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Association between Serum Total Cholesterol Levels and Unfavourable Outcome in Patients with Spontaneous Intracerebral Hemorrhage

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ABSTRACT

Background: To determine the association between low serum total cholesterol levels and unfavorable outcomes in patients with spontaneous ICH. **Methods:** This prospective cohort study was conducted in the Department of Neurosurgery, Shaikh Zayed Hospital, Lahore, from February 2025 to June 2025. A total of 200 patients aged 30–90 years presenting within 72 hours of ICH onset were enrolled and categorized into two groups based on fasting serum TC levels: exposed group (<160 mg/dL) and unexposed group (≥160 mg/dL). Neurological deficit at admission was objectively graded using the National Institutes of Health Stroke Scale (NIHSS) to determine stroke severity, and functional outcome was measured using the Modified Rankin Scale (mRS). Data were analyzed using SPSS version 21, and relative risk (RR) with 95% CI was calculated to assess association, significance was defined as a p-value less than or equal to 0.05. **Results:** Patients with low TC had a higher frequency of severe stroke (46% vs. 28%, p=0.009) and unfavorable outcome (61% vs. 38%, p=0.001). The relative risk of unfavorable outcome in the low cholesterol group was 1.60 (95% CI: 1.21–2.13). The association remained significant after stratification by age, gender, hypertension, and diabetes. **Conclusion:** Low serum total cholesterol levels are significantly associated with greater stroke severity and increased risk of unfavorable outcomes in patients with spontaneous ICH. Serum cholesterol may serve as an independent prognostic biomarker in acute ICH.

INTRODUCTION

Intracerebral hemorrhage (ICH) is a major cause of morbidity and mortality worldwide, accounting for 10–15% of all strokes[1]. The condition results from bleeding into the brain parenchyma due to rupture of small cerebral vessels, most commonly related to chronic hypertension, cerebral amyloid angiopathy, or vascular malformations [2]. Despite advances in critical care and neuroimaging, ICH continues to carry a high 30-day case fatality rate of 40–50%, and many survivors are left with long-term disability [3].

Dyslipidemia is a well-recognized risk factor for ischemic stroke, but its relationship with hemorrhagic stroke is more complex[4]. Recent evidence suggests that lower levels of serum total cholesterol (TC) may be associated with an increased risk of ICH and poorer clinical outcomes. Hypocholesterolemia has been hypothesized to impair vascular wall integrity, predisposing to microaneurysm formation and rupture, which may contribute to hematoma expansion and worse neurological deficits. Studies from Taiwan, China, and Bangladesh have reported higher rates of severe neurological impairment and poor functional outcomes among patients with low TC levels compared to those with normal or elevated levels [5-7].

In the Pakistani population, evidence linking serum cholesterol with prognosis in intracerebral hemorrhage remains scarce. Recognizing measurable prognostic factors is essential for better risk categorization and for planning targeted management strategies. This study was designed to determine the association between serum TC levels and unfavorable outcomes in spontaneous ICH, using validated clinical tools (NIHSS, mRS) to assess stroke severity and functional recovery.

MATERIALS AND METHODS

This was a prospective cohort study designed to investigate the association between serum total cholesterol levels and unfavorable among individuals diagnosed with intracerebral hemorrhage (ICH). The study adhered to STROBE guidelines for observational studies.

The research was conducted at the Department of Neurosurgery, Shaikh Zayed Hospital, Lahore, from February 2025 to June 2025 which serves as a tertiary care center and referral unit with inpatient, emergency, and neuroimaging facilities.

Ethical clearance was obtained from the 'Research Evaluation Unit (REU) of the College of Physicians and Surgeons Pakistan (CPSP) under reference number CPSP/REU/NSG-2023-072-954, dated February 4, 2025'. The study was carried out, following ethical approval and written informed consent was obtained from all participants or their legally authorized representatives prior to enrollment.

A total of 200 patients (100 exposed, 100 unexposed) were included. The sample size was calculated using OpenEpi version 3.01, with a 95% confidence interval and 80% power, based on previously reported rates of unfavorable outcomes in low cholesterol patients (27.2%) compared to normal/high cholesterol patients (13.2%). To account for dropouts and maintain study power, the final sample size was fixed at 200.

Inclusion Criteria

- Patients aged 30–90 years with a diagnosis of spontaneous ICH confirmed on CT/MRI brain.
- Admission within 72 hours of symptom onset.
- Baseline fasting serum cholesterol measured at admission.

