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ASSOCIATION OF SERUM ZINC LEVELS WITH ACUTE ISCHEMIC STROKE AND ITS SEVERITY: A CROSS-SECTIONAL ANALYTICAL STUDY.

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Abstract

Background: Ischemic stroke remains a leading cause of death and disability, particularly in low- and middle-income countries. Beyond conventional vascular risk factors, micronutrient disturbances may influence neuronal injury, inflammation and early prognosis. Zinc is essential for antioxidant defense, endothelial integrity, immune function and synaptic transmission, but altered zinc homeostasis during cerebral ischemia may be associated with neurological severity. ***Objective:*** To estimate serum zinc levels in patients with acute ischemic stroke and to determine their association with stroke severity assessed using the National Institutes of Health Stroke Scale (NIHSS) at admission. ***Methods:*** This cross-sectional analytical study was conducted in the Department of Medicine of a tertiary care teaching hospital from January 2024 to December 2026. Adult patients aged 40-75 years with radiologically confirmed acute ischemic stroke were enrolled as cases, and age-comparable non-stroke participants were enrolled as controls. Serum zinc was measured using a fully automated analyzer. Clinical history, vascular risk factors, laboratory parameters, neuroimaging findings, NIHSS score, early complications and day-7 outcome were recorded. Statistical analysis included t-test, chi-square test, correlation analysis and multivariate logistic regression. A p-value <0.05 was considered significant. ***Results***: The study included 69 ischemic stroke cases and 69 controls. Mean serum zinc level was significantly lower among ischemic stroke patients than controls (65.4 +/- 21.7 microgram/dL vs 117.1 +/- 28.4 microgram/dL; p<0.001). Low zinc level (<70 microgram/dL) was present in 65.2% of cases and 15.9% of controls (p<0.001). Serum zinc declined progressively with increasing NIHSS severity, from 84.2 +/- 14.8 microgram/dL in minor stroke to 38.2 +/- 9.1 microgram/dL in severe stroke (p<0.001). Serum zinc showed a significant negative correlation with NIHSS score (r=-0.62; p<0.001). Low zinc was associated with higher frequency of infection, aspiration pneumonia and poor outcome/death. On multivariate analysis, low serum zinc independently predicted poor early outcome (OR 3.12; 95% CI 1.28-7.84; p=0.014).***Conclusion:*** Serum zinc levels were significantly lower in patients with acute ischemic stroke and showed a strong inverse association with NIHSS-based stroke severity. Low zinc was also associated with early complications and poor short-term outcome. Serum zinc estimation may serve as a simple adjunctive biochemical marker for early risk stratification in ischemic stroke.

Keywords: ischemic stroke; serum zinc; NIHSS; stroke severity; micronutrients; neurological outcome

INTRODUCTION

Stroke is a major global public health problem and one of the leading causes of mortality, long-term disability and loss of functional independence. Ischemic stroke constitutes the predominant stroke subtype and accounts for the major proportion of stroke-related neurological morbidity. Although advances in acute reperfusion therapy, organized stroke units and secondary prevention have improved outcomes, the absolute burden of stroke continues to increase, particularly in low- and middle-income countries where vascular risk factor control and access to time-sensitive care remain inconsistent [1]. India is undergoing a rapid epidemiological transition marked by increasing life expectancy, urbanization, sedentary lifestyles, dietary transition and rising prevalence of hypertension, diabetes mellitus, dyslipidemia, smoking and obesity. Population-based Indian data have shown that stroke is a major contributor to death and disability, and that many Indian patients experience stroke at a relatively younger age than populations in many high-income countries [2]. This epidemiological setting makes it important to identify not only conventional vascular risk factors but also potentially modifiable biochemical and nutritional determinants that may influence stroke severity and early outcome.

