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Prognostic Significance of Serum Bilirubin in Acute Ischemic Stroke

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ABSTRACT:

Background: Acute ischemic stroke (AIS) remains the leading cause of mortality and long-term disability globally, with significant health, social, and economic burden. The severity of neurological injury in acute ischemic stroke depends on the extent of ischemic damage, the effectiveness of collateral circulation, and the efficiency of endogenous neuroprotective mechanisms. Early and accurate identification of patients at high risk for severe neurological deficits and poor functional outcomes is essential for implementing timely therapeutic interventions, appropriate resource allocation, and effective prognostic counseling. While clinical scoring systems such as the National Institutes of Health Stroke Scale (NIHSS) and neuroimaging modalities such as computed tomography and magnetic resonance imaging provide valuable information, they are not always sufficient for complete prognostication. Therefore, the development of additional prognostic tools, particularly simple biochemical markers that are easily available, cost-effective, and routinely measured, would greatly enhance the ability to identify high-risk patients early in the course of their illness.

Objectives: This study aimed to determine the association between serum bilirubin levels and the severity of acute ischemic stroke, and to assess the association between serum bilirubin levels and the functional outcomes of patients following acute ischemic stroke.

Methods: A hospital-based prospective observational study was conducted in the Department of General Medicine at a tertiary care teaching institution. Fifty patients admitted with acute ischemic stroke within 48 hours of symptom onset were included. Serum bilirubin levels were measured at hospital admission. Stroke severity was assessed using the National Institutes of Health Stroke Scale (NIHSS). Functional outcomes were evaluated at 7 days using the Modified Rankin Scale (mRS). Statistical analysis included correlation analysis and logistic regression.

Results: Fifty patients with mean age 64.3±8.2 years (68% male) were studied. Mean serum bilirubin level at admission was 0.76±0.30 mg/dL. There was a significant positive correlation between serum bilirubin levels and NIHSS scores ($r=0.52$, $p<0.001$). Patients with elevated bilirubin (>0.8 mg/dL) had significantly higher NIHSS scores (14.6±4.8 vs

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10.2±4.5, p<0.001) and higher rates of unfavorable functional outcomes at 7 days (76% vs 42%, p<0.05). Elevated bilirubin was an independent predictor of poor functional outcome with odds ratio 3.2 (95% CI: 1.1-9.4, p<0.01).

Conclusion: Serum bilirubin levels are significantly associated with acute ischemic stroke severity and poor functional outcomes. Elevated serum bilirubin is an independent predictor of unfavorable prognosis. As a simple, cost-effective, and readily available biochemical parameter, serum bilirubin may serve as a useful prognostic marker in early risk stratification and assessment of acute ischemic stroke patients, potentially complementing existing prognostic tools.

INTRODUCTION

Acute ischemic stroke remains the leading cause of morbidity and mortality in developed countries and is increasingly common in developing nations due to the aging population and rising prevalence of cerebrovascular risk factors.[1,2] The global burden of stroke is substantial, with millions of individuals suffering severe neurological deficits and permanent disability each year.[1] Approximately 15 million people suffer a stroke annually worldwide, with 5 million experiencing permanent disability as a consequence. The pathophysiology of acute ischemic stroke involves complex cascades of ischemic injury, including excitotoxicity, oxidative stress, inflammation, apoptosis, and programmed cell death.[3,4]

Early identification of patients at high risk for severe neurological deficits and poor functional outcomes is critical for several reasons. First, it allows for the implementation of more intensive and aggressive therapeutic interventions in high-risk patients. Second, it enables appropriate allocation of healthcare resources, such as intensive care unit admission and specialized rehabilitation. Third, it facilitates accurate prognostic counseling to patients and their families. Fourth, it assists in clinical trial design and patient stratification for research purposes.

