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# Association of Serum Bilirubin with Ischemic Stroke Outcomes

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## Abstract

**Background—**Higher levels of serum bilirubin may offer a therapeutic advantage in oxidative stress-mediated diseases, but may also simply reflect intensity of oxidative stress. Little is known about the role of bilirubin in stroke. We assessed the relation of serum bilirubin levels with clinical presentation and outcomes among patients hospitalized with ischemic stroke.

**Methods—**Data were collected prospectively during a 5-year period on consecutive ischemic stroke admissions to a university hospital. Serum bilirubin levels, total (Tbil) and direct (Dbil), were measured on admission. Presenting stroke severity was assessed with the National Institutes of Health Stroke Scale (NIHSS). Functional outcome at discharge was assessed using the modified Rankin scale.

**Results—**Among 743 patients, mean age was 67.3 years and 47.5% were women. Median presenting NIHSS score was 4, and 24% had a poor (modified Rankin scale 4–6) functional outcome at discharge. Higher Dbil levels were associated with greater stroke severity ($P$ =.001) and poorer discharge outcome ($P$ =.034). Multivariable regression analyses showed that those with higher Dbil levels (≥0.4 mg/dL) had significantly greater admission NIHSS scores compared with those with lower levels (≤0.1 mg/dL) (odds ratio 2.79, 95% confidence interval 1.25–6.20, $P$ =.012), but no independent relationship was confirmed between Dbil and discharge outcome. Although higher admission Tbil was associated with greater stroke severity in crude analyses ($P$ =.003), no independent relationship between Tbil versus stroke severity or outcome was noted after adjusting for confounders.

**Conclusions—**Higher Dbil level is associated with greater stroke severity but not outcome among ischemic stroke patients, possibly reflecting the intensity of initial oxidative stress. Further study into the underlying pathophysiology of this relationship is needed.

### Keywords

Bilirubin; stroke; severity; outcomes

Bilirubin is an end product of heme metabolism and when accumulated in high concentrations within biological tissues, is usually seen as a very toxic substance.[1] However, it has also been suggested that bilirubin harbors powerful antioxidant properties,[1] with some studies indicating that higher levels of serum bilirubin might offer a therapeutic advantage in oxidative stress-

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mediated diseases.[2] Other data suggest that elevated serum bilirubin levels may reflect the intensity of oxidative stress.[3] Interestingly, these potentially contradictory properties have also been observed with uric acid, another end product of a major metabolic pathway.[4–6] The acute stroke setting may represent an opportunity to further examine the role of bilirubin in the pathophysiology of brain injury or as a neuroprotectant because early cerebral ischemia involves oxidative stress,[7] and identifying therapeutic avenues to limit the damage from stroke remains an area of extremely active investigation.[7] Nonetheless, few studies have examined any role for bilirubin in acute stroke.[3,8]

The objective of this study was to preliminarily assess the relation of admission serum bilirubin levels with clinical outcomes among patients with acute ischemic stroke.

## Methods

Data were collected prospectively on consecutive patients older than 18 years who presented to a university hospital stroke program with ischemic stroke during a 5-year period beginning September 1, 2002. Study entry criteria were: (1) admission for acute ischemic stroke; (2) bilirubin levels obtained on admission; and (3) no established history of hepatic disease. Stroke was defined, according to the World Health Organization definition, as rapidly developing clinical signs of focal (or global) disturbance of cerebral function, lasting more than 24 hours or leading to death with no apparent cause other than of vascular origin.[9] The time of onset of the stroke was defined as the time when the patient was last known to be well or at baseline status. Medical history was obtained directly from the patient or by family/caregiver report. All patients had a detailed diagnostic assessment, comprising neurologic examination, blood pressure measurements, blood tests, cardiac rhythm monitoring for at least 24 hours, echocardiography, and cervical and cephalic arterial imaging. Serum total (Tbil) and direct (Dbil) bilirubin levels were collected at the time of hospital admission. Magnetic resonance imaging of the brain (unless contraindicated, in which case computed tomography scan was done) was performed in all patients.