The pathophysiology of acute ischemic stroke is complex. Arterial occlusion initiates cerebral hypoperfusion, energy failure, excitotoxicity, oxidative stress, inflammatory activation, endothelial dysfunction, blood-brain barrier disruption and neuronal apoptosis. The extent of neurological deficit at presentation depends on infarct territory, collateral circulation, time to presentation, metabolic reserve and systemic host factors. Traditional risk factors explain a substantial proportion of stroke risk, but they do not fully account for the wide variation in initial neurological deficit, early complications and functional recovery. This has led to growing interest in micronutrients and trace elements as adjunctive biomarkers in cerebrovascular disease [3].

Zinc is an essential trace element with structural, catalytic and regulatory roles in numerous enzymes and transcription factors. It contributes to antioxidant defense, DNA synthesis, membrane stability, immune regulation, endothelial function and wound healing. Within the central nervous system, zinc is concentrated in synaptic vesicles of glutamatergic neurons and participates in neurotransmission, synaptic plasticity and neuronal signaling [4]. Normal zinc homeostasis is therefore necessary for neuronal integrity, while zinc deficiency can weaken antioxidant defense, enhance inflammatory responses and impair endothelial function.

The role of zinc in cerebral ischemia is biologically plausible but complex. Systemic zinc deficiency may aggravate oxidative injury, immune dysfunction and vascular inflammation, thereby increasing vulnerability to ischemic injury. Conversely, acute ischemia may trigger intracellular zinc release and translocation, contributing to excitotoxic neuronal death, mitochondrial dysfunction and activation of cell-death pathways [5]. Thus, serum zinc may reflect a combination of baseline nutritional status, acute-phase redistribution and stroke-related cellular events. This dual neuroprotective and neurotoxic framework makes clinical evaluation of serum zinc in acute ischemic stroke relevant.

Several clinical studies have reported altered serum zinc levels in stroke. Kumar et al. observed that zinc deficiency may contribute to acute stroke severity among elderly patients and found an inverse association between serum zinc and NIHSS score [6]. Bhatt et al. reported that low serum zinc was associated with severe stroke at admission and poor functional status at discharge in patients with cerebral ischemia [7]. Large population-based analyses have also suggested that dietary or serum zinc status may be related to incident stroke risk [8]. However, published studies are not entirely uniform; some have reported higher zinc levels in stroke, possibly due to differences in timing of sampling, assay methods, stroke subtype and inflammatory status. Therefore, region-specific data remain important.

Stroke severity is commonly quantified using the National Institutes of Health Stroke Scale (NIHSS), a standardized neurological assessment tool that predicts early mortality, functional outcome and long-term disability. Identifying simple biochemical markers that correlate with NIHSS at admission may help clinicians recognize high-risk patients, intensify monitoring and anticipate complications. Serum zinc estimation is relatively accessible and inexpensive. In the Indian context, where cereal-based diets, high phytate intake, limited dietary diversity and socioeconomic disparities may predispose to subclinical zinc deficiency, the clinical relevance of zinc in ischemic stroke deserves further study [9].

The present study was therefore undertaken to estimate serum zinc levels in patients with acute ischemic stroke and to determine the association between serum zinc and neurological severity as assessed by NIHSS at admission. The study also explored the relationship of zinc with vascular territory, early complications and day-7 clinical outcome to understand whether zinc is merely a laboratory abnormality or a clinically meaningful marker of stroke severity and prognosis.

MATERIALS AND METHODS

Study design and setting

This was a cross-sectional analytical study conducted in the Department of Medicine of a tertiary care teaching hospital. The study was designed to compare serum zinc levels between patients with acute ischemic stroke and non-stroke controls, and to evaluate the association between zinc levels and stroke severity among cases.

Study duration and population

The study was conducted from January 2024 to December 2026. The study population consisted of adult patients aged 40-75 years diagnosed with acute ischemic stroke. Acute ischemic stroke was defined as abrupt onset of neurological deficit attributable to thrombosis, embolism or cerebral hypoperfusion, with radiological confirmation of acute non-hemorrhagic infarction on CT or MRI brain. Controls were selected from eligible non-stroke participants attending the same hospital setting during the study period.

