866
LDL cholesterol mean(SD) (mmol/l)	2.975(0.855)	3.047(1.035)	3.237(1.236)	0.3241
serum level of Tbil (umol/l) mean(SD)	14.727 (7.311)	17.772 (8.808)	17.505 (8.382)	<0.0001
serum level of Dbil (umol/l) mean(SD)	3.41 (2.506)	4.66 (3.605)	3.805 2.011)	<0.0001
History of hypertension no. (%)	1345 (61.4)	91 (59.9)	12 (70.6)	0.687
History of diabetes no. (%)	320 (14.6)	18 (11.8)	7 (41.2)	0.005
History of coronary heart disease, no. (%)	345 (15.7)	25 (16.4)	3 (17.6)	0.952
History of atrial fibrillation, no. (%)	58 (2.6)	14 (9.2)	2 (11.8)	0.000*
History of stroke no. (%)	691 (31.5)	48 (31.6)	5 (29.4)	0.983
History of rheumatic heart disease, no. (%)	19 (0.9)	3 (2.0)	0 (0.00)	0.29*
history of dyslipidemia no. (%)	836 (38.1)	52 (34.2)	8 (47.1)	0.464
Family history of stroke, n (%)	147 (6.7)	7 (4.6)	1 (5.9)	0.596
Family history of hypertension, n (%)	144 (6.6)	7 (4.6)	0 (0.00)	0.54*
Family history of diabetes, n (%)	15 (0.7)	1 (0.7)	1 (5.9)	0.134*

* Fisher exact test; ** We categorize alcohol consumption as four ordinal levels (high: 4, median: 3, low: 2, none: 1).
SD=standard deviation

Table 3: Odds ratios and 95% confidence intervals (CI) of severity associated with total bilirubin and direct bilirubin among acute ischemic stroke patients

	Age-sex adjusted		Multivariable-adjusted	
variables	odds ratio 95%(CI)	p value for linear trend*	odds ratio 95%(CI)	p value for linear trend*
Total bilirubin				
Q1 （1.0-10.0）	1.0(ref)	0.0003	1.0(ref)	0.0032
Q2 （10.1-13.4）	1.245 (0.873, 1.777)		1.088(0.711, 1.665)	
Q3 （13.5-17.9）	1.484 (1.048, 2.102)		1.328(0.877, 2.011)	
Q4 （18.0-88.0）	2.869 (2.076, 3.966)		2.336(1.579, 3.458)	
Direct bilirubin				
Q1 （0.4-2.0）	1.0(ref)	0.0012	1.0(ref)	0.0126
Q2 （2.1-2.9）	1.276(0.895, 1.818)		1.436(0.94, 2.193)	
Q3 （3.0-4.1）	1.628(1.158, 2.289)		1.647(1.092, 2.485)	
Q4 （4.2-37）	2.765(1.996, 3.828)		3.079(2.049, 4.623)	

Primary outcome: In admission, NIHSS≥10 was considered higher severity. Multivariable adjustment included age, sex, alcohol consumption, cigarette smoking, blood levels of glucose and lipids, admission SBP and DBP, blood urea nitrogen, serum creatinine, sodium, hematocrit, history of stroke, hypertension, diabetes, coronary heart disease, rheumatic heart disease, and atrial fibrillation, family history of stroke, hypertension and diabetes. SBP=systolic blood pressure, DBP=diastolic blood pressure. * p values for linear trends were estimated by using bilirubin as continuous variables in multiple logistic models.

Our findings are consistent with other studies that have reported a significant association between elevated bilirubin levels and greater stroke severity instead of patients' outcome[18,19]. However, in these studies, only Dbil levels showed a significant association with stroke severity on admission whereas Tbil did not. A possible reason for this discrepancy is that several studies have suggested Dbil level is more sensitive among individuals with general medical conditions[20-22]. However, the sample size of our study is more than three fold the previous study, so that a relationship between serum Tbil levels and stroke severity is more likely to be discovered.

The generation of free radicals leading to oxidative stress is one of the mechanisms involved in brain damage induced by ischemia[23,24]. Bilirubin, which, for many years, was thought to have no physiological function other than that of a waste product of heme catabolism, has been proved a potent antioxidant[5,6]. Dohi et al suggested that serum bilirubin might serve as a useful marker of oxidative stress in hemorrhagic stroke patients and high levels of bilirubin in patients with neurotrauma reflect its pathophysiological role in free radical scavenging[25]. Our results also indicated that the production of bilirubin in serum could be attributable to systemic oxidative stresses caused by vascular and brain damage, which could occur after stroke via heme oxygenases pathway activation[26]. Therefore, further study is warranted to investigate the relationship between serum bilirubin and oxidative stress and to confirm that the concentration of serum bilirubin may reflect intensity of oxidative stress, which may be closely associated with degree of stroke severity in our population.

A study including 453 stroke patients indicated that increment in bilirubin level was associated with reduced odds of an adverse stroke outcome. A possible explanation for this inconsistency is that admission severity was not chosen as an adjusted variable in multivariable model in this study[27]. As a matter of fact, admission severity was considered as a strong confounding factor influencing prognosis among stroke patients[28], especially in our study which focused on short-term clinical outcomes.

This is the largest study in a Chinese population to examine the association of serum bilirubin levels with stroke admission severity and short-term clinical outcomes. The study data were collected with rigid quality control and important covariate variables were measured and controlled in the analysis. However, two limitations of this study should be mentioned. Firstly, association between serum bilirubin levels and admission severity was analyzed in a cross-sectional study. Therefore, a causal relationship between them could not be established. Secondly, the follow-up period of our study is relatively short, which prevented an evaluation of the long-term effects of serum bilirubin levels on acute ischemic stroke outcomes. Although serum bilirubin level may be used as a biomarker in predicting severity of stroke in our study, future research comparing bilirubin levels among stroke patients, healthy people, and other neurological disorders are warranted in Chinese population.

Conclusion

In summary, our study found that serum levels of bilirubin were significantly and positively associated with admission NIHSS≥10. A significant association was not observed between serum bilirubin levels and death or NIHSS≥10 at discharge.

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Tian Xu and Jintao Zhang contributed equally to this work.

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