

e-ISSN: 3108-8171

Volume: 3

Issue: 1

Year: 2026

Academic Journal of
Neuropsychiatry
and
Neuropsychology

AJNN



EDITORS-IN-CHIEF

Assoc. Prof. Şeyda ÇANKAYA

Department of Neurology, Faculty of Medicine, Alanya Alaaddin Keykubat University, Antalya, Türkiye

ASSOCIATE EDITORS-IN-CHIEF

Prof. Yasir ŞAFAK

Department of Psychiatry, Ankara Etlik City Hospital, University of Health Sciences, Ankara, Türkiye

Asst. Prof. Gülhan Gökçe CERAN

Division of Clinical Psychology, Department of Psychology, Faculty of Literature, Hacı Bayram Veli University, Ankara, Türkiye

EDITORIAL BOARD

Prof. Bülent BAKAR

Department of Neurosurgery, Faculty of Medicine, Kırıkkale University, Kırıkkale, Türkiye

Prof. Burak YULUĞ

Department of Neurology, Faculty of Medicine, Alanya Alaaddin Keykubat University, Antalya, Türkiye

Prof. Burak KAZANCI

Department of Neurosurgery, Faculty of Medicine, Ufuk University, Ankara, Türkiye

Prof. Burçak GÜMÜŞ

Department of Interventional Radiology, İstanbul Ataşehir Medicana Hospital, İstanbul, Türkiye

Prof. Hasan Rifat KOYUNCUOĞLU

Department of Neurology, Faculty of Medicine, Süleyman Demirel University, Isparta, Türkiye

Prof. Mehmet SEÇER

Department of Neurosurgery, Faculty of Medicine, Alanya Alaaddin Keykubat University, Antalya, Türkiye

Prof. Murat ALTAŞ

Department of Neurosurgery, Faculty of Medicine, Akdeniz University, Antalya, Türkiye

Prof. Tuba Tülay KOCA

Department of Physical Therapy and Rehabilitation, Faculty of Medicine, Kahramanmaraş Sütçü İmam University, Kahramanmaraş, Türkiye

Prof. Yeşim GÜZEY ARAS

Department of Neurology, Sakarya University Training and Research Hospital, Sakarya, Türkiye

Assoc. Prof. Çağatay ÖZDÖL

Department of Neurosurgery, Antalya Training and Research Hospital, Antalya, Türkiye

Assoc. Prof. Engin YÜCEL

Department of Neurosurgery, Alanya Alaaddin Keykubat University Alanya Training and Research Hospital, Antalya, Türkiye

Assoc. Prof. Halime ÇEVİK CENKERİ

Department of Interventional Radiology, İstanbul Bayındır İçerenköy Hospital, İstanbul, Türkiye

Assoc. Prof. İdris KOCATÜRK

Department of Neurology, Faculty of Medicine, Kastamonu University, Kastamonu, Türkiye

Assoc. Prof. İlker Deniz CİNGÖZ

Department of Neurosurgery, Faculty of Medicine, Uşak University, Uşak, Türkiye

Asst. Prof. Barış ÇANKAYA

Department of Anesthesiology and Reanimation, Faculty of Medicine, İstanbul Medipol University, İstanbul, Türkiye

Asst. Prof. Serhat YÜKSEL

Psychiatrist, Department of Psychology, Faculty of Arts and Sciences, Doğuş University, İstanbul, Türkiye

Spec. Mehmet Tunç, MD

Department of Neurology, Gülhane Training and Research Hospital, University of Health Sciences, Ankara, Türkiye

Spec. Ömer ARAS, MD

Department of Radiology, Amric Radiology Center, Newyork, USA

Spec. Tuba AKINCI, MD

Department of Neurology, İstanbul Haydarpaşa Numune Training and Research Hospital, İstanbul, Türkiye

LAYOUT EDITOR

Kübra YÜRÜMEZ

Graphic/Design, MediHealth Academy Publishing, Ankara, Türkiye

Dear Readers,

In this issue of the Academic Journal of Neuropsychiatry and Neuropsychology, we present a collection of articles addressing a range of important topics in neuropsychiatry and clinical neurology.