Exclusion Criteria

- Patients with known cardiac disease on lipid-lowering therapy.
- Diabetes mellitus with a duration of more than 20 years.
- Hemorrhagic transformation of ischemic stroke, tumor-related hemorrhage, subarachnoid hemorrhage, or traumatic ICH.
- ICH due to vascular malformations, venous sinus thrombosis, or aneurysmal rupture.
- Patients receiving anticoagulant therapy at presentation.

Non-probability consecutive sampling was used. Eligible patients presenting to the neurosurgical emergency or OPD during the study period were recruited consecutively until the desired sample size was reached.

After obtaining informed consent, demographic details (age, gender, weight), comorbidities (hypertension, diabetes), and neuroimaging findings were recorded on a predesigned proforma. Blood samples were drawn in the fasting state for serum total cholesterol measurement and processed in the hospital's central laboratory. Based on cholesterol levels, patients were classified as exposed (<160 mg/dL) or unexposed (≥160 mg/dL). Stroke severity was graded at presentation with the NIHSS, and functional status was reassessed using the 'Modified Rankin Scale (mRS)' during scheduled visits or telephone follow-up

All neurological assessments were performed by trained clinicians using standardized scoring systems to minimize observer bias. Laboratory analysis was performed in the same facility for all patients to ensure consistency. Data entry was double-checked by an independent researcher to reduce clerical errors.

Data were analyzed using SPSS version 21. Quantitative variables such as 'age were expressed as mean ± standard deviation, while qualitative variables such as gender, comorbidities, stroke severity, and outcomes were presented as frequencies and percentages'. The normality of quantitative data was tested using the Shapiro-Wilk test. Associations between cholesterol levels and outcomes were evaluated using the Chi-square test. Relative risk (RR) with 95% confidence interval (CI) was calculated, and a p-value ≤0.05 was considered statistically significant. Stratification by age, gender, hypertension, and diabetes was performed to control for confounding variables, followed by post-stratification RR and p-values.

RESULTS

This study enrolled 200 individuals diagnosed with spontaneous intracerebral hemorrhage, allocating '100 to the low-cholesterol (exposed) group and 100 to the normal or high-cholesterol group' The mean age was comparable between groups (61.3 ± 11.4 vs. 60.8 ± 10.9 years, p=0.68). Males constituted 58% of the exposed group and 55% of the unexposed group, with no significant difference (p=0.67). Hypertension was the most frequent comorbidity, present in 67% and 64% of patients in the exposed and unexposed groups respectively. Diabetes mellitus was reported in roughly one-third of patients. There were no statistically significant differences in baseline characteristics between groups, suggesting that the two cohorts were comparable at enrollment.

Table 1

Baseline characteristics of patients with spontaneous intracerebral hemorrhage according to serum cholesterol status

Variable	Exposed (n=100)	Unexposed (n=100)	Total (n=200)	p-value
Age (years) (Mean ± SD)	61.3 ± 11.4	60.8 ± 10.9	61.1 ± 11.2	0.68
Gender				
Male	58 (58%)	55 (55%)	113 (56.5%)	0.67
Female	42 (42%)	45 (45%)	87 (43.5%)	
Hypertension	67 (67%)	64 (64%)	131 (65.5%)	0.64
Diabetes Mellitus	34 (34%)	29 (29%)	63 (31.5%)	0.45

Stroke severity was assessed using the NIH Stroke Scale (NIHSS) at presentation. Severe stroke (NIHSS ≥15) was more frequently observed in the exposed group (46%) compared to the unexposed group (28%). The difference was statistically significant (p=0.009), indicating that low cholesterol levels were associated with more severe neurological deficits at admission.

Table 2

Stroke severity on admission (NIHSS score) in relation to cholesterol levels

NIHSS Score on Admission	Exposed (n=100)	Unexposed (n=100)	Total (n=200)	p-value
Mild/Moderate (<15)	54 (54%)	72 (72%)	126 (63%)	0.009
Severe (≥15)	46 (46%)	28 (28%)	74 (37%)	

Functional outcome was evaluated using the Modified Rankin Scale (mRS). Unfavorable outcomes (mRS 2–6) were significantly higher in the exposed group (61%) compared to the unexposed group (38%) (p=0.001). These findings suggest that low cholesterol levels were strongly associated with poorer functional recovery.

Table 3
Functional outcomes (Modified Rankin Scale) between cholesterol groups

Modified Rankin Scale (mRS)	Exposed (n=100)	Unexposed (n=100)	Total (n=200)	p-value
Favorable (0–1)	39 (39%)	62 (62%)	101 (50.5%)	0.001
Unfavorable (2–6)	61 (61%)	38 (38%)	99 (49.5%)	

Relative risk (RR) analysis confirmed that patients with low cholesterol levels had a 1.60 times higher risk of unfavorable outcomes compared to patients with normal/high cholesterol levels. This association was statistically significant (p=0.001), supporting the hypothesis that hypocholesterolemia is linked with poorer prognosis in intracerebral hemorrhage.

