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Serum Bilirubin as a Severity and Prognostic Indicator in Acute Ischemic Stroke a Tertiary Care Hospital-Based I-Year Observational Study

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ABSTRACT

Background: Acute Ischemic Stroke (AIS) remains a leading cause of morbidity and mortality. Identifying simple biochemical markers that predict severity and outcomes may improve early risk stratification. Serum bilirubin, despite its antioxidant properties, has shown conflicting associations with AIS outcomes.
Aim: To evaluate the role of serum bilirubin (total, direct, and indirect) as a severity and prognostic indicator in AIS.
Methods: A prospective observational study was conducted over one year at a tertiary care centre in Tamil Nadu, including 96 newly diagnosed AIS patients. Serum bilirubin levels were measured at admission, while stroke severity and functional outcomes were assessed using the NIHSS and mRS, respectively. Correlation analysis, ROC curve analysis, and multivariate logistic regression were performed to determine the predictive value of bilirubin.
Results: Total, direct, and indirect bilirubin showed significant positive correlations with NIHSS ($r = 0.482, 0.461, 0.291$; $p < 0.01$) and mRS scores ($r = 0.551, 0.544, 0.324$; $p < 0.01$). Total bilirubin demonstrated the highest predictive accuracy for severe mRS outcomes (AUC = 0.798), with an optimal cutoff of ≥2 mg/dL. Multivariate analysis identified total bilirubin <2 mg/dL as an independent predictor of better outcomes (Adjusted OR = 9; $p = 0.012$).
Conclusion: Elevated serum bilirubin, particularly total bilirubin ≥2 mg/dL, is strongly associated with increased stroke severity and poorer functional outcomes in AIS. As a simple and routinely available biomarker, serum bilirubin can support early risk stratification and clinical decision-making.

Keywords*: Acute Ischemic Stroke, Serum Bilirubin, NIHSS, mRS, Prognostic Marker, Oxidative Stress.*

INTRODUCTION

Acute Ischemic Stroke (AIS) is a major cause of morbidity and mortality worldwide and accounts for nearly 85% of all stroke cases (1). The global burden continues to rise, especially in developing countries, due to increasing prevalence of vascular risk factors such as hypertension, diabetes mellitus, and smoking (2). Early identification of prognostic indicators in AIS is essential for guiding treatment strategies, predicting clinical outcomes, and reducing long-term disability (3). Although clinical assessment tools like the National Institutes of Health Stroke Scale (NIHSS) and the modified Rankin Scale (mRS) are widely used, there is a growing interest in biochemical markers that may serve as reliable severity predictors.

Serum bilirubin, typically a marker of liver function, has gained scientific attention because of its antioxidant, anti-inflammatory, and cytoprotective properties (4). Emerging evidence suggests that bilirubin levels may influence vascular function and oxidative stress, both of which are implicated in the pathogenesis of ischemic stroke (5). However, studies examining bilirubin in AIS have yielded conflicting results. Some report that elevated bilirubin is associated with greater stroke severity and worse outcomes (6,7), whereas others suggest a protective antioxidant role (8).

Given these inconsistent findings and the limited data available from South Indian populations, further research is necessary. Therefore, this one-year prospective observational study aimed to assess the role of serum bilirubin (total, direct, and indirect) as a severity and prognostic indicator in AIS. The study evaluated correlations between bilirubin levels and NIHSS scores, mRS outcomes, and determined diagnostic accuracy using ROC curve analysis. Multivariate logistic regression was performed to identify bilirubin as an independent predictor of AIS outcome.

MATERIALS AND METHODS

Study Design and Setting

This prospective observational study was conducted in the Emergency Department of Villupuram Medical College, a tertiary care centre in Tamil Nadu.

Study Duration

The study was conducted over a period of one year, from April 2024 to April 2025.

Study Population

The study included newly diagnosed adult patients presenting with Acute Ischemic Stroke (AIS).

Inclusion Criteria

- Patients aged ≥18 years.
- Newly diagnosed AIS presenting within **48 hours** of symptom onset.

Exclusion Criteria

- Haemorrhagic stroke.
- Post-traumatic stroke.
- Post-surgical stroke.
- Transient Ischaemic Attack (TIA).
- Patients/attenders unwilling to provide consent.

Sample Size Calculation

Based on a study by Ushalakshmi et al., where the mean ± SD serum bilirubin level among AIS patients was 0.6 ± 0.249 mg/dL, the sample size was calculated using the formula:

$$n = \left(\frac{Z_{1-\alpha/2} \times \sigma}{d}\right)^2$$

Where:

- $Z_{1-\alpha/2} = 1.96$(95% confidence),
- $d = 0.05$(absolute precision),
- $\sigma = 0.249$.

The calculated sample size was **96**.