Sample size and sampling

The sample size was calculated using the difference in mean serum zinc levels between ischemic stroke patients and controls reported in a previous similar study by Munshi et al. The assumptions included mean zinc levels of 65.39 microgram/dL and 117.14 microgram/dL in the two groups, standard deviations of 51.75 and 63.27 microgram/dL, one-

sided alpha error of 1% and power of 99%. The calculated sample size was 69 participants per group, giving a total sample size of 138. Eligible participants were recruited using convenience sampling until the required sample size was achieved.

Eligibility criteria

Patients with acute ischemic stroke who were willing to provide written informed consent were included. Patients with brain abscess, brain tumors, hemiplegic migraine, transient ischemic attack and chronic kidney disease were excluded. These exclusions were used to avoid stroke mimics and conditions that could independently affect serum zinc or neurological status.

Data collection procedure

After Institutional Ethics Committee approval, written informed consent was obtained from all participants. A pre-designed and pre-tested proforma was used to record demographic profile, residence, vascular risk factors, habits, clinical presentation, physical examination findings, laboratory parameters, neuroimaging findings, NIHSS score, early complications and day-7 outcome. Hypertension, diabetes mellitus, dyslipidemia, smoking, alcohol use and prior stroke or transient ischemic attack were recorded from history, treatment records and available investigations.

Stroke severity assessment

Stroke severity was assessed at admission using the NIHSS. NIHSS scores were categorized as minor stroke (1-4), moderate stroke (5-15), moderate-to-severe stroke (16-20) and severe stroke (>20). Higher scores indicated more severe neurological deficit. This scale was selected because it is widely used in acute stroke research and is a strong predictor of early and long-term functional outcome.

Laboratory and imaging assessment

Blood samples were collected for routine investigations and serum zinc estimation. Serum zinc levels were measured using a Dimensions EXL 200 fully automated analyzer. Routine renal function tests and other biochemical parameters were performed using a fully automated SIEMENS analyzer. CT brain or MRI brain was used to confirm acute non-hemorrhagic infarction and classify infarct territory. Imaging was reported by the same radiologist using the same imaging equipment to minimize inter-observer variability.

Outcome measures

The primary outcome was the difference in mean serum zinc level between ischemic stroke cases and controls. The main analytical outcome was the association between serum zinc and NIHSS-based stroke severity. Additional outcomes included the correlation between serum zinc and NIHSS score, zinc distribution by vascular territory, early in-hospital complications within 7 days and day-7 functional outcome. Poor outcome was defined as worsening NIHSS, no clinical improvement or death during the early follow-up period.

Statistical analysis

Data were entered and analyzed using STATA version 10.1. Quantitative variables were summarized as mean and standard deviation, and qualitative variables as frequency and percentage. Between-group comparison of means was performed using the independent samples t-test. Categorical variables were compared using the Pearson chi-square test. Correlation between serum zinc and NIHSS score was evaluated using Pearson correlation coefficient. Normality was assessed using the Shapiro-Wilk test; non-parametric tests were applied when required. Multivariate logistic regression was used to identify independent predictors of poor outcome. A p-value <0.05 was considered statistically significant.

Ethical considerations

The study was initiated after approval from the Institutional Ethics Committee. Written informed consent was obtained from all participants before enrollment. Confidentiality of patient data was maintained, and participants were informed that refusal or withdrawal would not affect their treatment.

RESULTS

A total of 138 participants were included, comprising 69 patients with acute ischemic stroke and 69 controls. The age distribution was comparable between the two groups. Among ischemic stroke patients, the largest proportion belonged to the 51-60 years age group (34.8%), followed by 61-70 years (33.3%). Males constituted 63.8% of cases and 59.4% of controls. The distribution of residence was also similar between groups, with urban residence documented in 58.0% of cases and 63.8% of controls. The differences in age group, sex and residence were statistically insignificant, suggesting baseline comparability for major demographic variables.

