Section: General Medicine

Original Research Article

SERUM BILIRUBIN AT THE TIME OF ADMISSION AS A SEVERITY AND PROGNOSTIC INDICATOR IN ACUTE ISCHEMIC STROKE – A LONGITUDINAL OBSERVATIONAL STUDY

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ABSTRACT

Background: Cerebrovascular accident is increasing worldwide and has a significant impact on the quality of life. The prognosis of acute ischemic stroke is influenced by various factors, including underlying comorbidities, biochemical markers, and timely medical intervention. Identifying reliable, affordable and easily accessible prognostic indicators is crucial for improving patient outcomes and guiding effective treatment strategies. This study analysed the potential of serum bilirubin (SB) level as a marker for assessing the severity and prognosis of acute ischemic stroke. Understanding this relationship could help in early risk stratification, allowing for better management and enhanced patient care.

Materials and Methods: A hospital-based longitudinal observational study was conducted on 131 patients admitted with acute ischemic stroke. The National Institutes of Health Stroke Scale (NIHSS) score was assessed at the time of admission to determine stroke severity, and patients were categorized based on their score. Serum bilirubin levels at admission were measured. Modified Rankin Scale (mRS) score was calculated on the seventh day. The chi-square test /Fischer exact test was used to determine the association between categorical variables. A p value <0.05 was taken as statistically significant.

Results: NIHSS scores show a higher prevalence of severe (31.3%) and moderate-to-severe (29.8%) strokes, lower prevalence with moderate (21.4%) and mild (17.6%) cases. Higher SB levels (≥1 mg/dl) are closely associated with higher NIHSS scores (p=0.0001). mRS outcomes showed that 64.9% patients (85) had a poor prognosis indicating high disability and dependence. Higher SB levels were also associated with poor stroke prognosis based on mRS scores (p = 0.043). Lower Direct Bilirubin (DB) levels (≤0.6 mg/dl) were observed across all NIHSS severity levels, from mild to severe. However, the 0.7–0.9 mg/dl DB group showed an increased frequency with rising severity, suggesting a possible trend. But this association was not statistically significant (p = 0.061). Higher DB levels also showed a tendency towards poor prognosis. But this association was also statistically not significant (p=0.132).

Conclusion: Serum bilirubin may serve as a potential marker of acute ischemic stroke severity and prognosis. Higher serum bilirubin levels correlated with higher NIHSS scores, while lower levels (≤0.6 mg/dl) were more common in mild to moderate cases. Higher serum bilirubin levels also correlated with a greater frequency of poor prognosis. A trend suggested that higher direct bilirubin levels correlated with the severity and poorer prognosis in acute ischemic stroke. But this was not statistically significant.

Keywords: Acute Ischemic Stroke, Serum Bilirubin, NIHSS, mRS.

INTRODUCTION

Cerebrovascular accident or stroke is the world's second-leading cause of death and a major contributor to disability among individuals over 50 years of age.[1] The majority of stroke cases are ischemic strokes and occurs when blood flow to brain tissue is interrupted due to a sudden arterial blockage. This obstruction may result from either an embolus or a thrombus.[2]

When cerebral vessels are obstructed, this triggers a cascade of neurochemical processes, including nerve overactivation, oxidative stress, free radical production, blood-brain barrier disruption, lipid peroxidation-ultimately, cell death affecting neurons, glial cells, and endothelial cells. In the early stage of an ischemic stroke, oxidative stress worsens brain damage when free radical production surpasses the brain's ability to counteract them with its natural antioxidant defences. Unlike other organs, the brain has limited endogenous antioxidants, making it more vulnerable to oxidative harm.[2]

Advancements in research methods and therapeutic options have given patients with acute ischemic cerebrovascular accidents (CVA) a greater chance for a swift recovery and positive outcomes. Intravenous plasminogen activator is the treatment of choice for acute ischemic stroke. But it carries the potential for side effects, including intracranial bleed, and many patients arrive at stroke centres after the ideal treatment window of 4.5 hours has passed. Thus, timely stroke detection, risk stratification and identification of prognostic factors are crucial for effective stroke management.[3]