Ethical Approval

Approval was obtained from the Institutional Ethics Committee (IEC) of Government Medical College, Villupuram. The study details were explained to the patients or their attenders in their native Tamil language, and written informed consent was obtained. Confidentiality and anonymity were strictly maintained.

Sampling Technique

A **consecutive sampling technique** was used. All AIS patients presenting to the emergency department and meeting the eligibility criteria were enrolled until the sample size of 96 was achieved.

Study Procedure

Following ethical clearance, 96 newly diagnosed AIS patients were recruited. A predesigned semi-structured pro forma (Annexure) was used to collect sociodemographic details, clinical history, examination findings, laboratory parameters, and imaging results. All patients received treatment as per standard management protocols.

- Stroke severity was assessed at admission using the **National Institutes of Health Stroke Scale (NIHSS)**.
- Functional outcome was assessed at discharge using the **modified Rankin Scale (mRS)**.

Data Collection Steps

1. Obtained IEC approval prior to study initiation.
2. Written informed consent was collected from patient attenders.
3. Semi-structured pro forma was completed in Tamil for all participants.

4. Each patient underwent clinical evaluation, laboratory investigations, and radiological imaging.
5. Treatment was provided according to clinical condition and institutional protocol.
6. Stroke severity (NIHSS) and functional outcome (mRS) were recorded.

Potential Risks
No risks were anticipated for the study participants.

Data Analysis
Data were entered into Microsoft Excel and analysed using SPSS version 16.0. Missing or invalid entries were removed prior to analysis to ensure accuracy. Categorical variables such as gender and smoking status were summarized using frequencies and percentages, while continuous variables, including age and serum bilirubin, were expressed as mean ± SD for normally distributed data or as median values for non-normally distributed data. The Kolmogorov–Smirnov test was used to assess the normality of continuous variables. Depending on the number of groups and distribution of data, comparisons of continuous variables were performed using the independent t-test or ANOVA. Pearson's correlation coefficient was applied to evaluate the linear relationship between continuous variables. Associations between categorical variables were examined using the chi-square test or Fisher's exact test as appropriate. Multivariate logistic regression analysis was carried out to identify predictors, such as serum bilirubin, influencing Acute Ischaemic Stroke outcomes measured by the modified Rankin Scale (mRS). A p-value of <0.05 was considered statistically significant.

RESULT AND OBSERVATION

Table 1 Age and Sex Distribution of Study Participants (N = 96)

Variable	Category	Frequency (n)	Percentage (%)
Age Group	< 45 years	34	35%
	45–59 years	35	37%
	≥ 60 years	27	28%
Sex	Male	57	59%
	Female	39	41%

Table:2Sociodemographic and Clinical Characteristics of Study Participants (N = 96)

Variable	Category / Value	Frequency (n)	Percentage (%)	Mean ± SD	Median
Age Group	< 45 years	34	35%	—	—
	45–59 years	35	37%	—	—
	≥ 60 years	27	28%	—	—
Sex	Male	57	59%	—	—
	Female	39	41%	—	—
Smoking History	Yes	45	47%	—	—
	No	51	53%	—	—
Diabetes Mellitus (DM)	Present	43	45%	—	—
	Absent	53	55%	—	—
Systemic Hypertension (SHTN)	Present	71	74%	—	—
	Absent	25	26%	—	—
BMI Category	Underweight	3	3%	—	—
	Normal	49	51%	—	—
	Pre-obese	37	39%	—	—
	Obese Class I	7	7%	—	—
Continuous Variables	Age (years)	—	—	50 ± 13.5	50
	BMI (kg/m²)	—	—	24.2 ± 3.4	24
	SBP (mmHg)	—	—	142 ± 23.3	140
	DBP (mmHg)	—	—	89 ± 10.7	90
	AST (U/L)	—	—	50.1 ± 14.5	45
	ALT (U/L)	—	—	53.2 ± 17.5	50