The contributions in this issue include original research and reviews focusing on cognitive and neurological conditions, as well as studies exploring the role of biological markers in disease processes. In addition, case reports highlight rare and clinically significant conditions, emphasizing the importance of careful diagnosis and clinical awareness.

Together, these articles reflect the multidisciplinary nature of the field and the ongoing efforts better to understand complex interactions between neurological and psychiatric disorders. They also signed that the value of both research and clinical observation lies in advancing knowledge and improving patient care.

We hope that the studies presented in this issue will provide useful insights for clinicians and researchers and contribute to future developments in neuropsychiatry.

We want to thank all authors and reviewers for their valuable contributions.

Assoc. Prof. Şeyda Çankaya
Editor-in-Chief

Volume: 3 Issue: 1 Year: 2026

ORIGINAL ARTICLE

The comparison of cognitive impairment between depression in Parkinson's disease and major depressive disorder 1-5

Çankaya Ş, Çankaya G, Yuluğ B.

Examining the correlation of CRP, MPV, and NLR levels with the severity of stroke in ischemic stroke patients 6-12

Varan E, Baraklı S, Ateş Malone S, Bektaş H.

REVIEW

Disruption of the microbiota-gut-brain-axis in severe traumatic brain injury: implications for novel therapeutic strategies-a narrative review 13-21

Adekunle OO, Odebode OT, Aliu-Ibrahim SA, et al.

CASE REPORT

Lateral meningocele syndrome in a Nigerian child: a case report and literature review 22-24

Yusuf AS, Idris MM, Adekunle OO, Bakwa ND, Muhammed AS.

Seizure-related head injury with rare etiology-Fahr's syndrome: a case report 25-27

Nugraha KYW.

The comparison of cognitive impairment between depression in Parkinson's disease and major depressive disorder

 Şeyda Çankaya¹,  Gül Çankaya²,  Burak Yuluğ^{*1}

¹Department of Neurology and Neuroscience, Faculty of Medicine, Alanya Alaaddin Keykubat University, Antalya, Türkiye

²Department of Nursing, Kosuyolu High Specialization Training and Research Hospital, İstanbul, Türkiye

Received: 19/11/2025

Accepted: 13/01/2026

Published: 29/03/2026

Cite this article: Çankaya Ş, Çankaya G, Yuluğ B. The comparison of cognitive impairment between depression in Parkinson's disease and major depressive disorder. *Acad J Neuropsychiatry Neuropsychol.* 2026;3(1):1-5. doi:10.51271/AJNN-0042

*Corresponding Author: Burak Yuluğ, burakyulug@gmail.com

ABSTRACT

Aim: Depression is not only a significant disorder that impacts the population, but it also manifests as a prevalent non-motor symptom associated with Parkinson's disease (PD). Despite considerable clinical and neuroimaging data regarding the pathophysiology of major depressive disorder (MDD), the neural mechanisms underlying depression in PD remain unresolved. This study aims to compare cognitive and demographic features in PD patients with depression and MDD patients.

Methods: Thirty-one Parkinson's patients with depression (PD-DEP) and 29 MDD individuals were recruited to the study. All participants underwent cognitive assessment with The Montreal Cognitive Assessment (MoCA) and The Mini-Mental State Examination (MMSE). Hamilton Depression Rating Scale (HDRS) was used to evaluate depression severity. Also, participants' demographic data was recorded.

Results: Compared with MDD, PD-DEP patients were older, less educated, and showed poorer MoCA/MMSE performance. A negative HDRS-MoCA correlation was found only in PD-DEP ($p=0.011$, $r=-0.464$). In binomial regression analyses age, Abstracting/Delayed Recall of MoCA subtests, education and, HDRS remained significant predictors for PD-DEP in the Backward Wald model.