Stroke severity was assessed with the widely validated National Institutes of Health Stroke Scale (NIHSS), which measures stroke severity on a 42-point scale.[10] All patients were examined within 24 hours of admission by investigators who were certified in the application of the NIHSS. All patients were assessed at discharge using the modified Rankin scale (mRS). A score of greater than 3 on the mRS was used to define a poor functional outcome at discharge. Stroke subtypes were classified by the use of modified TOAST classification.[11] Admission NIHSS was analyzed with Kruskal-Wallis rank sum tests and logistic regression, and the discharge mRS score (>3) was analyzed with contingency table$^2$ tests and logistic regression. To evaluate the role of possible confounding factors, other potential determinants of incident stroke severity were also analyzed based on prior reports in the literature: age, sex, history of atrial fibrillation, history of hypertension, hyperlipidemia, diabetes, smoking status, admission glucose, premorbid antithrombotic use, premorbid statin use, and premorbid functional status.[12–17] Potential baseline covariate predictors of functional status at hospital discharge included all the aforementioned potential determinants of stroke severity and admission NIHSS score.[12]

The pool of potential covariates (listed above) were then selected using backward elimination at $P = .2$. Covariates were retained if any of them remained in the model. The study was approved by the university hospital institutional review board.

## Results

Among 1046 patients seen during the study period, 743 (71.0%) met study criteria; serum bilirubin levels were not obtained initially in 303 patients. Characteristics of patients who were not enrolled in this study were largely similar to the study population, but there were more large artery atherosclerotic subtypes and individuals with hyperlipidemia in the unenrolled patients, and more unknown subtypes in the enrolled patients (Table 1).

Among the 743 study patients, mean age was 67.3 years (range 18–101) and 353 (47.5%) were women. Analysis by race showed that 81.1% were white, 9.7% Asian, and 9.2% black, whereas 10.4% were of Hispanic ethnicity. Median presenting NIHSS score was 4 (interquartile range, 1–12; full range, 0–38). At discharge, 175 (23.6%) had a poor outcome by mRS. Those with higher Dbil levels were less likely to be female, more likely to have a history of atrial fibrillation or cardioembolic subtype, and more likely to have a higher admission NIHSS score (Table 2).

Tbil levels demonstrated a significant association with initial stroke severity in unadjusted analyses ($P$ =.003), but no association with either initial stroke severity or discharge stroke outcome was noted after multivariable analysis (data not shown). However, higher Dbil was associated with greater stroke severity ($P$ =.001) and poorer discharge outcome ($P$ =.034). Crude regression analysis showed that higher admission serum glucose, history of atrial fibrillation, history of hypertension, high premorbid mRS score, and higher admission Dbil level were all associated with an odds of greater initial stroke severity, whereas premorbid antithrombotic use was associated with lesser stroke severity (Table 3). After multivariable analysis (Table 4), those with elevated Dbil levels still had significantly higher admission NIHSS scores compared with those with lower levels, and the associations among serum glucose, history of atrial fibrillation, history of hypertension, premorbid mRS score, and premorbid antithrombotic use versus stroke severity remained significant. After multivariable analyses, the relationship previously noted between Dbil versus discharge outcome, however, lost significance (data not shown).

## Discussion

We found that higher admission Dbil level was independently associated with greater admission stroke severity, but not discharge outcome, among patients with ischemic stroke. Although elevated Dbil was significantly associated with both admission stroke severity and discharge outcome in crude analysis, adjusting for initial stroke severity eliminated this correlation, suggesting that initial stroke severity may be a mediator of the relationship between the discharge outcome and Dbil.

The independent relationship between initial stroke severity and Dbil level was substantial with patients with higher Dbil levels having almost 3 times the odds of presenting with a severe stroke compared with those with lower Dbil levels. This result is in accord with a study that showed serum bilirubin to be a marker of oxidant stress in hemorrhagic stroke.[3] Several studies have suggested that bilirubin acts as a physiologic antioxidant,[1] with its synthesis being induced in response to oxidative stress.[18] For instance, numerous reports have shown significant increases in serum bilirubin when using halogenated hydrocarbons as oxidative stress inducers.[18]

We did not find any significant relationships between admission Tbil versus initial stroke severity or discharge outcome in these patients with ischemic stroke. It is not immediately apparent why Dbil showed a significant association with initial stroke severity, whereas Tbil did not, and this discrepancy will require future investigation. Prior work did not distinguish between Tbil and Dbil levels.[3] However, various studies among individuals with general

medical conditions including hepatic disease have suggested that Dbil levels may be of better prognostic value than Tbil levels.[19–22]