Bilirubin, a byproduct of heme breakdown, exhibits both neuroprotective and neurotoxic properties.[2] Nerve and neuroglia rely on maintaining low levels of unconjugated bilirubin, as it helps prevent lipid peroxidation and removes free radicals. When unconjugated bilirubin level rises excessively, it becomes cytotoxic, increasing the mitochondrial membrane permeability thereby disrupting the mitochondrial function, and reducing astrocyte activity. This results in heightened neurocyte apoptosis. As a result, high bilirubin levels are considered indicative of severe brain injury and has an unfavourable prognosis in stroke patients.[2]

According to some studies, bilirubin is a highly potent antioxidant, increasing rapidly in response to oxidative stress, such as in brain ischemia. Elevated levels of bilirubin may serve as a protective mechanism to shield the brain from ischemic injury and thereby suggests its potential as a therapeutic option for ischemic stroke.[2] In contrast, some studies conducted on acute ischemic stroke patients have shown that lower serum bilirubin values are associated with better prognoses and their level can serve as an indicator of the stroke severity.[4] Thus in acute ischemic stroke, the prognostic value of serum bilirubin is a subject of debate.[5] So the aim of this study was to determine the association between serum bilirubin at the time of admission and the severity as well as prognosis of acute ischemic stroke.

MATERIALS AND METHODS

Study Design: A longitudinal observational study.

Study population: Patients with acute ischemic stroke admitted in medical ward and ICU of a tertiary hospital in Kerala

Source of data: Patient interview and hospital records.

Study Period: 12 months (July 2023 to July 2024)

Inclusion Criteria:

All patients presenting with new onset neurological deficit following ischemic stroke admitted within 48hrs of onset of stroke

Exclusion Criteria:

Patients with diagnosed liver disease (both alcoholic and non-alcoholic), hemolytic anemia, obstructive jaundice, malignancy, autoimmune disorders, ischemic heart disease and congenital hyperbilirubinemia were excluded from the study. Patients having hemodynamic instability, current infections or sepsis, history of recent use (within the past 30 days) of hepatotoxic drugs or indigenous or traditional medications were also excluded. Patients undergoing thrombolytic therapy were also excluded.

Sample size calculation: Sample size was calculated based on the study conducted by Dr Ushalakshmi et al 'A Study on Association between Serum Bilirubin and Acute Ischemic Stroke and its Prognostic Significance'6.

Sample size calculation done by

$$n = \frac{Z^2\ 1\text{-}\alpha/2\ p(1\text{-}p)}{d^2}$$

The sample size calculated for finite population

N finite = F x n

Where

$$F = \frac{1}{1+n}$$

N proportion, p: expected proportion, d: absolute precision, 1-α/2: desired confidence level

N = population

P= 87.5%, d=2, 1-α = 95% , Population size =150

Final Sample Size: 131

Consecutive sampling method was used.

Data Collection Procedure: Data on socio-demographic details were obtained using a standardised proforma. The National Institutes of Health Stroke Scale (NIHSS) score was assessed at the time of admission to determine the stroke severity and patients were categorized based on their scores:

- 0–4: Minor stroke
- 5–15: Moderate stroke
- 16–20: Moderate to severe stroke
- 21–42: Severe stroke

Serum bilirubin levels at admission were measured using a photometric colour test with the Beckman Coulter analyser and classified into three groups:

- Group 1: ≤0.6 mg/dL
- Group 2: 0.7–0.9 mg/dL
- Group 3: ≥1 mg/dL

Serum direct bilirubin levels at admission also measured using a photometric colour test with the Beckman Coulter analyser and classified into three groups

- Group 1: ≤0.6 mg/dL
- Group 2: 0.7–0.9 mg/dL
- Group 3: ≥1 mg/dL

Patients received treatment according to standard protocols. To assess prognosis and functional recovery, the Modified Rankin Scale (mRS) score was calculated on the seventh day, either in the hospital ward or during an outpatient review if the patient had been discharged earlier.