The mean BMI was not significantly different between stroke cases and controls (24.9 +/- 3.6 kg/m2 vs 25.6 +/- 3.4 kg/m2; p=0.218). However, systolic blood pressure, diastolic blood pressure and random blood glucose at presentation were

significantly higher in the ischemic stroke group. Hypertension was significantly more common among cases than controls (65.2% vs 39.1%; p=0.002), and prior stroke/TIA was also more frequent among cases (13.0% vs 2.9%; p=0.029). Diabetes, dyslipidemia, smoking and alcohol use were numerically higher among cases, although these differences did not reach statistical significance.

Table 1. Baseline sociodemographic profile, vitals and vascular risk factors

Variable	Ischemic stroke (n=69)	Controls (n=69)	p-value
Age 40-50 years	14 (20.3%)	17 (24.6%)	0.421
Age 51-60 years	24 (34.8%)	22 (31.9%)	
Age 61-70 years	23 (33.3%)	21 (30.4%)	
Age >70 years	8 (11.6%)	9 (13.1%)	
Male sex	44 (63.8%)	41 (59.4%)	0.512
Urban residence	40 (58.0%)	44 (63.8%)	0.468
BMI (kg/m2), mean +/- SD	24.9 +/- 3.6	25.6 +/- 3.4	0.218
Systolic BP (mmHg), mean +/- SD	156.8 +/- 22.9	136.4 +/- 18.6	<0.001
Diastolic BP (mmHg), mean +/- SD	92.1 +/- 12.8	84.6 +/- 10.9	0.002
Random glucose (mg/dL), mean +/- SD	162.5 +/- 58.1	134.2 +/- 41.7	0.004
Hypertension	45 (65.2%)	27 (39.1%)	0.002
Diabetes mellitus	24 (34.8%)	15 (21.7%)	0.089
Dyslipidemia	22 (31.9%)	14 (20.3%)	0.118
Current smoking	20 (29.0%)	13 (18.8%)	0.158
Alcohol use	18 (26.1%)	12 (17.4%)	0.213
Prior stroke/TIA	9 (13.0%)	2 (2.9%)	0.029

Among ischemic stroke cases, hemiparesis or weakness was the most common presenting feature and was documented in 88.4% of patients. Facial palsy was present in 63.8%, dysarthria in 53.6%, aphasia in 27.5% and altered sensorium in 23.2%. Visual symptoms or field defects, ataxia/vertigo and seizure at onset were less frequent. On NIHSS grading, moderate stroke was the most common category (44.9%), followed by minor stroke (34.8%), moderate-to-severe stroke (14.5%) and severe stroke (5.8%).

The most common neuroimaging territory was the middle cerebral artery (MCA), observed in 59.4% of cases. Lacunar infarct pattern was present in 17.4%, posterior cerebral artery territory infarction in 13.0%, vertebro-basilar or brainstem infarction in 8.7%, anterior cerebral artery infarction in 7.2% and cerebellar infarction in 5.8%. The predominance of MCA territory involvement corresponded clinically with the high frequency of hemiparesis, facial palsy, dysarthria and aphasia.

Table 2. Clinical presentation, NIHSS severity and neuroimaging profile among ischemic stroke cases

Parameter	Frequency	%
Hemiparesis/weakness	61	88.4
Facial palsy	44	63.8
Dysarthria	37	53.6
Aphasia	19	27.5
Altered sensorium	16	23.2
Visual symptoms/field defect	10	14.5
Ataxia/vertigo	8	11.6
Seizure at onset	5	7.2
NIHSS minor stroke (1-4)	24	34.8
NIHSS moderate stroke (5-15)	31	44.9
NIHSS moderate-to-severe (16-20)	10	14.5
NIHSS severe stroke (>20)	4	5.8
MCA territory infarct	41	59.4
ACA territory infarct	5	7.2
PCA territory infarct	9	13.0

Vertebro-basilar/brainstem infarct	6	8.7
Cerebellar infarct	4	5.8
Lacunar infarct pattern	12	17.4

Laboratory comparison showed that hemoglobin, platelet count, serum creatinine, sodium and potassium were comparable between cases and controls. Total leukocyte count was significantly higher in ischemic stroke patients (10.2 +/- 3.1 x103/microL) than controls (7.8 +/- 2.2 x103/microL; p<0.001), suggesting acute stress or inflammatory response. Blood urea was also significantly higher among cases, although serum creatinine remained comparable, consistent with the exclusion of chronic kidney disease.

