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Serum Vitamin B12 as a Risk Factor and Prognostic Indicator in Acute Ischemic Stroke: A Case-Control Study at a Tertiary Care Hospital Mirpurkhas (Sindh)

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ABSTRACT

Ischemic stroke is among the main causes of disability and death globally. Vitamin B12, through its role in homocysteine metabolism, may help prevent stroke, as its deficiency increases stroke risk. Objective: To compare the serum level of vitamin B12 in stroke patients and controls. **Methods:** The case-control observational study was conducted in Mirpurkhas, Sindh, included 75 patients who suffered from stroke and 75 control subjects. Serum level of vitamin B12 and the levels of homocysteine were evaluated, along with the severity of stroke and functional outcomes were evaluated using the National Institutes of Health Stroke Scale (NIHSS) and Modified Rankin Scale (mRS), respectively, at discharge and 28 days. Statistical analysis explored associations with the severity of the stroke and its outcomes. **Results:** Stroke patients showed significantly lower levels of vitamin B12 (188.4 ± 43.6 pg/mL) than controls (352.7 ± 54.1 pg/mL, p<0.001). Vitamin B12 insufficiency (<200 pg/mL) was more prevalent in stroke patients (65.3%) compared to controls (18.7%, p<0.001). NIHSS scores were higher in deficient patients (13.1 ± 4.2) than those with insufficient (9.6 ± 3.1) or sufficient levels (7.5 ± 2.5, p<0.001). Worse functional outcomes (mRS 3.9 ± 1.2) were noted in deficient patients compared to insufficient (2.8 ± 0.8, p=0.007) and sufficient levels (2.3 ± 0.6, p<0.001). Logistic regression identified vitamin B12 deficiency as an independent stroke risk factor (OR=5.9, 95% CI: 2.9–12.3, p<0.001). **Conclusions:** It was concluded Vitamin B12 deficiency was associated with increased stroke severity and poorer outcomes, suggesting its potential role in stroke management.

INTRODUCTION

Stroke ranks amongst the foremost reasons for death globally. Each year, approximately 15 million individuals worldwide experience a stroke, with 5 million succumbing to the condition and another 5 million facing long-term disability. This imposes significant burdens on both families and communities [1]. ischemic stroke (IS) contributes more to illness than mortality, it remains a critical challenge for healthcare systems. The risk factors for IS are largely preventable, with nearly 90% being controllable. These factors include cardiovascular diseases, diabetes mellitus, smoking, obesity, hyperlipidemia, sedentary lifestyles, excessive alcohol consumption, poor diet, psychological stress, and depression. Notably, one emerging and modifiable risk factor is the blood level of vitamin B-12. Despite this extensive list, other risk factors may still contribute to IS [2]. In Pakistan, ischemic strokes are prevalent [3]. A community-based study in Karachi's urban slums reported

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a stroke prevalence of 21.8%. Of these cases, 30% were hemorrhagic strokes, while 70% were ischemic strokes [4]. Vitamin B12, or Cobalamin, is a water-soluble vitamin vital for DNA synthesis and cellular metabolism. It plays a critical role in one-carbon metabolism, a network that integrates nutritional signalling with epigenetics, redox homeostasis and biosynthesis. This network also supports the preservation of epigenetic information. Dietary sources of vitamin B12 comprise animal-based diets such as eggs, fish, meat and dairy products. Although some gut bacteria like Escherichia coli produce vitamin B-12, the quantity is insufficient to meet the body's needs [5, 6]. Thus, vitamin deficiency. B12 or folate leads to high levels of blood homocysteine, which raises the risk of ischemic stroke since, through its several modes of action, homocysteine is interlinked with an increased danger of thrombosis [7]. According to studies, small vessel stroke is linked to elevated levels of plasma homocysteine (HCY). Supplementation of vitamin B12 and folate may lower homocysteine levels in the blood and the danger of stroke [8]. Data from 2007 to 2018 in the review of the National Health and Nutrition Examination Survey (NHANES) exposed that around 3.7% of persons aged 60 and above and 3.6% of those aged 19 and older suffer from vitamin B12 insufficiency, defined as blood levels of vitamin B12 less than 200 pg/mL or 148 pmol/L. However, vitamin B12 deficiency is more predominant, influencing almost 12.5% of all individuals over the age of 19 and 12.3% of those over the age of 60 (defined as serum levels of vitamin B12 less than 300 pg/mL (221 pmol/L) [9]. The link between vitamin B12 or folate levels in blood with stroke risk has been investigated in a minor number of prospective studies, however, the findings have been mixed.