Conclusion: Depression associated with PD is correlated with specifically impaired cognitive domains compared to MDD. These findings reinforce the hypothesis that depression related to PD constitutes a unique neuropsychiatric condition that needs more attention for the increased risk of cognitive deficit by clinicians.

Keywords: Parkinson's disease with depression, major depressive disorder, cognition, moca

INTRODUCTION

Parkinson's disease (PD) is traditionally diagnosed based on motor symptoms, including tremor, rigidity, and bradykinesia. However, clinical management must also address non-motor symptoms, which represent a significant aspect of the disease. These non-motor symptoms include neuropsychiatric disturbances such as depression, anxiety, sleep disorders, psychosis, behavioral changes, and cognitive impairments.^{1,2} Depression is one of the most prevalent and impactful non-motor symptoms, affecting 20% to 50% of PD patients,^{3,4} a rate much higher than that in the general population.⁵ Despite its prevalence, depression in PD is often underdiagnosed and undertreated in clinical practice.^{6,7} This can significantly worsen the progression and prognosis of the disease.⁸⁻¹¹ Although depression in PD may appear to represent a psychological reaction to coping with the chronic and debilitating effects of the disease, research suggests that it frequently predates the onset of motor symptoms. Studies

have found that individuals who later develop PD have an increased risk of depression even before diagnosis of PD.¹² This implies that PD itself serves as a biological risk factor for depression, independently of psychological reactions to the disease's motor symptoms. On the other hand, some studies have proposed the reverse, suggesting that depression may predispose individuals to develop PD later in life, as observed in other neurodegenerative diseases, such as Alzheimer's disease (AD).^{13,14}

Due to the intricate relationship between PD, depression, and cognitive impairment, including both neurobiological and psychological factors, it is crucially important to understand the shared pathophysiological mechanisms underlying these conditions,¹⁵ which could be essential for the development of effective therapeutic strategies, such as in other neurological diseases with a non-degenerative nature.¹⁶ In



that context, various pathophysiological theories have been proposed to explain depression in PD, including disrupted neurotransmitter function, brain metabolic abnormalities, and circuit dysfunction¹⁷⁻²³ as previously defined in Alzheimer's Disease²⁴⁻²⁶. Among them, there is strict evidence showing a decrease in frontal hypoperfusion and striatal dopamine transporter availability in PD-DEP compared to MDD patients.²⁷

These findings also align with neuroimaging studies in PD-DEP, which showed degree centrality abnormalities in the right middle prefrontal gyrus, anterior cingulate cortices, and supplementary motor cortices compared to PD without depression.²⁸ Also, a review based on SPECT analyses has found that several brain regions appear to be involved in depression, particularly the limbic system and the basal ganglia.²⁹ In addition, the serotonergic, dopaminergic, and noradrenergic systems also appear to be associated with depressive symptoms in PD.^{30,31} Despite this huge progress in understanding the underlying pathophysiological mechanism, a major limitation of clinical research into PD depression is that most studies rely on correlational analyses to examine depressive symptoms rather than directly comparing PD-DEP and MDD.³² Herein, a primary clinical approach to studying depressive symptoms and their influence on cognition in both groups may help determine whether depression should be considered an intrinsic feature of PD or a separate psychological reaction to it.

To the best of our knowledge, no research to date has directly compared patients with PD and depression and those with pure MDD in terms of cognitive changes.

METHODS

Ethics

The study was conducted with the permission of the Clinical Researches Ethics Committee of Alanya Alaaddin Keykubat University Faculty of Medicine (Date: 09/24/2025, Decision No: 13-14). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Participants

Thirty-one PD-DEP and 29 individuals with MDD were recruited from the Alanya Research and Training Hospital, Department of Neurology. PD was diagnosed by an experienced neurologist based on the UK PD Society Brain Bank criteria. Selection criteria for the patients included a diagnosis of MDD in accordance with the DSM-5 as determined by experienced psychiatrists.