This study's novel finding of a relation between Dbil and incident stroke severity is lent support by the study's concordance with prior investigations regarding other predictors of initial stroke deficit. We observed that higher admission serum glucose, a history of atrial fibrillation, a history of hypertension, or poor premorbid functional status were all associated with greater initial stroke severity. Premorbid antithrombotic use was associated with better admission stroke severity. All these aforementioned associations have been identified in prior work.[12–15]

Our study has some limitations. This was a single center study, in which patients were not randomized, and we did not collect data on the exact timing of bilirubin levels or stroke severity assessment. To mitigate the lack of non-randomization we adjusted for known confounders, but cannot completely exclude residual confounding. The results of this relatively modest-sized study are hypothesis generating, and should lead to future larger, more rigorously designed prospective studies geared at confirming or refuting the association we observed, and to explore potential pathophysiologic underpinnings or prognostic value to this relationship.

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**Table 1**

Comparison of clinical characteristics between patients with stroke enrolled versus those not enrolled because of missing serum bilirubin levels

| Variable | Not enrolled (n = 303) | Enrolled (n = 743) |
|---|---|---|
| Age | 66.8 ± 18.1 | 67.5 ± 16.6 |
| Female | 149 (49.3%) | 353 (47.6%) |
| Race ethnicity | | |
| Non-Hispanic whites | 222 (74.5%) | 524 (70.8%) |
| Blacks | 27 (9.1%) | 68 (9.2%) |
| Hispanics | 23 (8.1%) | 77 (10.4%) |
| Asians | 24 (8.1%) | 65 (8.8%) |
| Stroke mechanisms | | |
| Cardioembolism | 98 (32.6%) | 256 (34.8%) |
| Large artery atherosclerosis | 79 (26.2%) | 137 (18.6%)* |
| Small arterial occlusion | 44 (14.6%) | 130 (17.7%) |
| Other | 47 (15.6%) | 86 (11.7%) |
| Unknown | 33 (11.0%) | 126 (17.1%)* |
| NIH Stroke Scale score on admission | 7.7 ± 8.6 | 7.3 ± 8.1 |
| Hypertension history | 204 (67.5%) | 495 (67.0%) |
| Diabetes history | 69 (22.8%) | 180 (24.3%) |
| Atrial fibrillation history | 59 (19.5%) | 146 (19.7%) |
| Hyperlipidemia history | 127 (42.1%)* | 256 (34.5%)* |
| Metabolic syndrome presence | 136 (54.8%) | 382 (60.2%) |
| Smoking habits | | |
| Nonsmoker | 197 (65.4%) | 471 (63.6%) |
| Ex-smoker | 61 (20.3%) | 176 (23.8%) |
| Current smoker | 43 (14.3%) | 94 (12.7%) |
| History of stroke | 69 (22.9%) | 166 (22.4%) |
| History of TIA | 35 (11.6%) | 76 (10.2%) |
| History of coronary heart disease | 76 (25.2%) | 158 (21.3%) |
| Laboratory findings on admission | | |
| Glucose | 124.4 ± 43.8 | 127.0 ± 53.9 |
| Premorbid medications | | |
| Antithrombotics | 135 (45.0%) | 367 (49.6%) |
| Warfarin | 28 (9.3%) | 72 (9.7%) |
| Statins | 100 (33.3%) | 230 (31.1%) |
| mRS at discharge | | |
| Poor outcome (mRS 4–6) | 64 (27.0%) | 175 (26.2%) |

*mRS*, modified Rankin score; *NIH*, National Institutes of Health; *TIA*, transient ischemic attack.

*$P$ value for comparison <.05.

**Table 2**

Baseline sociodemographic and clinical characteristics by direct serum bilirubin level