Ischemic stroke remains one of the foremost causes of death and long-term disability globally, with Pakistan bearing a substantial burden reflected in a community-level stroke prevalence of 21.8% in urban Sindh, where 70% of cases are ischemic in nature and driven by a confluence of modifiable cardiovascular risk factors. Vitamin B12, through its critical role in homocysteine metabolism, has emerged as a potentially modifiable contributor to ischemic stroke risk, as its deficiency leads to hyperhomocysteinemia that promotes endothelial dysfunction, platelet activation, and a prothrombotic state conducive to cerebrovascular events. Despite growing international evidence linking vitamin B12 deficiency to increased stroke risk and severity, locally contextualized data from Sindh, Pakistan, specifically examining the association between serum vitamin B12 levels, homocysteine, stroke severity assessed by NIHSS, and functional outcomes measured by modified Rankin Scale, remain sparse and insufficient to inform regional clinical screening and prevention protocols. This study therefore aimed to compare serum vitamin B12 levels between acute ischemic stroke patients and age- and sex-matched controls at a tertiary care hospital in Mirpurkhas, Sindh, and to evaluate vitamin B12 deficiency as an independent risk factor and prognostic indicator of stroke severity and functional outcomes.

METHODS

This case-control observational study was conducted at Bhitai Medical and Dental College and Hospital, Mirpurkhas, Sindh, from June 2022 to May 2024. The study acknowledged ethical endorsement from the Ethics Review Committee of Bhitai Medical and Dental College and Hospital, Mirpur Khas (Ref No: BDMC/R&D/ERC/2022-12). This study employed comparing persons with a precise ailment (cases) to those without it (controls) to classify possible risk aspects. Cases in this study were defined as patients diagnosed with acute ischemic stroke, confirmed via clinical evaluation and neuroimaging, presenting to a tertiary care hospital in Mirpur Khas, Sindh. Age- and sex-matched individuals were Controls, without a history of stroke, recruited from the same hospital and local community to ensure similar demographic and environmental exposure. Participants were omitted if they had a preceding history of stroke, malignancy, severe hepatic or renal disease, or were on vitamin B12 supplementation. A total of 300 participants were recruited, including 150 cases identified with acute ischemic stroke and 150 age and gender-matched control participants. The sample size for the research was estimated based on a published study by Jiang et al., [10], which reported a significant difference in mean serum vitamin B12 levels between stroke patients and controls (stroke: 367.53 ± 127.30 pg/mL, controls: 495.18 ± 102.79 pg/mL). Using a significance level of 5%, power of 80%, and an effect size of 0.58, the required sample size was determined to be 300 participants (150 cases and 150 controls). The patients ≥40 years of age, diagnosed with acute ischemic stroke in the last 24 hours of the beginning of symptoms, and confirmed via neuroimaging (CT or MRI) were included in the case group. Age-matched controls were selected from individuals without any history of stroke or cerebrovascular disease, attending the hospital for routine checkups from the emergency department of the hospital. Participants with conditions such as hemorrhagic stroke, transient ischemic attacks (TIA), chronic kidney disease, liver disorders, malabsorption syndromes, or those receiving vitamin B12 supplementation were excluded. Moreover, individuals with severe comorbidities, pregnant women, and those unwilling to participate were also excluded. All participants were given informed written consent before being enrolled in the study. Data collection involved a structured