All patients were evaluated with the HDRS, the MoCA, and the MMSE. Depressive symptoms were assessed using the 17-item Hamilton Depression Rating Scale (HDRS-17), a clinician-administered instrument widely used to evaluate the severity of depressive symptoms. Total scores range from 0 to 52, with higher scores indicating greater symptom severity. MMSE and MoCA were applied to measure cognitive impairment, while the MMSE test was used to rule out dementia. The MMSE assesses orientation, memory, attention, language, and visuospatial abilities, with total scores ranging from 0 to 30, and lower scores indicating

greater impairment.³³ Cognitive performance was further assessed with MoCA, a brief screening instrument designed to detect mild cognitive impairment. The MoCA evaluates multiple cognitive domains, including visuospatial/executive, naming, attention, concentration and calculation, language, abstraction, delayed recall, orientation abilities, with total scores ranging from 0 to 30.³⁴

Exclusion criteria for all subjects were the following: a) MMSE score less than 22, b) history of head trauma, stroke, and substance abuse/dependence currently or in the past, c) clinical evidence of any other significant current or past psychiatric or neurological illnesses, and d) usage of antimentia medication. G*power (ver. 3.1.6.6) software was used to determine the sample size. This analysis indicated that a minimum sample size of 40 subjects would be required to achieve 90% power at $\alpha=0.05$.

Statistical Analysis

Data analysis was carried out using the commercial statistical package software for social sciences (SPSS version 25.0, IBM, USA). The Shapiro-Wilk test was used to check the normality of the variables. Continuous variables are presented as mean \pm standard deviation (mean \pm SD) or median (IQR), depending on the normality test of the variable. Normally distributed data were analyzed with Student's t-test, non-normally distributed data were analyzed with a Mann-Whitney U test, and binary variables were analyzed with Fisher's exact test. Categorical variables were presented as frequency (n) and percentage (%). Binomial logistic regression was used to assess the association between diagnosis (PD-DEP versus MDD) and MoCA subtests, adjusted by age, education, gender, and HDRS scores. Two-sided p-values and 95% CIs were used in SPSS software. Significance was determined at $p<0.05$.

RESULTS

PD patients with depression were older (68.42 \pm 8.57) and less educated (5.51 \pm 5.51) than depressive patients (age: 49.41 \pm 15.00, $p<0.001$; education years: 10.82 \pm 0.66, $p<0.001$). Also, cognitive tests scores were lower in PD-DEP (MoCA: 20.58 \pm 4.35, MMSE: 25.52 \pm 2.66) than MDD (MoCA: 24.17 \pm 2.48, $p<0.001$; MMSE: 27.24 \pm 1.72, $p=.004$). While male gender was more observed in the PD-DEP group, female patients were significantly dominant in MDD (Fisher's exact test, $p=0.036$, **Table 1**). Comparing the Z scores of MoCA subtests revealed that Visuospatial/Executive, Naming, Attention, Abstracting, and Orientation were more impaired in PD-DEP subjects compared to MDD subjects (**Table 1**).

We have also investigated the relationship between MoCA and HDRS with partial correlation by adjusting for age and education. While these two variables were negatively correlated with each other in the PD-DEP group ($r: -0.464$, $p: 0.011$), there was no correlation between them in the MDD group ($r: -0.123$, $p: 0.542$). Also, HDRS and MoCA were shown to have a negative correlation in the whole sample ($r: -0.446$, $p<0.001$, **Table 2**).