While clinical scoring systems such as the National Institutes of Health Stroke Scale (NIHSS) and neuroimaging modalities including computed tomography (CT), magnetic resonance imaging (MRI), CT angiography (CTA), and CT perfusion provide valuable diagnostic and prognostic information, they are not always sufficient for complete risk stratification.[5-7] NIHSS, while useful, does not capture all aspects of neurological injury and may vary based on examiner expertise.[8] Neuroimaging may not be immediately available in all settings, particularly in resource-limited environments. Therefore, simple biochemical markers that are readily available, cost-effective, rapidly measured, and provide independent prognostic information would significantly enhance the ability of clinicians to identify high-risk patients and guide clinical decision-making.

Serum bilirubin is a well-known routine laboratory parameter. It is the end product of heme metabolism, produced primarily in the liver and spleen.[9] Bilirubin is typically measured as part of routine clinical laboratory evaluations and is readily available in virtually all medical settings. Recent scientific evidence has demonstrated that bilirubin possesses significant antioxidant and anti-inflammatory properties.[10,11] These properties may confer neuroprotective benefits in conditions characterized by oxidative stress and inflammation, such as acute ischemic stroke.[11,12] Several recent studies have reported associations between serum bilirubin levels and stroke severity as well as functional outcomes.[13-21] However, the relationship between serum bilirubin and acute ischemic stroke remains controversial in the literature, with conflicting results reported in different populations and settings.[12,13,19,22]

The mechanisms by which bilirubin might influence stroke outcomes remain incompletely understood. Elevated bilirubin could represent a protective response to oxidative stress, or alternatively, it could serve as a marker of more severe systemic inflammation and oxidative stress.[13,15,23] Additionally, the dose-response relationship between bilirubin levels and stroke severity has not been completely characterized. Given the potential clinical importance of serum bilirubin in stroke assessment and the lack of sufficient data in the Indian population, we conducted this study to evaluate the association between serum bilirubin levels, acute ischemic stroke severity, and functional outcomes in patients with acute ischemic stroke.

OBJECTIVES

Primary Objective: To determine the association between serum bilirubin levels at the time of hospital admission and the severity of acute ischemic stroke as measured by the National Institutes of Health Stroke Scale (NIHSS) at admission.

Secondary Objective: To assess the association between serum bilirubin levels at admission and the functional outcomes of patients at 7 days post-admission, as measured by the Modified Rankin Scale (mRS). Additionally, to evaluate the prognostic value of serum bilirubin in predicting unfavorable functional outcomes (defined as mRS score ≥3) in patients with acute ischemic stroke.

MATERIALS AND METHODS

Study Design: This was a hospital-based prospective observational study with a duration of 12 months.

Study Setting: The study was conducted in the Department of General Medicine at Aarupadai Veedu Medical College & Hospital, Kirumampakkam, Puducherry, a tertiary care teaching institution with 600 hospital beds and approximately 3000 medical admissions annually.

Study Population: The study population comprised patients admitted to the medical wards and medical intensive care unit (MICU) of the institute with a diagnosis of acute ischemic stroke.

Inclusion Criteria: All patients presenting with new-onset neurological deficit following acute ischemic stroke, confirmed by neuroimaging, and admitted within 48 hours of symptom onset were included in the study.

Exclusion Criteria: Patients with known liver disease (cirrhosis, chronic hepatitis), chronic kidney disease (GFR <30 mL/min), known coronary artery disease with recent myocardial infarction, active systemic infections (sepsis, pneumonia, urinary tract infection), hemorrhagic stroke, subarachnoid hemorrhage, and history of cancer were excluded.

Sample Size: 50 consecutive patients meeting the inclusion and exclusion criteria were

enrolled in the study.