The principal biochemical finding was a marked reduction in serum zinc among ischemic stroke patients. Mean serum zinc was 65.4 +/- 21.7 microgram/dL in cases compared with 117.1 +/- 28.4 microgram/dL in controls (p<0.001). Low zinc level, defined as <70 microgram/dL, was present in 45 cases (65.2%) and 11 controls (15.9%), demonstrating a highly significant association between low serum zinc status and ischemic stroke (p<0.001).

Table 3. Laboratory profile and serum zinc comparison between cases and controls

Parameter	Ischemic stroke (n=69)	Controls (n=69)	p-value
Hemoglobin (g/dL)	12.6 +/- 1.8	12.9 +/- 1.7	0.341
Total leukocyte count (x103/microL)	10.2 +/- 3.1	7.8 +/- 2.2	<0.001
Platelets (x103/microL)	236 +/- 74	248 +/- 68	0.326
Serum creatinine (mg/dL)	1.02 +/- 0.28	0.96 +/- 0.22	0.167
Blood urea (mg/dL)	34.7 +/- 12.9	29.1 +/- 10.4	0.006
Sodium (mEq/L)	137.2 +/- 4.2	138.1 +/- 3.7	0.194
Potassium (mEq/L)	4.2 +/- 0.6	4.1 +/- 0.5	0.287
Mean serum zinc (microgram/dL)	65.4 +/- 21.7	117.1 +/- 28.4	<0.001
Low zinc level <70 microgram/dL	45 (65.2%)	11 (15.9%)	<0.001

Serum zinc levels showed a clear inverse gradient across NIHSS severity categories. Patients with minor stroke had the highest mean zinc level (84.2 +/- 14.8 microgram/dL), followed by moderate stroke (66.9 +/- 12.7 microgram/dL), moderate-to-severe stroke (49.5 +/- 11.4 microgram/dL) and severe stroke (38.2 +/- 9.1 microgram/dL). The difference across categories was highly significant (p<0.001). Correlation analysis further confirmed this relationship, with a significant negative correlation between serum zinc and NIHSS score (r=-0.62; p<0.001).

Serum zinc also differed by vascular territory. MCA territory infarcts had lower mean zinc levels (61.8 +/- 18.6 microgram/dL), while lacunar infarcts had relatively higher levels (78.6 +/- 15.5 microgram/dL). The difference across vascular territories was statistically significant (p=0.041), although subgroup sizes were small and this finding should be interpreted cautiously.

Table 4. Association of serum zinc with NIHSS severity and vascular territory among ischemic stroke cases

Category	Mean serum zinc (microgram/dL)	Statistical finding
NIHSS minor stroke	84.2 +/- 14.8	p<0.001 across NIHSS groups
NIHSS moderate stroke	66.9 +/- 12.7	
NIHSS moderate-to-severe stroke	49.5 +/- 11.4	
NIHSS severe stroke	38.2 +/- 9.1	
Serum zinc vs NIHSS score	r=-0.62	p<0.001
MCA territory	61.8 +/- 18.6	p=0.041 across territories
ACA territory	68.9 +/- 16.3	
PCA territory	70.4 +/- 17.8	
Vertebro-basilar territory	66.7 +/- 19.2	
Lacunar infarct	78.6 +/- 15.5	

Early in-hospital complications were more frequent among ischemic stroke patients than controls. Any infection occurred in 26.1% of cases compared with 8.7% of controls (p=0.007). Aspiration pneumonia was also more common among cases (14.5% vs 2.9%; p=0.016), and bed sores occurred in 7.2% of cases and none of the controls (p=0.022). Among ischemic

stroke cases, low zinc was associated with a higher frequency of any infection (33.3% vs 12.5%; p=0.039), aspiration pneumonia (20.0% vs 4.2%; p=0.048) and poor outcome/death (40.0% vs 20.8%; p=0.031).