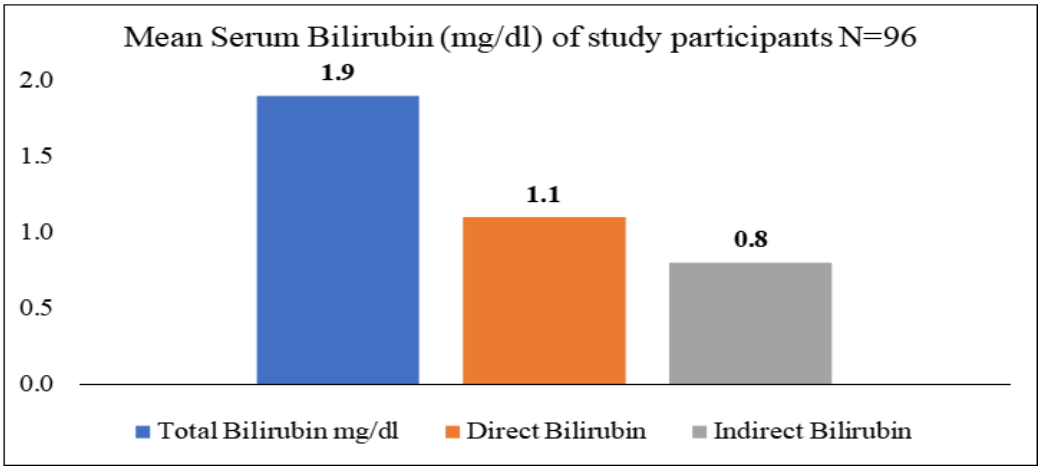

Figure 1: Mean Serum Bilirubin

Table:3 NIHSS and mRS Severity Scores and Outcome Distribution Among Study Participants (N = 96)

Variable	Category / Value	Frequency (n)	Percentage (%)	Mean ± SD	Median
NIHSS Score	—	—	—	**24.8 ± 7.7**	**25**
NIHSS Severity Grading	Minor (1–6)	1	1%	—	—
	Moderate (7–15)	14	15%	—	—
	Moderately Severe (16–20)	26	27%	—	—
	Severe (21–40)	55	57%	—	—
mRS Score	—	—	—	**3.3 ± 1.1**	**3**
Distribution of mRS Scores	mRS 1	28	29%	—	—
	mRS 2	23	24%	—	—
	mRS 3	32	33%	—	—
	mRS 4	13	14%	—	—
mRS Outcome Severity	Moderate Outcome (mRS 2–3)	51	53%	—	—
	Severe Outcome (mRS ≥ 4)	45	47%	—	—

Table 4: Correlation of Serum bilirubin and AIS outcome: (N = 96)

Variables	NIHSS		Mrs	
	Pearson Correlation	**p value**	**Pearson Correlation**	**p value**
TB	0.482**	<0.001	0.551**	**<0.001**
DB	0.461**	<0.001	0.544**	**<0.001**
IB	0.291**	0.004	0.324**	**0.001**
** Correlation is significant at the 0.01 level (2-tailed).				
* Correlation is significant at the 0.05 level (2-tailed).				

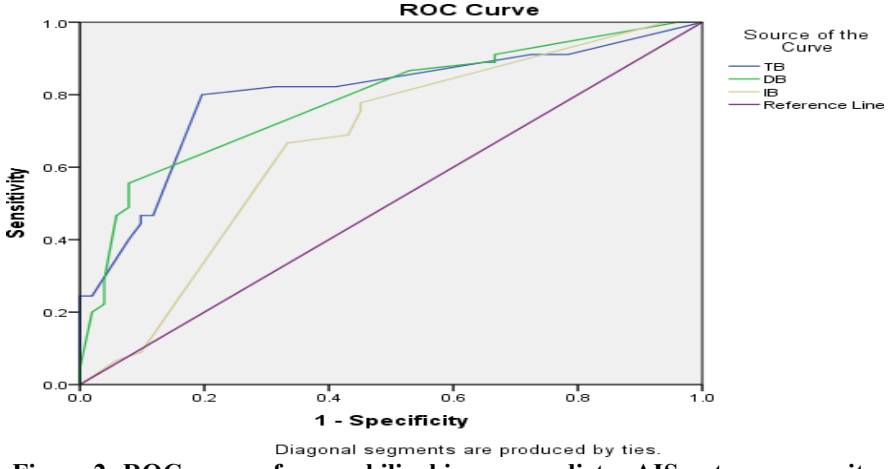

Figure 2: ROC curve of serum bilirubin as a predictor AIS outcome severity

Table 5: Area Under the Curve

Test Result Variables	Area	Std. Error[a]	p value	95% CI of AUC	
				Lower Bound	Upper Bound
Total Bilirubin (TB)	**0.798**	**0.048**	**<0.001**	**0.705**	**0.892**
Direct Bilirubin (DB)	**0.785**	**0.047**	**<0.001**	**0.692**	**0.878**
Indirect Bilirubin (IB)	**0.669**	**0.056**	**0.004**	**0.560**	**0.778**
a. Under the nonparametric assumption; b. Null hypothesis: true area = 0.5					

Table: 6ROC Curve Characteristics and Cutoff-wise Distribution of Serum Bilirubin Parameters (N = 96)

Parameter	Cutoff Value	Sensitivity	Specificity	Youden Index	Frequency (n)	Percentage (%)
Total Bilirubin	2.0* (Optimal)	0.800	0.804	**0.604**	46	48%
	< 2	—	—	—	50	52%
Direct Bilirubin	1.1* (Optimal)	0.556	0.922	**0.477**	29	30%
	< 1.1	—	—	—	67	70%
Indirect Bilirubin	1.0* (Optimal)	0.667–1.000	0.333–0.961	**0.059–0.667**	47	49%
	< 1.0	—	—	—	49	51%