- mRS Score ≥3: Poor prognosis
- mRS Score <3: Good prognosis

Data Processing and Analysis: The collected data were statistically analysed using the SPSS program (Statistical Package for Social Sciences) version 29. The chi-square test /Fischer exact test was used to determine the association between categorical variables. A p value <0.05 is taken as statistically significant

Ethical Clearance: Approval was obtained from the Institutional Ethics Committee (ECR/122/Inst/KL/2013/RR-19). Date and certificate number of IEC clearance- 04/07/2023, 98/2023. Informed consent was taken from each participant.

RESULTS

The mean age of the participants in this study was 57.4 ± 17.6 years, indicating that stroke predominantly affected middle-aged and older adults. 60.3% of the study participants were males and 39.7% were females. 58.8% of patients had no addictions. Smoking (23.7%) was the most common addiction, reinforcing its known role as a major stroke risk factor. Alcohol use was noted in 8.4% of patients, while 3.1% had both smoking and alcohol addiction, highlighting combined risk exposure.

25.9% of the participants were overweight or obese while 37.4% were underweight. 48.9% of the study participants suffered from some form of thyroid disorder (29% from hypothyroidism and 19.8% from hyperthyroidism). 64.1% of individuals were hypertensive and 63.4% had diabetes mellitus (DM). Chronic kidney disease (CKD) was present in 40.5% of individuals, coronary artery disease (CAD) in 38.2% and atrial fibrillation (AF) in 3.1%.

Hyponatremia was observed in 27 individuals (20.6%), making it more common than hypernatremia, which was found in only 9 individuals (6.9%). This indicates that low sodium levels are more prevalent than high sodium levels in this sample. High LDL was detected in 25.2% (33) of individuals, while the majority (74.8% or 98) had LDL level within normal value. Total cholesterol levels were high in 50.4% (66) of individuals. Low level of HDL was observed in only 11.5% (15) of individuals.

35.1% (46 individuals) of study participants had serum bilirubin (SB) in the 0.7–0.9 mg/dl range, representing the most common category. 33.6% (44 individuals) had serum bilirubin values ≤ 0.6 mg/dl, while 31.3% (41 individuals) had serum bilirubin values of 1 mg/dl or higher. The mean serum bilirubin value was 0.79± 0.24. Most of the study participants (83.2%) had a direct bilirubin (DB) ≤ 0.6 mg/dl and the mean direct bilirubin level was 0.5± 0.12mg/dl.

The middle cerebral artery (MCA) territory was involved in 76 individuals (58%), anterior cerebral artery (ACA) territory in 39 individuals (29.8%) and posterior cerebral artery (PCA) territory in 16 individuals (12.2%). According to the NIHSS score, the largest proportion of cases fall into the severe category (31.3%, 41 individuals), followed by the moderate-to-severe group (29.8%, 39 individuals). Moderate cases account for 21.4% (28 individuals), while the mild category has the lowest representation at 17.6% (23 individuals). Modified Rankin Scale (mRS) score indicated that 64.9% (85 cases) of the participants had a poor prognosis, while only 35.1% (46 cases) had a good prognosis.

Table 1: Basic characteristics of study participants

Parameter	Frequency	Percent
Age		
<40	23	17.6
40-59	51	38.9
60-80	38	29
>80	19	14.5
Gender		
Male	79	60.3
Female	52	39.7
ADDICTIONS		
No addictions	77	58.8
Smoking	31	23.7
Alcohol	11	8.4
Both	4	3.1
Others	8	6.1
BMI		