| | Direct serum bilirubin levels | | | |
|---|---|---|---|---|
| **Variable** | **≤0.1 (n = 277)** | **0.2 (n = 181)** | **0.3 (n = 56)** | **≥0.4 (n = 37)** |
| Age | 68.3 ± 15.9 | 69.2 ± 16.4 | 66.9 ± 17.5 | 70.5 ± 16.4 |
| Female* | 148 (53.6%) | 85 (47.0%) | 16 (28.6%) | 8 (21.6%) |
| Race ethnicity | | | | |
| Non-Hispanic whites | 199 (72.6%) | 130 (71.8%) | 41 (73.2%) | 28 (75.7%) |
| Blacks | 28 (10.2%) | 13 (7.2%) | 6 (10.7%) | 1 (2.7%) |
| Hispanics | 28 (10.2%) | 16 (8.8%) | 3 (5.4%) | 5 (13.5%) |
| Asians | 17 (6.2%) | 22 (12.2%) | 6 (10.7%) | 2 (5.4%) |
| Stroke mechanisms | | | | |
| Cardioembolism* | 84 (30.7%) | 67 (37.2%) | 31 (56.4%) | 20 (55.6%) |
| Large artery atherosclerosis | 59 (21.5%) | 30 (16.7%) | 9 (16.4%) | 6 (16.7%) |
| Small arterial occlusion | 43 (15.7%) | 31 (17.2%) | 7 (12.7%) | 6 (16.7%) |
| Other | 40 (14.6%) | 18 (10.0%) | 5 (9.1%) | 1 (2.8%) |
| Unknown | 48 (17.5%) | 34 (18.9%) | 3 (5.5%) | 3 (8.3%) |
| Risk factors | | | | |
| Hypertension | 181 (65.8%) | 120 (67.0%) | 39 (69.6%) | 29 (78.4%) |
| Diabetes | 67 (24.2%) | 40 (22.3%) | 17 (30.4%) | 7 (18.9%) |
| Atrial fibrillation* | 45 (16.2%) | 43 (23.9%) | 21 (37.5%) | 12 (32.4%) |
| Hyperlipidemia | 102 (36.8%) | 62 (34.6%) | 16 (28.6%) | 15 (40.5%) |
| Metabolic syndrome | 144 (62.1%) | 90 (57.0%) | 30 (60.0%) | 13 (44.8%) |
| Smoking habits | | | | |
| Nonsmoker | 177 (64.1%) | 121 (67.2%) | 35 (62.5%) | 22 (59.5%) |
| Ex-smoker | 63 (22.8%) | 44 (24.4%) | 17 (30.4%) | 11 (29.7%) |
| Current smoker | 36 (13.0%) | 15 (8.3%) | 4(7.1%) | 4 (10.8%) |
| History of stroke | 76 (27.5%) | 33 (18.2%) | 14 (25.0%) | 7 (18.9%) |
| History of TIA | 25 (9.0%) | 20 (11.0%) | 8 (14.3%) | 4 (10.8%) |
| Coronary heart disease | 54 (19.5%) | 42 (23.5%) | 18 (32.1%) | 13 (35.1%) |
| Laboratory findings on admission | | | | |
| Glucose | 125.3 ± 56.7 | 128.6 ± 52.6 | 134.9 ± 55.6 | 128.2 ± 51.8 |
| NIHSS score on admission, median (IQR) score* | 3 (1–10) | 5 (1–14) | 5 (1–15) | 8 (3–19) |
| Quartile 1 (0–1 point) | 102 (36.8%) | 47 (26.0%) | 15 (26.8%) | 7 (18.9%) |
| Quartile 2 (2–4 points) | 64 (23.1%) | 37 (20.4%) | 12 (21.4%) | 7 (18.9%) |
| Quartile 3 (5–12 points) | 51 (18.4%) | 48 (26.5%) | 13 (23.2%) | 9 (24.3%) |
| Quartile 4 (> 12 points) | 60 (21.7%) | 49 (27.1%) | 16 (28.6%) | 14 (37.8%) |
| Modified Rankin score at discharge | | | | |
| Excellent (0–1 point) | 156 (60.5%) | 75 (46.0%) | 25 (51.0%) | 14 (41.2%) |
| Fair (2–3 points) | 45 (17.4%) | 34 (20.9%) | 11 (22.4%) | 8 (23.5%) |
| Poor (4–6 points) | 57 (22.1%) | 54 (33.1%) | 13 (26.5%) | 12 (35.3%) |
| Premorbid medications | | | | |

| | Direct serum bilirubin levels | | | |
|---|---|---|---|---|
| **Variable** | **≤0.1 (n = 277)** | **0.2 (n = 181)** | **0.3 (n = 56)** | **≥0.4 (n = 37)** |
| Antithrombotics | 140 (50.9%) | 91 (50.3%) | 28 (50.0%) | 22 (59.5%) |
| Warfarin | 30 (10.9%) | 16 (8.8%) | 7 (12.5%) | 6 (16.2%) |
| Statins | 91 (33.1%) | 56 (30.9%) | 14 (25.0%) | 16 (43.2%) |

*IQR*, interquartile range (25–75%); *NIHSS*, National Institutes of Health Stroke Scale; *TIA*, transient ischemic attack.

