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Correlation of Serum Bilirubin with Severity of Acute Ischemic Stroke

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ABSTRACT

Serum bilirubin is associated with stroke severity, existing data on this relationship remain limited and inconclusive. **Objectives:** To determine the correlation between serum bilirubin and the National Institute of Health stroke scale score in patients with acute ischemic stroke. **Methods:** This cross-sectional study was done at the Medical Emergency of Mayo Hospital Lahore from June 2022 to December 2022. A total of 205 patients suffering from acute ischemic stroke were included. Serum bilirubin was obtained within 24 hours of the onset of stroke at presentation, and stroke severity was assessed same time using NIHSS. Data analysis was done using SPSS version 26.0. Pearson correlation was determined between serum bilirubin and NIHSS score at presentation. **Results:** In current study population, 44.5% of patients were diabetics, 77.6% were hypertensive, and 27.8% were smokers. Mean serum bilirubin level was 0.98 ± 0.19 mg/dL, and mean NIHSS score is 19.51 ± 8.94, Pearson correlation coefficient between bilirubin and NIHSS is -0.082, p-value=0.240, statistically not significant. **Conclusions:** It was concluded that in our study, a weak negative correlation was observed between serum bilirubin levels and NIHSS scores in patients with acute ischemic stroke. This suggests that higher bilirubin levels may have a slight protective effect, as stroke severity (NIHSS scores) tended to decrease minimally with increasing bilirubin levels.

INTRODUCTION

Stroke is a focal neurological deficit persisting for more than 24 hours and vascular in origin [1]. Ischemic stroke is caused by occlusion of the blood supply to a particular region of the brain [2]. The most important risk factors for stroke include hypertension, dyslipidemia, diabetes mellitus, smoking, advanced age, sex, and structural heart defects [3]. Stroke is the fifth major cause of hospitalization, according to the WHO, affecting 15 million people, out of which 5 million suffer death and 5 million experience permanent disability [4]. In Pakistan, the incidence of stroke per year is 95 per 100,000 [5]. Bilirubin is a byproduct of heme degradation with anti-inflammatory, antioxidant, antiproliferative, and blood lipid-modulating properties [6]. Studies have shown that serum bilirubin levels increase after stroke [7, 8]. It has been revealed that bilirubin possesses strong anti-inflammatory, antioxidant, and neuroprotective properties [9]. Another study supported the protective effect of bilirubin in patients with stroke [10]. However, various studies suggest that an increase in serum bilirubin is associated with more severe stroke [11]. Understanding this relationship is crucial, as bilirubin could serve as a potential biomarker for stroke prognosis and influence future therapeutic strategies. As previous studies have

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shown controversial results, the definitive verdict on this issue remains unclear. Moreover, no local studies have been conducted to explore this relationship.

Acute ischemic stroke is a leading cause of mortality and disability worldwide, and early prognostic biomarkers are essential for predicting disease severity and improving outcomes. Although serum bilirubin has been proposed as a potential neuroprotective antioxidant and prognostic marker in stroke, existing evidence remains conflicting, with studies reporting both protective and harmful associations with stroke severity. Moreover, limited local data are available to clarify this relationship in the Pakistani population. This research aims to contribute valuable insights to the existing body of knowledge and prove beneficial to healthcare providers and medical students.

METHODS

This cross-sectional study was done at the Medical Emergency of Mayo Hospital Lahore from June 2022 to December 2022, after taking formal approval from the College of Physicians and Surgeons, Pakistan, before (REU No: 44705). A sample size of 205 patients was estimated, expected correlation coefficient (r=0.224) was selected based on prior studies that have explored the association between serum bilirubin levels and ischemic stroke severity [12]. Specifically, previous research has reported weak to moderate correlations in similar clinical settings. To ensure adequate statistical power, sample size calculation was performed with α=5% and ß=10%, achieving a power of 90%. For enrollment of patient's non-probability consecutive technique was used. Patients of either gender, aged 20-80 years, presenting to the Medical Emergency or neurology department with acute ischemic stroke (weakness of one or more parts of the body, persisting for more than 24 hours, with hypodense area on CT brain plain) were included. Patients with history of previous ischemic stroke, cerebral infections (such as meningoencephalitis or brain abscess), space-occupying lesions, head trauma, elevated liver enzymes (ALT or AST ≥40 IU/L), chronic liver disease (cirrhotic liver on ultrasound), any active malignancy, or those on medications that can derange liver function tests (such as anti-epileptics and anti-tuberculous agents) were excluded. Before enrollment, written informed consent was obtained from the patient/or relative. After following aseptic protocols, a venous blood sample of 5 mL was collected within 24 hours of patient intake. In the pathology department of Mayo Hospital, Lahore, the total serum bilirubin level (mg/dL) was measured using the enzymatic colorimetric method, as per established laboratory standards. This technique utilizes the reaction of bilirubin with diazotized sulfanilic acid, which yields a colored compound whose intensity, and hence concentration of bilirubin, can be measured spectrophotometric-ally. Stroke severity was evaluated using the NIH Stroke Scale (NIHSS), which is a 15-item diagnostic checklist for stroke used to evaluate the severity of stroke-related disability or level of recovery from a stroke. These abilities include consciousness, visual fields, motor and sensory function, language, and coordination, with a possible score ranging from 0, which indicates no deficit, to 42, which indicates severe stroke [13]. Data were collected by the researcher using a specially designed Proforma and presented in the form of tables. Data were analyzed with SPSS version 26.0. Numerical variables were presented as mean ± SD, and qualitative variables as frequency and percentages. A relationship between serum bilirubin levels and the severity of acute ischemic stroke was examined by Pearson correlation; p-value≤0.05 was taken as significant.