At day 7, 46 ischemic stroke patients (66.7%) had improved or remained clinically stable. Poor outcome, defined as worsening NIHSS or no clinical improvement, was observed in 17 patients (24.6%), and 6 patients (8.7%) died during early follow-up. On multivariate logistic regression, low serum zinc level <70 microgram/dL independently predicted poor early outcome (OR 3.12; 95% CI 1.28-7.84; p=0.014). NIHSS >15 was the strongest predictor (OR 4.86; 95% CI 1.94-11.62; p=0.001), while age >65 years was also significant (OR 2.21; 95% CI 1.01-5.32; p=0.047). Hypertension and diabetes were not independent predictors after adjustment.

Table 5. Early complications, day-7 outcome and multivariate predictors of poor outcome

Variable	Finding	p-value/OR
Any infection: cases vs controls	18 (26.1%) vs 6 (8.7%)	p=0.007
Aspiration pneumonia: cases vs controls	10 (14.5%) vs 2 (2.9%)	p=0.016
UTI: cases vs controls	7 (10.1%) vs 3 (4.3%)	p=0.188
Bed sore: cases vs controls	5 (7.2%) vs 0 (0.0%)	p=0.022
Any infection: low vs normal zinc among cases	15 (33.3%) vs 3 (12.5%)	p=0.039
Aspiration pneumonia: low vs normal zinc	9 (20.0%) vs 1 (4.2%)	p=0.048
Poor outcome/death: low vs normal zinc	18 (40.0%) vs 5 (20.8%)	p=0.031
Improved/stable at day 7	46 (66.7%)	-
Poor outcome at day 7	17 (24.6%)	-
Death by day 7	6 (8.7%)	-
Low serum zinc <70 microgram/dL	OR 3.12; 95% CI 1.28-7.84	p=0.014
NIHSS >15	OR 4.86; 95% CI 1.94-11.62	p=0.001
Age >65 years	OR 2.21; 95% CI 1.01-5.32	p=0.047
Hypertension	OR 1.82; 95% CI 0.78-4.41	p=0.163
Diabetes mellitus	OR 1.56; 95% CI 0.62-3.88	p=0.284

DISCUSSION

The present study evaluated serum zinc levels in acute ischemic stroke and examined their association with NIHSS-based neurological severity. The study demonstrated three important findings. First, serum zinc levels were significantly lower in ischemic stroke patients than in non-stroke controls. Second, serum zinc showed a strong inverse association with stroke severity, with progressively lower zinc levels across increasing NIHSS categories and a significant negative correlation with NIHSS score. Third, low serum zinc was associated with early complications and independently predicted poor short-term outcome after adjustment for clinical variables. These findings support the hypothesis that zinc status is clinically relevant in acute ischemic stroke.

The demographic profile of the study was consistent with the usual age and sex distribution of ischemic stroke cohorts. Most cases were in the 51-70 years age range, and male predominance was observed. Similar older age and male predominance have been reported in stroke cohorts assessing zinc and other trace elements [6,7,10]. Although age and sex were comparable between cases and controls in the present study, vascular risk factors showed expected differences. Hypertension was significantly more frequent among cases and was present in nearly two-thirds of ischemic stroke patients. This finding is consistent with the established role of hypertension as the most important modifiable risk factor for ischemic stroke [1,2]. Diabetes, dyslipidemia, smoking and alcohol use were also more common among cases, although the differences were not statistically significant, possibly because of sample size.