Table 4
Relative risk of unfavorable outcomes in relation to cholesterol levels

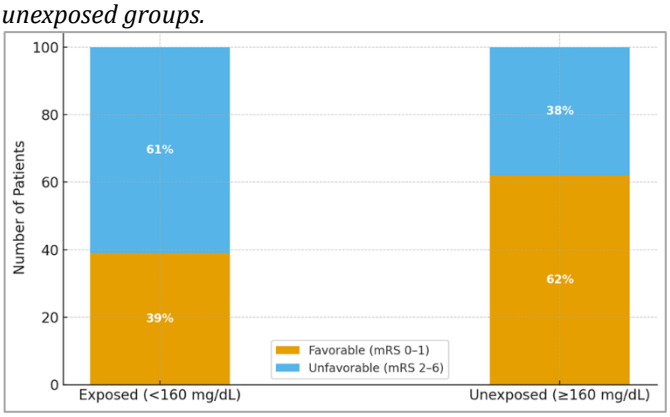
Outcome	Exposed (n=100)	Unexposed (n=100)	Relative Risk (95% CI)	p-value
Unfavorable Outcome (mRS 2–6)	61 (61%)	38 (38%)	1.60 (1.21–2.13)	0.001

After stratification by age, gender, hypertension, and diabetes, the association between low cholesterol and unfavorable outcomes remained significant across most subgroups. The effect appeared slightly stronger among hypertensive patients and those aged ≥60 years.

Table 5
Stratified analysis of cholesterol levels and unfavorable outcomes by demographic and clinical variables.

Stratification Variable	RR (95% CI)	p-value
Age <60 years	1.54 (1.12–2.12)	0.008
Age ≥60 years	1.63 (1.19–2.25)	0.004
Male	1.57 (1.14–2.16)	0.006
Female	1.63 (1.10–2.41)	0.015
Hypertension Present	1.68 (1.21–2.34)	0.003
Hypertension Absent	1.47 (1.02–2.12)	0.037
Diabetes Present	1.59 (1.11–2.29)	0.012
Diabetes Absent	1.61 (1.14–2.27)	0.007

Figure 1
Stacked bar graph comparing favorable and unfavorable outcomes between the exposed (low cholesterol) and unexposed groups.



DISCUSSION

This study observed that individuals diagnosed with spontaneous ICH presenting with lower serum total cholesterol levels (below 160 mg/dL) are significantly more likely to present with more severe neurological deficits (higher NIHSS at admission) and to experience unfavorable functional outcomes (mRS 2–6). The relative risk of unfavorable outcome in the low-cholesterol group compared to the normal/high cholesterol group was elevated, and this association held true even after stratification by age, gender, hypertension, and diabetes status [8, 9].

The findings are consistent with several recent investigations. Studies demonstrated that lower LDL-cholesterol levels independently correlated with more severe ICH and poorer short-term and long-term outcomes [10, 11]. Similarly, research into 'non-HDL cholesterol (non-HDLC) and 3-month prognosis among ICH patients showed that higher non-HDLC levels were associated with better functional outcomes' [12-14]. Study also suggested that lower LDL-C levels are associated with increased risk and poorer prognosis in ICH [15, 16].

These converging lines of evidence suggest possible pathophysiological mechanisms. Low cholesterol may impair structural integrity of vascular endothelium, reduce capacity for repair of small vessel walls, or reduce the ability to respond to injury [17, 18]. Cholesterol is a component of cell membranes, and low levels might render vessels more fragile, possibly contributing to larger hematoma expansion, worse perihematomal edema, or slowed recovery. Another possible mechanism is that very low cholesterol reflects poorer nutritional status or more systemic illness at baseline, which could independently worsen outcomes.

The current study adds strength to these earlier works by using a well-defined exposed and unexposed cohort, applying standard measures of severity (NIHSS) and outcome (mRS) [19, 20]. The stratification showing that the association persists across age, gender, hypertension, and diabetes also suggests that low total cholesterol is not simply a marker of other risk factors, but may independently contribute to poor prognosis in ICH.