In univariate regression analyses, MoCA subtest Z scores were used for predicting diagnosis, adjusting for age, education, gender, and HDRS score (**Table 3**). However, no subtest

Table 1. The comparison of clinic and demographic data between depressive patients with Parkinson's disease and patients with major depressive disorder

	PD (n=31) mean±SD	MDD (n=29) mean±SD	p
Age	68.42±8.57	49.41±15.00	<0.001*
Education	5.51±5.51	10.82±0.66	<0.001*
Gender (male)	16 (52%)	7 (24%)	0.036*
HDRS	17.10±10.85	10.96±5.00	0.007*
MoCA	20.58±4.35	24.17±2.48	<0.001*
MMSE	25.52±2.66	27.24±1.72	0.004*
MoCA subtests			
Visuospatial/executive (z score)	-0.37±1.12	0.40±0.67	0.002*
Naming (z score)	-0.26±0.89	0.28±1.05	0.035*
Attention (z score)	-0.27±1.13	0.29±0.75	0.029*
Language (z score)	-0.14±1.17	0.15±0.76	0.249
Abstraction (z score)	-0.41±0.99	0.44±0.82	<0.001*
Delayed recall (z score)	-0.12±0.97	0.13±1.03	0.333
Orientation (z score)	-0.31±1.29	0.35±0.25	0.008*

PD: Parkinson's disease, MDD: Major depressive disorder, HDRS: Hamilton Depression Rating Scale, MoCA: Montreal Cognitive Assessment, MMSE: Mini-Mental State Examination, n: Number of patients, SD: Standard deviation. *p<0.05: Significance level

Table 2. The correlation between HDRS and MoCA score in PD, MDD, and the whole sample

Groups	r	p
PD	-0.464	0.011*
MDD	-0.123	0.542
Whole group	-0.446	<0.001*

HDRS: Hamilton Depression Rating Scale; MoCA: Montreal Cognitive Assessment; PD: Parkinson's disease, MDD: Major depressive disorder. *p: Significance level

significantly predicted the diagnosis. When all variables were involved in multivariable regression analyses, only age (p: 0.0231, odds ratio (OR): 1.17, CI [1.02-1.34]) and education (p: 0.026, OR: 0.70 [0.51-0.95]) were shown to be significant in the model. But, in forward analyses, HDRS (p=0.041, OR: 1.188 [1.01-1.4]), Abstracting (p=0.026, OR:0.27 [0.09-0.86]), and Delayed Recall (p=0.047, OR: 4.08 [1.02-16.30]) remained beside age and education for predicting PD-DEP in the Backward Wald method (Table 3).

Table 3. Binary logistic regression model for depression in patients with Parkinson's disease by variables

	Univariate OR (95% CI)	p	Multivariable OR (95% CI)	p	Multivariable (BW-WALD) OR (95% CI)	p
Age	1.14 (1.06-1.22)	< 0.001*	1.17 (1.02-1.34)	.023*	1.170 (1.05-0.31)	.006*
Education	0.75 (0.65-0.87)	< 0.001*	0.70 (0.51-0.95)	.026*	.749 (0.59-0.95)	.017*
HDRS	1.12 (1.01-1.23)	.019*	1.14 (0.94-1.39)	.164	1.188 (1.01-1.4)	.041*
Gender						
	Male (reference category)					
Female	0.29 (0.99-0.9)	.032*	0.79 (0.07-8.88)	.849		
MoCA subtests						
Visuospatial/executive	0.39 (0.20-0.75)	.005*	0.42 (0.10-1.71)	.228		
Naming	0.53 (0.29-0.98)	.043*	2.21 (0.49-9.84)	.295		
Attention	0.52 (0.28-0.96)	.038*	1.40 (0.33-5.78)	.641		
Language	0.73 (0.42-1.24)	.248	2.16 (0.61-7.58)	.228		
Abstracting	0.35 (0.18-0.68)	.002*	0.29 (0.07-1.18)	.086	0.27 (0.09-0.86)	.026*
Delayed recall	0.77 (0.46-1.29)	.327	5.13 (0.85-31.0)	.074	4.08 (1.02-16.30)	.047*
Orientation	0.19 (0.03-0.94)	0.042*	0.19 (0.01-3.69)	0.277		

CI: Confidence interval, OR: Odds ratio; HDRS: Hamilton Depression Rating Scale; MoCA: Montreal Cognitive Assessment, *p<0.05: Significance level, BW-WALD: Backward Wald

DISCUSSION

Despite the relatively large body of data concerning depression, its effect on cognition in PD patients with depression has rarely been explored in the literature.