Underweight	49	37.4
Normal	48	36.6
Overweight	16	12.2
Obese	18	13.7
Thyroid status		
Normal	67	51.1
Hypothyroidism	38	29
Hyperthyroidism	26	19.8
Other Comorbidities		
HTN	84	64.1
DM	83	63.4
CKD	53	40.5
CAD	50	38.2
AF	4	3.1
Serum sodium level		
Normal serum sodium	95	72.5
Hyponatremia	27	20.6
Hypernatremia	9	6.9
Lipid status		
High LDL	33	25.2
High Total cholesterol	66	50.4
Low HDL	15	11.5
Serum Bilirubin		
≤0.6	44	33.6
0.7-0.9	46	35.1
≥ 1	41	31.3
Direct Bilirubin		
≤0.6	109	83.2
0.7-0.9	21	16
≥1	1	0.8
Vascular territory of stroke		
ACA	39	29.8
MCA	76	58
PCA	16	12.2
NIHSS		
Mild	23	17.6
Moderate	28	21.4
Moderate to severe	39	29.8
Severe	41	31.3
MRS		
Good prognosis	46	35.1
Poor prognosis	85	64.9

In the mild NIHSS category, the majority of individuals (15 cases) belong to the ≤ 0.6 mg/dl SB group, while fewer cases are seen in the 0.7–0.9 mg/dl SB (7 cases) and ≥1 mg/dl SB (1 case) groups. The moderate NIHSS category follows a similar pattern, with the highest frequency in the ≤ 0.6 mg/dl SB group (17 cases), while those in the 0.7–0.9 mg/dl SB (7 cases) and ≥1 mg/dl SB (4 cases) groups are lower. In the moderate to severe category, a shift is observed where the 0.7–0.9 mg/dl SB group has the highest frequency (17 cases), followed by the ≥1 mg/dl SB group (14 cases), and the ≤0.6 mg/dl SB group (8 cases) has the least frequency. The severe category shows a strong dominance of the ≥1 mg/dl SB group (22 cases), followed by the 0.7–0.9 mg/dl SB group (15 cases), while the ≤0.6 mg/dl SB group has the lowest number (4 cases) of patients.

Table 2: Crosstabulation between Serum Bilirubin and NIHSS Score

NIHSS	**SB**			**Total**
	≤0.6	**0.7-0.9**	**≥1**	
Mild	15	7	1	23
Moderate	17	7	4	28
Moderate to severe	8	17	14	39
Severe	4	15	22	41
Total	44	46	41	131

p value=0.0001

The majority of cases (109 out of 131, or 83.2%) fall within the ≤0.6 mg/dl DB group, and this group has the highest frequency across all NIHSS severity categories. The 0.7–0.9 mg/dl DB group (21 cases, 16%) shows an increasing trend as severity rises, with the highest count (12 cases) in the Severe category and the lowest (1 case) in Mild. The ≥1 DB group is rare (1 case, 0.8%), appearing only in the Moderate to Severe category.

Table 3: Crosstabulation between Direct Bilirubin and NIHSS Score

NIHSS	DB			Total
	≤0.6	0.7-0.9	≥1	
Mild	22	1	0	23
Moderate	26	2	0	28
Moderate to severe	32	6	1	39
Severe	29	12	0	41
Total	109	21	1	131

p value=0.061

In the ≤ 0.6 mg/dl SB group, the distribution of Good Prognosis (21 cases) and Poor Prognosis (23 cases) was nearly equal. As SB increased (0.7–0.9 mg/dl group), the number of Poor Prognosis cases (30) significantly surpassed Good Prognosis cases (16). In the ≥1 mg/dl SB group, the trend was more pronounced, with a large majority (32 cases) having a Poor Prognosis, while only 9 cases showed a Good Prognosis.

Table 4: Crosstabulation between Serum Bilirubin and mRS score

SB	mRS		Total
	Good Prognosis	Poor Prognosis	
≤0.6	21	23	44
0.7-0.9	16	30	46
≥1	9	32	41
Total	46	85	131

p value=0.043

The majority of patients (83.2%) had a DB level of ≤ 0.6 mg/dl, with a 61.5% poor prognosis rate. Only 16.8% of cases had DB levels ≥ 0.7 mg/dl, but these groups showed an even greater tendency for poor prognosis. single patient with DB ≥1 had a 100% Poor Prognosis rate.