Some limitations must be acknowledged. First, this study's sample size, while sufficient to detect statistically significant associations, may not be large enough to allow detailed subgroup analyses beyond those performed (e.g., location of hemorrhage or hematoma volume). Second, cholesterol subfractions (such as LDL, HDL, non-HDL) were not evaluated, so the relative contributions of different lipid types cannot be determined. Third, potential confounding variables such as hematoma size, location, intraventricular extension, and acute medical complications (e.g., blood pressure control, use of statins after admission) were not fully controlled for, which may influence outcome. Fourth, longer-term outcomes (six months, one year) were not assessed. Finally, nutritional status or other systemic conditions (like liver disease) that might influence cholesterol levels were not specifically measured.

Despite these limitations, the study has clinical implications. Measurement of serum total cholesterol at admission provides useful prognostic information in ICH. Low serum cholesterol may serve as an indicator of higher

risk, helping clinicians in stratifying patients, counseling families, and potentially guiding more intensive monitoring or supportive care. Future research should involve larger multi-center cohorts, include lipid subtypes, quantify hematoma characteristics, and investigate whether modifying cholesterol levels has any effect on outcome.

CONCLUSION

This study demonstrates that low total serum cholesterol levels are associated with greater likelihood of poor 'functional' recovery in individuals suffering from spontaneous ICH. Admission cholesterol level may serve as an independent prognostic marker in ICH.

