

PAKISTAN JOURNAL OF HEALTH SCIENCES

(LAHORE)

https://thejas.com.pk/index.php/pjhs ISSN (E): 2790-9352, (P): 2790-9344 Volume 6, Issue 04 (April 2025)



Original Article



Correlation of Serum Bilirubin with Severity of Acute Ischemic Stroke

Muhammad Naeem Awan¹, Sibgha Kanwal², Imran Ahmed Moinuddin³, Aniqa Ashfaq⁴, Anam Sadia², Fariha Munir¹ and Humaira Waseem⁵

- ¹Department of Medicine, Mayo Hospital, Lahore, Pakistan
- ²Department of Medicine, Fatima Jinnah Medical University, Sir Ganga Ram Hospital, Lahore, Pakistan
- ³Department of Medicine, University College of Medicine and Dentistry, Lahore, Pakistan
- ⁴Department of Medicine, Combined Military Hospital Lahore Medical College and Institute of Dentistry, Lahore, Pakistan

ARTICLE INFO

Keywords:

Ischemic Stroke, Stroke Severity, Serum Bilirubin, National Institute of Health Stroke Scale

How to Cite

Awan, M. N., Kanwal, S., Moinuddin, I. A., Ashfaq, A., Sadia, A., Munir, F., & Waseem, H. (2025). Correlation of Serum Bilirubin with Severity of Acute Ischemic Stroke: Serum Bilirubin with Severity of Acute Ischemic Stroke. Pakistan Journal of Health S c i e n c e s , 6 (4) , 1 8 5 - 1 8 8 . https://doi.org/10.54393/pjhs.v6i4.2845

*Corresponding Author:

Muhammad Naeem Awan

Department of Medicine, Mayo Hospital, Lahore,

Pakistan

awannaeem57@gmail.com

Received date: 2nd February, 2025 Revised date: 11th April, 2025 Acceptance date: 23rd April, 2025 Published date: 30th April, 2025

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

⁵Department of Data Sciences, Inti International University, Malaysia

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

This study aims to investigate the connection between serum bilirubin levels and ischemic stroke. 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 β =10%, achieving a power of 90%. For enrollment of patient's nonprobability 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 \leq 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 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.

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 review and editing: IAM, AA

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

REFERENCES

- [1] Murphy SJ and Werring DJ. Stroke: Causes and Clinical Features. Medicine. 2020 Sep; 48(9): 561-6. doi:10.1016/j.mpmed.2020.06.002.
- [2] Walter K. What is Acute Ischemic Stroke? Journal of the American Medical Association. 2022 Mar; 327(9): 885-. doi: 10.1001/jama.2022.1420.
- [3] Powers WJ. Acute Ischemic Stroke. New England Journal of Medicine. 2020 Jul; 383(3): 252-60. doi: 10.1056/NEJMcp1917030.
- [4] Saini V, Guada L, Yavagal DR. Global Epidemiology of Stroke and Access to Acute Ischemic Stroke Interventions. Neurology. 2021 Nov; 97(20_Supplement_2): S6-16. doi: 10.1212/WNL.0000 000000012781.
- [5] Zaidi DA, Yaqoob E, Chaurasia B, Javed S. Addressing Stroke Care Deficiencies in Pakistan: A Call for Nationwide Reforms and Strategic Initiatives. Neurosurgical Review. 2024 Aug; 47(1): 396. doi: 10.1007/s10143-024-02648-x.
- [6] Vitek L, Hinds TD, Stec DE, Tiribelli C. The Physiology of Bilirubin: Health and Disease Equilibrium. Trends in Molecular Medicine. 2023 Apr; 29(4): 315-28. doi: 10.1016/j.molmed.2023.01.007.
- [7] Ouyang Q, Wang A, Tian X, Zuo Y, Liu Z, Xu Q, Meng X, Chen P, Li H, Wang Y. Serum Bilirubin Levels Are Associated with Poor Functional Outcomes in Patients with Acute Ischemic Stroke or Transient Ischemic Attack. BioMed Central Neurology. 2021 Dec; 21: 1-2. doi: 10.1186/s12883-021-02398-z.
- [8] Zhao K, Wang R, Chen R, Liu J, Ye Q, Wang K, Li J. Association Between Bilirubin Levels with Incidence and Prognosis of Stroke: A Meta-Analysis. Frontiers in Neuroscience. 2023 Feb; 17: 1122235. doi:

- 10.3389/fnins.2023.1122235.
- [9] Jayanti S, Moretti R, Tiribelli C, Gazzin S. Bilirubin and Inflammation in Neurodegenerative and Other Neurological Diseases. Neuro-immunology and Neuro-inflammation. 2020; 2020(7): 92-108. doi: 10.20517/2347-8659.2019.14.
- [10] Wang G, Qiao L, Tang Z, Zhou S, Min J, Li M. Association Between Bilirubin Levels and Risk of Stroke: A Systematic Review and Meta-Analysis. British Medical Journal Open. 2023 May; 13(5): e064433.doi:10.1136/bmjopen-2022-064433.
- [11] Wang J, Zhang X, Zhang Z, Zhang Y, Zhang J, Li H et al. Baseline Serum Bilirubin and Risk of First Stroke in Hypertensive Patients. Journal of the American Heart Association. 2020 Jun; 9(12): e015799. doi: 10.1 161/JAHA.119.015799.
- [12] Luo Y, Li JW, Lu ZJ, Wang C, Guan DN, Xu Y. Serum Bilirubin After Acute Ischemic Stroke Is Associated with Stroke Severity. Current Neurovascular Research. 2012 May; 9(2): 128–32. doi: 10.2174/156720 212800410876.
- [13] Khan MS, Ahmad S, Ghafoor B, Shah MH, Mumtaz H, Ahmad W et al. Inpatient Assessment of the Neurological Outcome of Acute Stroke Patients Based on the National Institute of Health Stroke Scale (NIHSS). Annals of Medicine and Surgery. 2022 Oct; 82. doi: 10.1016/j.amsu.2022.104770.
- [14] Béjot Y, Duloquin G, Thomas Q, Mohr S, Garnier L, Graber M et al. Temporal Trends in the Incidence of Ischemic Stroke in Young Adults: Dijon Stroke Registry. Neuro-epidemiology. 2021 Jun; 55(3): 239-44. doi: 10.1159/000516054.
- [15] Kanwal S, Yousaf Q, Jamil A, Arshad W, Qadir M, Tahir MU et al. Association Between Acute Ischemic Stroke and Raised Serum Gamma Glutamyl Transferase: Association Between Acute Ischemic Stroke and Serum Gamma Glutamyl Transferase. Pakistan Journal of Health Sciences. 2024 Sep: 27-31. doi: 10.54393/pjhs.v5i09.2031.
- [16] Schaefer J, Bohmann FO, Misselwitz B, Foerch C. Diverging Time Trends of Gender-specific Ischemic Stroke Incidence-10-year-analysis of A State-wide Registry in Germany. Stroke. 2022 Feb; 53(Suppl_1): A60-. doi: 10.1161/str.53.suppl_1.60.
- [17] Yi X, Luo H, Zhou J, Yu M, Chen X, Tan L et al. Prevalence of Stroke and Stroke Related Risk Factors: A Population Based Cross Sectional Survey in Southwestern China. BioMed Central Neurology. 2020 Dec; 20: 1-0. doi: 10.1186/s12883-019-1592-z.
- [18] Xing L, Jing L, Tian Y, Liu S, Lin M, Du Z et al. High Prevalence of Stroke and Uncontrolled Associated Risk Factors Are Major Public Health Challenges in

- Rural Northeast China: A Population-Based Study. International Journal of Stroke. 2020 Jun; 15(4): 399-411. doi: 10.1177/1747493019851280.
- [19] Song Y, Zhang X, Li C, Xu S, Zhou B, Wu X. Is Bilirubin Associated with the Severity of Ischemic Stroke? A Dose Response Meta-Analysis. Journal of Clinical Medicine. 2022 Jun; 11(12): 3262. doi: 10.3390/ jcm11123262.
- [20] Yu F, Zhang L, Liao D, Luo Y, Feng X, Liu Z et al. Serum Bilirubin Levels and Extent of Symptomatic Intracranial Atherosclerotic Stenosis in Acute Ischemic Stroke: A Cross-Sectional Study. Frontiers in Neurology. 2021 Aug; 12: 714098. doi: 10.3389/ fneur.2021.714098.
- [21] Peng Q, Bi R, Chen S, Chen J, Li Z, Li J et al. Predictive Value of Different Bilirubin Subtypes for Clinical Outcomes in Patients with Acute Ischemic Stroke Receiving Thrombolysis Therapy. Cognitive Neuroscience Society Neuroscience and Therapeutics. 2022 Feb; 28(2): 226-36. doi: 10.1111/cns.13759.
- [22] Duan H, Cheng Z, Yun HJ, Cai L, Tong Y, Han Z et al. Serum Bilirubin Associated with Stroke Severity and Prognosis: Preliminary Findings on Liver Function After Acute Ischemic Stroke. Neurological Research. 2023 Jan; 45(1): 62-9. doi: 10.1080/01616412.2022.211 9724.