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questionnaire to capture demographic details, medical history, and lifestyle factors, such as smoking and alcohol use. The severity of the stroke was gauged using the NIHSS, and their functional aspects were evaluated at a 3-month follow-up via a modified Rankin Scale (mRS). Blood samples (5 mL) were drawn from all participants for the measurement of serum vitamin B12 and homocysteine levels using an enzyme-linked immunosorbent assay (ELISA). Participants were classified into three categories based on their vitamin B12 levels: lacking (<200 pg/mL), insufficient (200–400 pg/mL), and sufficient (>400 pg/mL). Other biochemical parameters, including blood glucose and lipid profiles, were also measured to adjust potential confounding factors. Data were examined using SPSS version 27.0. Quantitative data were represented as the mean ± standard deviation (SD). Qualitative data were expressed by frequency and proportion. To compare the proportions between two qualitative criteria, chi-square was employed. The mean values of the cases and controls were compared by analyzing with the help of an independent T-test. Logistic regression analysis was performed to assess the association of vitamin B12 deficiency with the risk of acute ischemic stroke. Less than 0.05 range for p-values was considered significant.

RESULTS

Results reflected the demographics and clinical aspects of the study participants. The mean value of the age of cases was 64.8 ± 9.8 years, while controls had a mean value of the age of control individuals was 63.4 ± 9.1 years. There was no statistically significant variance seen between the age of both groups (p=0.35) or gender distribution (p=0.64). However, diabetes mellitus, hypertension and smoking habits were significantly more prevalent in the cases as compared to the control individuals (p≤0.05 for all) (Table 1).

Table 1: Demographic Features and Clinical Profiles of Participants

Characteristic	Cases (n=150)	Controls (n=150)	p-value
Age (mean ± SD year)	64.8 ± 9.8	63.4 ± 9.1	0.350**
Gender (Male/Female)	92/58	89/61	0.640**
Hypertension (%)	104 (69.3%)	60 (40%)	<0.001*
Diabetes Mellitus (%)	86 (57.3%)	52 (34.7%)	<0.001*
Smoking (%)	60 (40%)	38 (25.3%)	0.030*
Mean Homocysteine (µmol/L)	16.33 ± 3.29	9.76 ± 4.55	<0.001*

*means that Independent sample t-test was used; ** represents that chi-square test was used

The mean serum vitamin B12 levels in the blood were found significantly decreased in the stroke group (188.4 ± 43.6 pg/mL) when compared to the control group (352.7 ± 54.1 pg/mL, p<0.001). Homocysteine levels in the blood were found meaningfully elevated in case patients with stroke (16.33 ± 3.29 µmol/L) compared to controls (9.76 ± 4.55 µmol/L, p<0.001). Additionally, a majority of stroke patients had vitamin B12 deficiency (65.3%) compared to controls (18.7%) (Table 2).

Table 2: Serum Vitamin B12 Levels and Stroke Severity

Vitamin B12 Category	Cases (n=150)	Controls (n=150)	p-value
Mean vitamin B12 (pg/mL)	188.4 ± 43.6	352.7 ± 54.1	<0.001*
Mean Homocysteine (µmol/L)	16.33 ± 3.29	9.76 ± 4.55	<0.001*
Deficient Vitamin B12 (<200 pg/mL)	98 (65.3%)	28 (18.7%)	<0.001**
Insufficient Vitamin B12 (200–400 pg/mL)	35 (23.3%)	60 (40%)	<0.002**
Sufficient Vitamin B12 (>400 pg/mL)	17 (11.3%)	62 (41.3%)	<0.001*

*means that the Independent sample t-test was used; **represents that the chi-square test was used.

Stroke severity, at the time of hospital admission, evaluated with the help of NIHSS, was significantly higher in patients with vitamin B12 deficiency (mean NIHSS: 13.1 ± 4.2) and elevated homocysteine levels (mean NIHSS: 12.9 ± 4.3). Functional outcomes at 3 months, as calculated using mRS, were worse in patients with both vitamin B12 deficiency (mean mRS: 3.9 ± 1.2) and high homocysteine levels (mean mRS: 3.7 ± 1.3) (Table 3).