REFERENCES

1. Xu, W., Wang, P., Wan, J., He, J., Zheng, Y., Liu, Y., Peng, L., Xiao, Y., Feng, Y., Cheng, X., Fang, F., & Zhang, Y. (2025). Neutrophil to high-density lipoprotein cholesterol ratio predicts deep venous thrombosis in spontaneous intracerebral hemorrhage. *Scientific Reports*, *15*(1). https://doi.org/10.1038/s41598-025-08520-2
2. Wu, L., Wang, A., Kang, K., Zhang, X., Zhao, X., & Wang, W. (2023). Low LDL-C/HDL-C ratio is associated with poor clinical outcome after Intracerebral hemorrhage: A retrospective analysis of multicenter, prospective cohort data in China. *Neurocritical Care*, *41*(1), 29-37. https://doi.org/10.1007/s12028-023-01905-z
3. Ismail, M. H., Khalil IbrahIm, G. A., & Elaidy, S. A. (2024). Serum biomarkers predicting prognosis of spontaneous Intracerebral hemorrhage. *Zagazig University Medical Journal*, *30*(7), 3298-3307. https://doi.org/10.21608/zumj.2024.303983.3473
4. Lee, K., & Hsu, L. (2025). Impact of LDL-C levels on severity and outcome of intracranial haemorrhage: A single-centre retrospective study. *BMJ Neurology Open*, *7*(1), e000850. https://doi.org/10.1136/bmjno-2024-000850
5. Wei, L., Liu, Z., Cai, H., Tian, H., Tan, J., Zhang, Y., Wang, L., Gao, Y., Wang, J., & Wang, L. (2024). Serum cholesterol and interleukin-10 are associated with post-intracerebral hemorrhage depression in patients with acute primary supratentorial intracerebral hemorrhage. *Brain Hemorrhages*, *5*(5), 237-242. https://doi.org/10.1016/j.hest.2024.05.006
6. Olalusi, O. V., Asowata, O. J., Sarfo, F. S., Akpa, O. M., Akinyemi, J., Yaria, J., Makanjuola, A., Okekunle, A. P., Alabi, F., Olowoyo, P., Fakunle, A., Adebayo, O., Ogah, O., Arulogun, O., Chukwuonye, I., Onyeonoro, U., Calys-Tagoe, B., Appiah, L., Singh, A., … Owolabi, M. (2025). Low-density lipoprotein cholesterol and severity of intracerebral hemorrhage: Insights from the SIREN study. *Journal of the Neurological Sciences*, *474*, 123555. https://doi.org/10.1016/j.jns.2025.123555
7. Sato, T., Tsuchimochi, Y., Hamada, Y., Kukihara, K., Kawabata, Y., Iwamoto, K., Takaguchi, G., Higuchi, Y., Matsuoka, H., & Takashima, H. (2025). Lower high-density lipoprotein cholesterol level is associated with hematoma expansion in acute intracerebral hemorrhage: Association with hypertensive microangiopathy. *Hypertension Research*, *48*(9), 2326-2338. https://doi.org/10.1038/s41440-025-02268-y
8. Lai, S., Wang, C., Lin, Y., Kang, B., Wang, J., Meng, H., & Cao, C. (2025). Neutrophil-to-High density lipoprotein cholesterol ratio predicts early hematoma expansion in patients with spontaneous intracerebral hemorrhage. *Neurosurgical Review*, *48*(1). https://doi.org/10.1007/s10143-025-03682-z
9. Zhang, G., Zhang, X., Gao, H., Lin, Y., & Zheng, Z. (2024). Exploration and comparison of stress hyperglycemia-related indicators to predict clinical outcomes in patients with spontaneous intracerebral hemorrhage. *Neurosurgical Review*, *47*(1). https://doi.org/10.1007/s10143-024-03130-4
10. Hu, X., Wang, Z., Liu, J., Liu, X., Luo, J., Meng, Z., Yang, T., & Li, Q. (2025). Statin use is associated with reduced risk of incident intracerebral hemorrhage: A prospective population-based cohort study. *International Journal of Stroke*. https://doi.org/10.1177/17474930251351103
11. Sasongko, A. B., Perdana Wahjoepramono, P. O., Halim, D., Aviani, J. K., Adam, A., Tsai, Y. T., Wahjoepramono, E. J., July, J., & Achmad, T. H. (2025). Potential blood biomarkers that can be used as prognosticators of spontaneous intracerebral hemorrhage: A systematic review and meta-analysis. *PLOS ONE*, *20*(2), e0315333. https://doi.org/10.1371/journal.pone.0315333
12. Siniscalchi, C., Basaglia, M., Meschi, T., Imbalzano, E., Futura Bernardi, F., Perrella, A., Trama, U., Passannanti, A., Di Micco, P., & Schiano, C. (2025). Low LDL-cholesterol and hemorrhagic risk: Mechanistic insights and clinical perspectives. *International Journal of Molecular Sciences*, *26*(12), 5612. https://doi.org/10.3390/ijms26125612
13. Zhang, X., Kang, L., Du, P., Xu, D., Li, H., & Jiang, Z. (2025). Association between nutritional status and pneumonia in patients with spontaneous intracerebral hemorrhage. *Frontiers in Nutrition*, *12*. https://doi.org/10.3389/fnut.2025.1547655
14. Li, Y., Lei, C., Wang, L., Lin, S., Zhao, L., Jiang, W., Deng, Q., & Yang, X. (2024). Systematic review and meta-analysis of the association between appearance of lesions on diffusion-weighted imaging and poor outcomes among patients with Intracerebral hemorrhage. *World Neurosurgery*, *190*, 323-328. https://doi.org/10.1016/j.wneu.2024.07.168
15. Wu, G., Li, S., Luo, M., Li, X., Zhu, X., Zhang, J., He, Q., Yang, Q., Zhao, G., Luo, S., & Yang, Z. (2024). Role of serum alkaline phosphatase as a potential biomarker of severity and prognosis in intracerebral hemorrhage. *Journal of Stroke and Cerebrovascular Diseases*, *33*(1), 107478. https://doi.org/10.1016/j.jstrokecerebrovasdis.2023.1
16. Liu, Y., Fu, H., Wang, Y., Zhong, Y., Zhang, R., Sun, J., Yang, T., Han, Y., Xiang, Y., Yuan, B., Zhou, R., Chen, M., & Wang, H. (2025). Association between the low-density lipoprotein to high-density lipoprotein ratio and prognosis in critically ill intracerebral hemorrhage patients: A retrospective cohort study from the MIMIC-IV database. *Lipids in Health and Disease*, *24*(1). https://doi.org/10.1186/s12944-025-02459-z
17. Yan, X., Huang, W., & Chen, Y. (2025). Serum MPO-DNA for predicting the risk of venous thromboembolism and the effect of statins in patients with spontaneous Intracerebral hemorrhage. *Thrombosis and Haemostasis*. https://doi.org/10.1055/a-2595-1927
18. Zhao, G., Chen, Y., Gu, Y., & Xia, X. (2024). The clinical value of nutritional and inflammatory indicators in predicting pneumonia among patients with intracerebral hemorrhage. *Scientific Reports*, *14*(1). https://doi.org/10.1038/s41598-024-67227-y
19. Yajun, Z., Diqing, O., Xingwei, L., Liuyang, T., Xiaofeng, Z., Xiaoguo, L., & Zongduo, G. (2024). High levels of blood lipid

and glucose predict adverse prognosis in patients with aneurysmal subarachnoid hemorrhage. *Heliyon*, *10*(19), e38601. https://doi.org/10.1016/j.heliyon.2024.e38601

20. Wen, Y., Xie, X., & He, K. (2025). Serum anion gap and its interaction with diabetes in predicting mortality among critically ill patients with non-traumatic intracerebral hemorrhage. *European Journal of Medical Research*, *30*(1). https://doi.org/10.1186/s40001-025-02810-1