* *P* value for comparison <.05.

**Table 3**

Unadjusted analysis of admission serum direct bilirubin versus severe stroke (National Institutes of Health Stroke Scale score >12)

| Variable | Beta estimate | Odds ratio | Confidence interval | *P* value |
|---|---|---|---|---|
| Age | 0.002 | 1.002 | 0.987–1.017 | .772 |
| Female | 0.312 | 1.366 | 0.876–2.130 | .169 |
| Serum glucose (per 1-mg/dL increase) | 0.006 | 1.006 | 1.002–1.010 | .002 |
| Nonsmoker* | — | — | — | — |
| Ex-smoker | −0.377 | 0.686 | 0.406–1.157 | .158 |
| Current smoker | 0.300 | 1.349 | 0.689–2.642 | .382 |
| Prior antithrombotic use | −0.632 | 0.531 | 0.333–0.849 | .008 |
| Prior statin use | −0.199 | 0.820 | 0.485–1.386 | .458 |
| History of hypertension | 0.624 | 1.866 | 1.118–3.115 | .017 |
| History of diabetes | −0.315 | 0.730 | 0.411–1.296 | .283 |
| History of hyperlipidemia | −0.142 | 0.868 | 0.520–1.447 | .587 |
| History of atrial fibrillation | 0.928 | 2.530 | 1.519–4.215 | <.001 |
| Premorbid modified Rankin score (< 1)* | — | — | — | — |
| Premorbid modified Rankin score = 1 | −0.174 | 0.840 | 0.454–1.556 | .580 |
| Premorbid modified Rankin score = 2 | −0.670 | 0.512 | 0.156–1.676 | .268 |
| Premorbid modified Rankin score = 3 | −0.571 | 0.565 | 0.151–2.117 | .397 |
| Premorbid modified Rankin score = 4–5 | 1.517 | 4.556 | 1.492–13.916 | .008 |
| Serum direct bilirubin (≤mg/dL)* | — | — | — | — |
| Serum direct bilirubin (0.2 mg/dL) | 0.323 | 1.382 | 0.863–2.213 | .179 |
| Serum direct bilirubin (0.3 mg/dL) | 0.250 | 1.284 | 0.619–2.665 | .502 |
| Serum direct bilirubin (≥mg/dL) | 1.024 | 2.785 | 1.25–6.202 | .012 |

*Reference group

**Table 4**

Multivariable analysis of admission serum direct bilirubin versus severe stroke (National Institutes of Health Stroke Scale score >12)

| Variable | Beta estimate | Odds ratio | Confidence interval | *P* value |
|---|---|---|---|---|
| Female | 0.391 | 1.479 | 0.960–2.276 | .076 |
| Serum glucose (per 1-mg/dL increase) | 0.005 | 1.005 | 1.001–1.008 | .005 |
| Prior antithrombotic use | −0.708 | 0.492 | 0.316–0.768 | .002 |
| History of hypertension | 0.558 | 1.748 | 1.090–2.802 | .020 |
| History of atrial fibrillation | 0.959 | 2.608 | 1.608–4.231 | <.001 |
| Premorbid modified Rankin score (< 1)* | — | — | — | — |
| Premorbid modified Rankin score = 1 | −0.196 | 0.822 | 0.453–1.492 | .520 |
| Premorbid modified Rankin score = 2 | −0.695 | 0.499 | 0.155–1.608 | .244 |
| Premorbid modified Rankin score = 3 | −0.653 | 0.521 | 0.139–1.953 | .333 |
| Premorbid modified Rankin score = 4–5 | 1.347 | 3.845 | 1.306–11.325 | .015 |
| Serum direct bilirubin (≤0.1 mg/dL)* | — | — | — | — |
| Serum direct bilirubin (0.2 mg/dL) | 0.323 | 1.382 | 0.863–2.213 | .179 |
| Serum direct bilirubin (0.3 mg/dL) | 0.250 | 1.284 | 0.619–2.665 | .502 |
| Serum direct bilirubin (≥0.4 mg/dL) | 1.024 | 2.785 | 1.25–6.202 | .012 |

*Reference group