Table 3: Stroke Severity and Outcomes Based on Vitamin B12 Levels in Cases

Category	NIHSS Scores	mRS Scores at 3 Months	p-value (NIHSS)	p-value (mRS)
Deficient Vitamin B12 (<200 pg/mL)	13.1 ± 4.2	3.9 ± 1.2	-	-
Insufficient Vitamin B12 (200–400 pg/mL)	9.6 ± 3.1	2.8 ± 0.8	0.001	0.007
Sufficient Vitamin B12 (>400 pg/mL)	7.5 ± 2.5	2.3 ± 0.6	<0.001	<0.001
Elevated Homocysteine (>15 µmol/L)	12.9 ± 4.3	3.7 ± 1.3	<0.001	<0.001
Normal Homocysteine (≤15 µmol/L)	8.4 ± 2.9	2.6 ± 0.7	0.002	0.004

Independent samples t-test was applied and Results are shown in Mean ± SD

Logistic regression examination revealed that vitamin B12 deficiency and elevated homocysteine levels in blood were independently linked with an increased acute ischemic stroke risk. vitamin B12 deficiency had an odds ratio (OR) of 5.9 (95% CI: 2.9–12.3, p<0.001), while elevated homocysteine levels had an OR of 4.5 (95% CI: 2.4–8.6, p<0.001), after the adjustment of confounding variables (Table 4).

Table 4: Association of Risk of Acute Ischemic Stroke with Vit. B12 insufficiency

Variables	Odds Ratio (OR)	95% Confidence Interval (CI)	p-value
Vitamin B12 Deficiency (<200 pg/mL)	5.9	2.9–12.3	<0.001
Elevated Homocysteine (>15 µmol/L)	4.5	2.4–8.6	<0.001
Age (per year increase)	1.04	0.99–1.08	0.220
Male Gender	1.3	0.7–2.3	0.570
Hypertension	2.7	1.5–4.8	0.001

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Diabetes Mellitus	1.9	1.1–3.5	0.030
Smoking	1.5	0.8–2.9	0.140

Logistic regression analysis

DISCUSSION

Vitamin B12 which is a water-soluble vitamin, plays a critical role in neurological function, red blood cell formation and DNA synthesis. Its deficiency is increasingly being recognized as a modifiable risk factor for several cardiovascular and neurological disorders, including acute ischemic stroke [7]. One of the primary mechanisms linking vitamin B12 deficiency to stroke is its impact on homocysteine metabolism. Elevated homocysteine levels, a result of vitamin B12 deficiency, can cause endothelial dysfunction, oxidative stress, and a pro-thrombotic state, all of which contribute to cerebrovascular events. Despite these established links, the prevalence and clinical implications of vitamin B12 deficiency in stroke patients remain underexplored, particularly in populations with limited access to vitamin-rich diets or a high burden of undiagnosed deficiencies [11]. This study highlights the significant character of vitamin B12 deficiency as both a prognostic biomarker and a risk factor for acute ischemic stroke. Our findings demonstrated that serum vitamin B12 levels were meaningfully lesser in stroke patients (190.5 ± 45.7 pg/mL) in comparison to the control group (350.2 ± 55.6 pg/mL), consistent with prior research linking vitamin B12 deficiency to an increased risk of cardiovascular diseases, including stroke.The deficiency of vitamin B12 contributes to elevated homocysteine (Hcy) levels, which promote thrombosis through mechanisms such as enhanced platelet activation, endothelial dysfunction, and impaired fibrinolysis [12, 13]. In our study, 64% of stroke cases exhibited vitamin B12 deficiency compared to only 16% of controls, highlighting a strong correlation between stroke risk and lower vitamin B12 levels. Logistic regression analysis confirmed that vitamin B12 deficiency independently increased the odds of ischemic stroke (OR: 5.8, 95% CI: 2.4–13.9, p<0.001), even after regulating for traditional risk factors including age, gender, smoking, diabetes and hypertension. These results align with previous studies, such as Huang *et al.*, which demonstrated that supplementation with folate and vitamin B12 reduces the risk of stroke [14]. Moreover, earlier investigations have highlighted that vitamin B12 deficiency is a major contributor to hyper-homo-cysteinemia (HHC) in ischemic stroke patients, further reinforcing the connection between vitamin B12 status and stroke pathophysiology [14]. Stroke severity, assessed via the NIHSS score, was known to be significantly developed in patients with vitamin B12 deficiency (mean score: 12.6 ± 3.8) compared to those with sufficient levels. Additionally, a negative correlation between the modified Rankin Scale (mRS) and vitamin B12 levels at discharge and 28 days after that suggested that patients with higher vitamin B12 levels experienced improved recovery. These conclusions are in line with previous research, which demonstrated that maintaining adequate vitamin B12 levels improves cardiovascular outcomes and reduces stroke-related mortality [15]. For instance, studies have shown that widespread grain fortification with vitamin B12 in the United States and Canada contributed to a decline in stroke-related mortality, further supporting the role of vitamin B12 in cerebrovascular health [16]. Emerging evidence also supports a mechanistic link between vitamin B12 deficiency and stroke via homocysteine metabolism. Yuan *et al.* observed that homocysteine levels and the risk of cerebrovascular disease were influenced by the body's vitamin B12 status, emphasizing its crucial role in cardiovascular health [17]. Similarly, Wolffenbuttel *et al.*, found a significant inverse relationship between homocysteine and vitamin B12 levels (r=-0.59), highlighting the widespread prevalence of vitamin B12 deficiency even in non-vegetarian populations [18]. Manapurath *et al.*, reported a similar trend, noting a noteworthy correlation between low vitamin B12 levels and elevated homocysteine levels (r=0.41), with 67% of their study population being vitamin B12 deficient [19]. Interestingly, dietary habits alone may not fully explain the occurrence of vitamin B12 deficiency. While vegetarianism has been traditionally related to a higher risk of deficiency, studies have indicated that non-vegetarians can also exhibit deficiency due to factors such as impaired intestinal absorption or limited access to vitamin B12-rich foods due to economic constraints [20]. This finding aligns with our study, where no substantial variance was observed in dietary patterns between cases and controls, suggesting that other underlying factors may contribute to vitamin B12 deficiency in the population. Although no noteworthy variations in vitamin B12 levels were observed across TOAST stroke subtypes in our study, the overall findings highlight the importance of monitoring the position of vitamin B12 in stroke patients. Given the association between low vitamin B12 levels and worse clinical outcomes, addressing this deficiency may assist as a promising therapeutic strategy to progress stroke prognosis. Our findings emphasize the potential clinical value of screening and treating vitamin B12 deficiency as part of stroke prevention and management strategies.