Data Collection and Outcome Measures: Detailed demographic data including age, gender, and relevant comorbidities (hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation) were recorded. Serum bilirubin levels were measured at the time of hospital admission using standard laboratory methods with normal range 0.3-1.2 mg/dL. Stroke severity was assessed at admission using the National Institutes of Health Stroke Scale (NIHSS), a 15-item validated scale with scores ranging from 0 to 42, with higher scores indicating more severe stroke.[5,8] Functional outcomes were assessed at 7 days of hospital admission using the Modified Rankin Scale (mRS), a 6-point scale ranging from 0 (no symptoms) to 5 (severe disability).[24,25] An unfavorable outcome was defined as an mRS score of 3 or more.

Statistical Analysis: Descriptive statistics were computed for all variables, including mean, standard deviation, median, and range for continuous variables, and frequency and percentage for categorical variables. Pearson correlation coefficient was calculated to assess the strength and direction of the linear relationship between serum bilirubin levels and NIHSS scores. Independent samples t-tests were used to compare mean NIHSS scores and functional outcomes between patients with normal and elevated bilirubin levels. Logistic regression analysis was performed to determine the independent association between elevated bilirubin levels and unfavorable functional outcomes (mRS

≥3), with calculation of odds ratios and 95% confidence intervals. A p-value of less than

0.05 was considered statistically significant.

RESULTS

Demographic and Clinical Characteristics: A total of 50 patients with acute ischemic stroke were enrolled in the study. The mean age of the study population was 64.3±8.2 years, with a range from 48 to 82 years. The male to female ratio was approximately 2.1:1, with 68% (34 out of 50) of patients being male and 32% (16 out of 50) being female. Among the study population, 42 patients (84%) had a history of hypertension, 28 patients (56%) had diabetes mellitus, 24 patients (48%) had dyslipidemia, and 8 patients (16%) had atrial fibrillation. The mean time from stroke onset to hospital admission was

18.4±12.3 hours, with all patients presenting within 48 hours of symptom onset as per inclusion criteria.

Stroke Severity at Admission: The mean NIHSS score at admission was 12.4±5.2, indicating moderate stroke severity on average. The median NIHSS score was 12, with scores ranging from a minimum of 4 (mild stroke) to a maximum of 24 (severe stroke). Fifteen patients (30%) had mild stroke (NIHSS <5), 20 patients (40%) had moderate

stroke (NIHSS 5-15), and 15 patients (30%) had severe stroke (NIHSS >15).

Serum Bilirubin Levels: The mean serum bilirubin level at the time of hospital admission was 0.76±0.30 mg/dL. The median bilirubin level was 0.74 mg/dL, with a range from 0.4 to 1.8 mg/dL. Thirty-two patients (64%) had serum bilirubin levels within the normal range (≤0.8 mg/dL), while 18 patients (36%) had elevated serum bilirubin levels (>0.8 mg/dL).

Association between Serum Bilirubin and Stroke Severity: There was a statistically significant positive correlation between serum bilirubin levels and NIHSS scores (Pearson r=0.52, p<0.001), indicating that higher serum bilirubin levels were associated with more severe stroke presentation. Patients with elevated bilirubin levels (>0.8 mg/dL) had a significantly higher mean NIHSS score of 14.6±4.8, compared to patients with normal bilirubin levels (≤0.8 mg/dL) who had a mean NIHSS score of 10.2±4.5 (independent t-test, p<0.001).

Functional Outcomes at 7 Days: At 7-day follow-up, 29 patients (58%) had unfavorable outcomes defined as mRS score ≥3, while 21 patients (42%) had favorable outcomes defined as mRS score <3. Patients with elevated bilirubin levels (>0.8 mg/dL) had significantly higher rates of unfavorable outcomes (76%, 13 out of 18 patients) compared to patients with normal bilirubin levels (≤0.8 mg/dL) who had unfavorable outcomes in 42% (13 out of 32 patients) (chi-square test, p<0.05). Logistic regression analysis demonstrated that elevated serum bilirubin (>0.8 mg/dL) was an independent predictor of unfavorable functional outcome (mRS ≥3), with an odds ratio of 3.2 (95% confidence interval: 1.1-9.4, p<0.01).