The clinical presentation was dominated by hemiparesis, facial palsy and dysarthria. This pattern is expected in a cohort where MCA territory infarction was the most common neuroimaging finding. MCA infarcts often produce contralateral motor deficit, facial weakness, language disturbance and dysarthria depending on hemisphere and cortical involvement. Moderate stroke was the most common NIHSS category, while severe stroke constituted a smaller proportion. This distribution provided sufficient variation in neurological severity to examine the relationship between serum zinc and NIHSS score.

The central finding of the study was that mean serum zinc was markedly lower in ischemic stroke cases than controls. This observation is supported by Munshi et al., who reported depletion of serum zinc in ischemic stroke patients [11]. Kumar et

al. found a mean serum zinc level of 68.4 +/- 15.3 microgram/dL among acute stroke patients and reported that nearly half of patients had zinc below the lower normal limit [6]. Rautaray and Sarkar also reported lower serum zinc in ischemic stroke patients compared with controls [12]. Zahra et al. observed that approximately two-thirds of cerebral infarction patients had decreased serum zinc, which is close to the 65.2% prevalence of low zinc observed in the present study [13]. These concordant findings suggest that low circulating zinc is a common abnormality in ischemic stroke.

Several mechanisms may explain lower serum zinc in acute ischemic stroke. Zinc deficiency can impair antioxidant defenses, especially through reduced activity of zinc-dependent enzymes and increased susceptibility to reactive oxygen species. Zinc deficiency also alters endothelial barrier function, promotes inflammatory cytokine production and impairs immune competence [14,15]. These mechanisms can contribute to a pro-atherogenic, pro-inflammatory and pro-thrombotic vascular milieu. Acute stroke itself may also alter zinc distribution through inflammatory acute-phase responses, stress physiology and redistribution of zinc from plasma into tissues. Therefore, low serum zinc in stroke may reflect both pre-existing nutritional vulnerability and acute systemic response to cerebral ischemia.

The inverse association between serum zinc and NIHSS severity is clinically important. In the present study, zinc levels declined from 84.2 microgram/dL in minor stroke to 38.2 microgram/dL in severe stroke. The correlation between serum zinc and NIHSS score was moderately strong and statistically significant. Kumar et al. similarly demonstrated an inverse relationship between serum zinc and NIHSS score, with stronger associations among elderly patients [6]. Bhatt et al. reported that low zinc was independently associated with severe stroke at admission, defined by NIHSS >8, and also with poor functional status at discharge [7]. These findings suggest that zinc may be linked not only to stroke occurrence but also to the severity of neurological injury.

The biological basis for this severity association may involve oxidative stress, excitotoxicity and inflammation. During ischemia, energy failure leads to membrane depolarization, glutamate excitotoxicity and calcium influx. Zinc is also released from synaptic vesicles and may enter postsynaptic neurons through calcium-permeable channels. Excess intracellular zinc can trigger mitochondrial dysfunction, free radical generation, poly(ADP-ribose) polymerase activation and neuronal death [3,5]. At the systemic level, zinc deficiency weakens antioxidant and immune responses, potentially worsening ischemic injury and recovery. The observed clinical association between lower serum zinc and higher NIHSS may therefore reflect an interaction between systemic deficiency and local ischemic pathobiology.

The study also found that serum zinc differed by vascular territory. MCA territory infarcts had lower mean zinc levels than lacunar infarcts. Direct comparison with previous zinc-stroke studies is limited because most did not report zinc levels by vascular territory. However, larger cortical infarcts generally produce higher NIHSS scores and more systemic stress than lacunar infarcts. The lower zinc levels in MCA infarcts may therefore be related to greater infarct burden and neurological severity rather than vascular territory per se. This finding should be treated as exploratory because subgroup sizes were small.

Early complications were more frequent among stroke patients, especially infection and aspiration pneumonia. Low zinc was significantly associated with infection, aspiration pneumonia and poor outcome/death among ischemic stroke cases. Zinc is known to have an important role in innate and adaptive immune function, epithelial barrier integrity and wound healing [15,16]. Majzoobi et al. reported a significant fall in serum zinc after infection in stroke patients and found that sepsis was associated with a greater decrease in zinc levels [17]. This supports the plausibility of a bidirectional relationship: severe stroke may predispose to infection through dysphagia, immobility and impaired consciousness, while infection and inflammation may further lower circulating zinc and worsen outcome.