Table 7: Association of serum bilirubin with AIS outcome (mRS): N = 96

Variables		mRS outcome Severity		Odds Ratio (95% CI)	p value
		Moderate n = 36 Frequency (%)	Severe n = 36 Frequency (%)		
Total Bilirubin	< 2 (50)	41 (82)	9 (18)		
	≥ 2 (46)	10 (22)	36 (78)	16 (6 – 45)	**<0.001**
Direct Biliribin	< 1.1 (67)	47 (70)	20 (30)		
	≥ 1.1 (29)	4 (14)	25 (86)	15 (5 – 48)	**<0.001**
Indirect Bilirubin	< 1 (49)	34 (69)	15 (31)		
	≥ 1 (47)	17 (36)	30 (64)	4 (2 – 9)	**0.001**

Table 8: Multinomial Logistic Regression of Serum Bilirubin with mRS severity: (N = 96)

mRS Severity [a]		Adjusted OR	95% Confidence Interval for Adjusted OR		p value
			Lower Bound	Upper Bound	
Intercept					0.002
Total Bilirubin	< 2	**9**	**2**	**45**	**0.012**
	≥ 2	-	-	-	-
Direct Bilirubin	< 1.1	3	0.7	15	0.1
	≥ 1.1	-	-	-	-
Indirect Bilirubin	< 1	0.9	0.2	4	0.9
	≥ 1	-	-	-	-

DISCUSSION

This prospective observational study demonstrated a significant association between serum bilirubin levels and both stroke severity and functional outcomes in patients with Acute Ischemic Stroke (AIS). Total, direct, and indirect bilirubin showed strong positive correlations with NIHSS and mRS scores, indicating that higher bilirubin levels were associated with more severe neurological deficits and poorer outcomes. These findings support earlier research conducted by Ushalakshmi et al. (6) and Vala et al. (7), who also reported a similar pattern of association between elevated bilirubin and increased stroke severity.

The elevation of serum bilirubin in AIS may reflect the underlying oxidative stress occurring during ischemic neuronal injury. Activation of heme oxygenase-1 during ischemia leads to increased heme breakdown and subsequent bilirubin production, which may serve as a biomarker of cellular oxidative burden (9). Therefore, although bilirubin possesses antioxidant properties, its elevated levels in AIS likely represent a compensatory response to severe oxidative and inflammatory stress rather than a protective mechanism. This biological explanation aligns with the significant correlations observed in the present study.

The ROC analysis further revealed that total bilirubin had excellent predictive accuracy for determining severe mRS outcomes, with an AUC of 0.798, followed by direct bilirubin with an AUC of 0.785. These diagnostic characteristics are comparable to the findings of Zhai et al. (10), who demonstrated the utility of bilirubin as a predictor of stroke prognosis. The cutoff value of ≥2 mg/dL for total bilirubin achieved high sensitivity and specificity, supporting its clinical relevance in early risk stratification.

Multivariate logistic regression analysis showed that total bilirubin <2 mg/dL was independently associated with better functional outcomes (Adjusted OR = 9, p = 0.012), while direct and indirect bilirubin did not remain significant predictors after adjustment. This emphasizes that total bilirubin, reflecting the combined effect of both its fractions, is likely the most reliable prognostic marker.

The findings of this study are largely consistent with the majority of available literature, which supports the association between higher bilirubin levels and poor AIS outcomes (6,7,10). However, some studies propose a protective antioxidant role of bilirubin (8), leading to conflicting interpretations. These discrepancies may be attributed to differences in genetic factors, baseline bilirubin levels, patient demographics, sampling times, and variations in stroke severity across study populations.

The study has several strengths, including its prospective design, standardized assessment tools, and robust statistical analyses incorporating ROC characteristics and multivariate regression. However, certain limitations should be considered. This was a single-center study with a relatively small sample size, and bilirubin levels were measured only once, preventing evaluation of dynamic changes during the clinical course. Additionally, radiological parameters such as infarct volume were not included, which could further strengthen prognostic assessment.

Despite these limitations, the study highlights a practical and low-cost biomarker that is routinely measured in clinical laboratories. The strong association between elevated bilirubin and poorer outcomes suggests that serum bilirubin, particularly total bilirubin ≥2 mg/dL, may serve as a valuable early prognostic indicator in AIS, aiding in risk stratification and guiding treatment planning.

CONCLUSION

Serum bilirubin, especially total bilirubin ≥2 mg/dL, is strongly associated with greater stroke severity and poorer functional outcomes in Acute Ischemic Stroke. It demonstrated good diagnostic accuracy and remained an independent predictor of prognosis. As a simple and routinely available marker, serum bilirubin can aid early risk stratification in AIS patients.

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