This study was constrained by its single-center case-control design conducted at one tertiary care hospital in Mirpurkhas, which limits the generalizability of findings to

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Sindh's broader and ethnically diverse stroke population, including rural communities with distinct dietary patterns and healthcare access challenges. The absence of folate level measurements alongside vitamin B12 and homocysteine precluded a comprehensive assessment of the full one-carbon metabolic pathway's contribution to stroke risk, and the exclusion of patients with hemorrhagic stroke, TIA, and major comorbidities may have introduced selection bias by restricting the study to a relatively less medically complex ischemic stroke subpopulation. Furthermore, while functional outcomes were tracked at three months via mRS, the absence of longer-term follow-up and data on vitamin B12 supplementation interventions post-stroke limited conclusions about whether correcting deficiency improves prognosis. Future research should employ multicenter, prospective cohort designs across Sindh and other high-burden provinces with diverse dietary profiles, incorporating comprehensive micronutrient panels including folate and vitamin D alongside homocysteine profiling and genetic polymorphisms affecting B12 metabolism such as MTHFR variants. Randomized controlled trials evaluating the impact of routine vitamin B12 supplementation on stroke recurrence, severity, and functional recovery in deficient patients would provide the definitive evidence needed to incorporate B12 screening into Pakistan's national stroke prevention and management guidelines.

CONCLUSIONS

It was concluded that vitamin B12 deficiency is a significant contributor to both the risk and severity of ischemic stroke. Stroke patients with lower serum vitamin B12 levels experienced more severe strokes and poorer functional outcomes, as indicated by higher NIHSS and mRS scores. Logistic regression analysis demonstrated that vitamin B12 deficiency independently increases the risk of stroke, reinforcing its role as a prognostic biomarker and a modifiable risk factor. Clinically, these findings emphasize the importance of routine screening and early management of vitamin B12 deficiency to reduce stroke risk.

Authors' Contribution

Conceptualization: NA
Methodology: NA, LS, SA, HE
Formal analysis: HE
Writing and Drafting: NA, SA, MAA, AJ
Review and Editing: NA, SA, MAA, AJ

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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