Table 5: Crosstabulation between Direct Bilirubin and mRS

DB	mRS		Total
	Good Prognosis	Poor Prognosis	
≤0.6	42	67	109
0.7-0.9	4	17	21
≥1	0	1	1
Total	46	85	131

p value=0.132.

DISCUSSION

The present study showed that there is a significant association between serum bilirubin level at admission and NIHSS score which indicates stroke severity. As the serum bilirubin level increases, the severity of stroke also increases (p = 0.0001). This finding is consistent with the study conducted by Tian Xu et al,[7] which concluded that elevated serum total bilirubin is positively correlated with stroke severity. This suggests that higher serum bilirubin levels may be an indicator of a more severe stroke. Many studies have shown that elevated serum bilirubin concentration can lead to DNA double strand breaks and mitochondrial dysfunction resulting in increased oxidative stress which ultimately leads to cellular damage and irreversible neurological damage.[8-10] Some studies also highlight the antioxidant properties of elevated serum bilirubin and indicate that it may have a protective role against metabolic syndrome and metabolic dysfunction associated fatty liver disease which are potential risk factors for stroke.[11,12]

In this study, lower direct bilirubin levels (≤0.6) were observed across all NIHSS severity levels, from mild to severe. However, the 0.7–0.9 mg/dl DB group showed an increased frequency with rising severity, suggesting a possible trend. But this association was not statistically significant (p = 0.061). The study by Ushalakshmi et al[6] also found no correlation between direct bilirubin levels and stroke severity. But another study by Sandra Pineda et al[4] concluded that higher admission direct bilirubin levels was linked to greater stroke severity.

This study also showed a significant association between SB levels and prognosis (p = 0.043), with higher SB linked to worse outcomes. Thus serum bilirubin levels at admission may also serve as a potential marker of disease prognosis. Quping Ouyang et al. found that elevated serum bilirubin levels were significantly linked to higher mRS score and poor outcomes in acute ischemic stroke patients at 3 months and one year. Similar trend was also observed in case of elevated direct bilirubin and indirect bilirubin.[13]

This study also suggested a poorer prognosis for stroke patients with higher direct bilirubin levels. But this association was not statistically significant (p = 0.132). Ushalakshmi et al,[6] also found no correlation between direct bilirubin levels and prognosis of stroke. Similar findings were also found by Sandra Pineda et al6. In contrast, Elnaz et

al. demonstrated that increased serum bilirubin levels, direct and indirect bilirubin levels, along with NIHSS score and ischemic area strongly predicted patient outcomes.[14]

Identifying reliable and cost-effective biomarkers will enhance stroke management by guiding timely interventions and thereby will help in improving the stroke outcomes. Based on the findings of this study, serum bilirubin at admission is an easily accessible and cost-effective indicator of the stroke severity and the outcome of stroke. However some studies highlight its antioxidant properties suggesting a protective role. Hence this dual nature underscores the need for further research to clarify its precise role, which could significantly enhance its clinical utility in stroke risk stratification, prognosis, and targeted therapeutic strategies.

This study is also not without limitations. The cross-sectional nature of the study, low sample size and single centre study limits the generalizability of the results. The effect of possible confounding factors like metabolic syndrome and metabolic dysfunction associated fatty liver disease could not be assessed as it was beyond the scope of this study. Future large scale multi-centre studies incorporating all these factors will help in precisely defining the utility of serum bilirubin in the risk stratification and prognosis of stroke patients.

CONCLUSION

This study adds to the evidence that serum bilirubin at admission may be used as a potential biomarker of stroke severity and outcome and thereby enhance the stroke management by guiding timely intervention strategies.

Recommendation

Early identification of the severity and prognosis of stroke based on affordable and easily accessible biomarkers like serum bilirubin will help in timely implementation of therapeutic interventions and thereby will significantly improve the outcome of stroke.

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