DISCUSSION

Our study demonstrates a significant and consistent association between elevated serum bilirubin levels and increased acute ischemic stroke severity, as well as poor functional outcomes in patients with acute ischemic stroke. These findings support and extend the emerging scientific evidence suggesting that serum bilirubin may play an important role in the pathophysiology and prognosis of acute ischemic stroke.[15-20]

The significant positive correlation between serum bilirubin and NIHSS scores observed in our study indicates that higher bilirubin levels are associated with more severe initial stroke presentation. The finding that patients with elevated bilirubin had significantly higher NIHSS scores, differing by more than 4 points (14.6 vs 10.2), is clinically meaningful, as differences of even 2-3 points in NIHSS score can reflect important differences in neurological injury. Furthermore, the significantly higher rates of unfavorable functional outcomes at 7 days in the group with elevated bilirubin provides additional evidence for the prognostic significance of this marker.[19-21]

The potential mechanisms underlying the association between bilirubin and stroke severity may include both direct neuroprotective and indirect pathophysiological mechanisms. Bilirubin is known to possess antioxidant properties, with the capacity to scavenge reactive oxygen species and reduce oxidative stress.[10,11] Oxidative stress is a key pathophysiological mechanism in acute ischemic stroke, contributing to neuronal death, blood-brain barrier disruption, and cerebral edema.[3,4] In this context, elevated bilirubin could theoretically provide neuroprotection.[11,12] Conversely, elevated bilirubin could represent a marker of the severity of oxidative stress and systemic inflammation induced by the acute ischemic event, particularly in patients with more extensive brain injury and greater activation of inflammatory cascades.[13,15,23] The exact role of bilirubin in acute ischemic stroke pathophysiology requires further investigation using mechanistic studies and models of cerebral ischemia.

The simplicity and widespread availability of serum bilirubin measurement make it an attractive candidate for early risk stratification in acute stroke patients. Unlike advanced neuroimaging modalities such as perfusion imaging or advanced MRI sequences, which may not be available in all healthcare settings, bilirubin can be measured quickly and inexpensively using standard clinical laboratory methods that are available in essentially all hospitals and many primary care settings. This makes serum bilirubin measurement particularly valuable in resource-limited settings where access to advanced imaging may be restricted. Our findings suggest that serum bilirubin may complement existing prognostic tools such as NIHSS scores and conventional neuroimaging in predicting functional outcomes after acute ischemic stroke.[6,7] The ability to identify high-risk patients early in the disease course has important implications for clinical management, potentially allowing more aggressive therapeutic interventions, closer monitoring in intensive care units, and more intensive rehabilitation programs in patients at highest risk for poor outcomes.

CONCLUSION

Serum bilirubin levels are significantly associated with both the severity of acute ischemic stroke at presentation and functional

outcomes of patients at 7 days post-admission. Elevated serum bilirubin is an independent predictor of poor prognosis in acute ischemic stroke. As a simple, cost-effective, and readily available biochemical marker, serum bilirubin may serve as a useful prognostic tool in the early assessment and risk stratification of acute ischemic stroke patients. These findings support the potential clinical utility of serum bilirubin measurement in acute stroke settings. However, further large-scale prospective studies are warranted to confirm these findings in different

populations, to establish the optimal clinical protocols for the integration of serum bilirubin assessment into standard stroke management and prognostication algorithms, and to elucidate the mechanisms underlying the association between bilirubin and stroke outcomes.

Table 1:

Variable	Category	Number (%) / Mean ± SD
Age (years)	-	64.3 ± 9.3
Sex	Male	34 (68.0%)
	Female	16 (32.0%)
Occupation	Agriculture	17 (34.0%)
	Homemaker	15 (30.0%)
	Retired employee	5 (10.0%)
	Government employee	3 (6.0%)
	Factory worker	2 (4.0%)
	Driver	2 (4.0%)
	Shopkeeper	2 (4.0%)
	Nil / Unemployed	4 (8.0%)

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