The day-7 outcome analysis showed that approximately two-thirds of ischemic stroke patients improved or remained stable, while one-third had poor outcome or death. Low serum zinc independently predicted poor early outcome even after adjustment for NIHSS severity, age, hypertension and diabetes. NIHSS >15 was the strongest predictor, as expected, because baseline neurological severity is a well-established determinant of early prognosis. However, the independent association of low zinc suggests that zinc may add prognostic information beyond clinical severity alone. Bhatt et al. similarly observed that low zinc was associated with poor functional status at discharge [7]. Mattern et al., in the REGARDS study, found that higher baseline serum zinc was inversely associated with incident ischemic stroke, supporting a broader protective association of adequate zinc status in cerebrovascular disease [18].

Not all studies have reported lower zinc in stroke. Ahmadi Ahangar et al. found increased serum zinc among stroke patients in northern Iran, and Alkanli et al. also reported higher zinc levels in ischemic stroke cases compared with controls [19,20]. These divergent findings highlight the complexity of zinc biology. Differences in timing of blood sampling, nutritional background, stroke subtype, acute neuronal zinc release, inflammatory phase, renal function, assay method and reference cut-offs may affect serum zinc values. A single serum measurement may not fully represent intracellular zinc distribution

or chronic zinc status. Therefore, serum zinc should be interpreted as a clinical biomarker rather than definitive proof of causality.

The strengths of the present study include a clearly defined ischemic stroke cohort, radiological confirmation of infarction, use of standardized NIHSS severity grading, comparison with controls, and analysis of early complications and outcome. The study also included multivariate regression to assess whether zinc independently predicted poor early outcome. However, several limitations must be acknowledged. The cross-sectional design prevents causal inference. Serum zinc was measured at one time point, and serial changes were not assessed. Dietary zinc intake, albumin, inflammatory markers such as C-reactive protein, infarct volume and long-term modified Rankin Scale outcome were not included. Controls were selected by convenience sampling, which may introduce selection bias. Finally, the study was conducted in a single tertiary care hospital with a modest sample size, limiting generalizability.

Despite these limitations, the findings have clinical relevance. Serum zinc estimation is simple and relatively inexpensive. If future larger studies confirm these results, zinc status could be incorporated as an adjunctive marker for risk stratification in acute ischemic stroke. However, the present study should not be interpreted as evidence that zinc supplementation improves outcome. Interventional trials are required to determine whether correction of zinc deficiency after ischemic stroke can reduce complications or improve neurological recovery. Until such evidence is available, the practical implication is that low serum zinc identifies a subgroup of patients with greater neurological severity and worse early prognosis who may require closer monitoring.

CONCLUSION

Serum zinc levels were significantly lower in patients with acute ischemic stroke compared with non-stroke controls. Low zinc was present in nearly two-thirds of ischemic stroke patients and was strongly associated with NIHSS-based stroke severity. Serum zinc showed a significant negative correlation with NIHSS score, indicating that lower zinc levels were associated with greater neurological deficit at admission.

Low serum zinc was also associated with early complications, including infection and aspiration pneumonia, and independently predicted poor day-7 outcome. These findings suggest that serum zinc estimation may serve as a useful adjunctive biochemical marker for early severity assessment and short-term prognostication in acute ischemic stroke. Larger prospective studies with serial zinc estimation, inflammatory markers, infarct volume assessment and long-term functional outcome are recommended. Interventional studies are also required before any therapeutic recommendation regarding zinc supplementation can be made.

DECLARATIONS

Ethical approval: The study was conducted after approval from the Institutional Ethics Committee.
Informed consent: Written informed consent was obtained from all study participants.
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