RESULTS

Among 205 patients, 126 patients (61.5%) were males and 79 patients (38.5%) were female, and the mean age of our sampled population was 59.0 ± 8.8 years, with an age range of 38- 77 years. 120 patients (59%) were under ≤60 years' age, and 85 patients (41%) were classified as >60 years of age. Risk factors studied found 45% of patients were diabetics, 78% were hypertensive, and 28% were active smokers. Regarding the timing of their presentation, 48% arrived within 8 hours of symptom onset, 42% presented between 8 and 14 hours, and 18% between 14 and 24 hours after symptoms began(Table 1).

Table 1: Patient Related Socio-Demographic Characteristics (n=205)

Characteristics		n (%)
Age (Years) Mean ± SD		56.8 ± 8.8
Age	≤60 Years	120 (59%)
	>60 Years	85 (41%)
Gender	Female	79 (38.5%)
	Male	126 (61.5%)
Diabetes	Yes	92 (45%)
	No	113(55%)
Hypertension	Yes	159 (78%)
	No	46 (22%)
Active smokers	Yes	57 (28%)
	No	148 (72%)
Onset of symptoms	Up to 8 Hours	83 (40%)
	>8-14 Hours	86 (42%)
	>14-24 Hours	36 (18%)
Serum Bilirubin(mg/dl)	0.98 ± 0.19	
NIHSS	19.51 ± 8.94	

The mean serum bilirubin level was 0.98 ± 0.19 mg/dL, and the mean NIHSS score was 19.51 ± 8.94. The Pearson correlation coefficient (r) between bilirubin and NIHSS was -0.082, indicating a weak negative correlation between the two variables. The p-value of 0.240 suggests that this

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correlation was not statistically significant, at a threshold of 0.05 (Table 2).

Table 2: Pearson Correlation (r) Between Serum Bilirubin and Stroke Severity

Variables	Mean ± SD	r	p-Value
Bilirubin (mg/dl)	0.98 ± 0.19	-0.082	0.240
NIHSS	19.51 ± 8.94		

DISCUSSION

The incidence of ischemic stroke among younger adults has been rising, with rates increasing from 11.0 to 22.9 per 100,000 in individuals aged 18–55 years and from 5.4 to 12.8 per 100,000 in those aged 18–45 years [14]. Our study aligns with these trends, as 59% of patients were aged ≤60 years, while 41% were older than 60 years. Male predominance observed (61.5% male vs. 38.5% female) is consistent with findings from Kanwal *et al.*, who reported a similar distribution (64% male vs. 36% female) [15], as well as a study from Germany that documented an increasing incidence of ischemic stroke among men [16]. Regarding risk factors, hypertension emerged as most prevalent (78%), followed by diabetes (45%) and smoking (28%). This is in line with prior studies that have consistently identified hypertension as the leading risk factor for stroke [17]. However, some studies report variations, such as higher prevalence of hypertension (86.7%) and lower prevalence of diabetes (24.5%) in ischemic stroke patients [18]. These differences may stem from variations in study populations, ethnicity, lifestyle factors, or healthcare accessibility influencing risk factor distribution. Our study primarily investigated the correlation between serum bilirubin levels and severity of acute ischemic stroke. We found that higher bilirubin levels were associated with decrease in NIHSS scores at admission (r=-0.082), suggesting potential neuroprotective role. Several studies have explored this association, with meta-analysis reporting significant positive correlation between total bilirubin levels and stroke severity, particularly in patients with NIHSS scores ≥8. The pooled OR of 1.14 indicated that elevated bilirubin levels were linked to increased stroke severity, with sensitivity analyses reinforcing this trend [19]. Yu *et al.*, also found that lower bilirubin levels correlated with more severe and extensive intracranial atherosclerosis (p<0.001) [20], supporting the notion that bilirubin's antioxidant properties may have a protective effect. However, conflicting evidence exists. Peng *et al.*, reported that elevated bilirubin levels were associated with more severe strokes and poorer outcomes (p=0.014) [21]. Another study found significant differences in bilirubin levels between patients with good and poor prognoses, highlighting bilirubin's potential as a prognostic marker [22]. These discrepancies may be attributed to differences in patient populations, stroke subtypes, bilirubin metabolism, and statistical methodologies. The variability in study designs, including sample size, adjustment for confounding factors, and inclusion criteria, could also contribute to differing conclusions.

This study is limited by its single-center design, use of non-probability consecutive sampling, and cross-sectional nature, which restricts causal interpretation and generalizability of findings. Additionally, potential confounders such as inflammatory markers and long-term outcomes were not assessed. Future research should include large-scale multicenter longitudinal studies to better evaluate the prognostic role of serum bilirubin in stroke severity and recovery. Further studies incorporating serial bilirubin measurements and adjustment for broader clinical variables are recommended to clarify its true clinical utility.

CONCLUSIONS

It was concluded that in our study, a weak negative correlation was observed between serum bilirubin levels and NIHSS scores in patients with acute ischemic stroke. This suggests that higher bilirubin levels may have a slight protective effect, as stroke severity (NIHSS scores) tended to decrease minimally with increasing bilirubin levels.

Authors' Contribution

Conceptualization: MNA
Methodology: MNA, SK, IAM, AA, AS, FM
Formal analysis: MNA, HW
Writing and Drafting: IAM, AA
Review and Editing: MNA, SK, IAM, AA, AS, FM

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

All the authors declare no conflict of interest.

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