Our sensitive logistic regression analysis supported previous literature, indicating specifically impaired cognition in PD-DEP patients. In the present study, one of our major findings was that cognition in PD was negatively affected by mood, which was not evident in the MDD group. In detailed regression analysis, PD was negatively affected by the severity of HDRS and certain MoCA subtests (Abstracting, Delayed Recall), consistent with previous literature on specific cognitive impairments in PD-DEP patients.³⁵⁻³⁷

From another point of view, this suggests the detrimental effect of mood on cognition in PD, which our study confirmed with a significant correlation observed between HDRS scores and cognition only in the PD-DEP group. Despite this, it is challenging to draw a concrete conclusion, as we have not included a pure PD group, a topic that warrants further study.

Here, it is worth mentioning that one possible explanation for the lack of significance between the groups could be the relatively small sample size, which may have compromised our ability to detect differences between the two PD subgroups. Nevertheless, the comparable mean values and minimal standard deviations indicate that sample size alone is unlikely to explain these findings fully. Furthermore, since this study concentrated on examining subclinical cognitive differences among the groups, we incorporated participants with MMSE scores of 22 points or higher. By excluding participants with cognitive impairment, we may have overlooked more pronounced group differences, since these were only identified in specific subtests, which were further affected by the small sample size.

Another important observation in this study is the slightly higher HDRS scores among PD-DEP patients compared to those with MDD. This difference may initially appear to derive from the additional effects of the degenerative nature of PD and its association with disease neurobiology.³⁸⁻⁴²

From the cognitive point of view, numerous studies have shown that individuals with PD encounter more significant specific cognitive symptoms (i.e., concentration difficulties) relative to those suffering from depression alone⁴³ although a recent novel study suggested that the comorbidity of MDD and PD is likely the result of certain shared pathological processes, rather than a direct mutual cause-and-effect relationship.^{40,44}

This observation is consistent with previous evidence that PD-DEP may constitute a unique clinical entity,⁴⁵ which poses diagnostic challenges, since specific symptoms may not entirely fulfil the criteria for MDD and dementia^{3,4} but lead to significant disability.^{46,47}

Limitations

Several limitations to this study should be noted. First, the participants were relatively healthy and older at the time of enrolment, with a narrow age range. The findings may not, therefore, be fully generalizable to the broader PD population with depression. Second, the sample size was relatively small, with a limited number of PD cases involving individuals with normal cognition, making it difficult to draw clear comparisons with the healthy control group. Our findings should therefore be regarded as exploratory and preliminary, requiring validation in larger, future studies with a similar design.

Despite these limitations, our research sheds valuable light on an underexplored area, specifically, whether cognitively and functionally healthy individuals with MDD exhibit differences in cognitive features compared to PD patients with depression.

CONCLUSION

As a conclusion, the results of this study suggest that clinical differences between PD-DEP and MDD are multifactorial, and the cognitive status of PD patients might be affected by the depressive state and characteristics of PD patients, emphasizing the significant role of brain circuits in depression associated with PD that should be evaluated in further studies.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was conducted with the permission of the Clinical Researches Ethics Committee of Alanya Alaaddin Keykubat University Faculty of Medicine (Date: 09/24/2025, Decision No: 13-14).

Informed Consent

Written informed consent was obtained from all individual participants prior to their inclusion in the study. Participants were fully informed about the study's aims, procedures, potential risks and benefits, and their rights-including the right to withdraw at any time without consequence. All participants voluntarily signed a written informed consent form.

Peer Review Process

This manuscript was subject to external peer review.

Conflict of Interest

The authors declare no conflicts of interest related to this study.

Financial Disclosure

The authors received no financial support for the conduct or publication of this research.

Author Contributions

Concept: SC, GC, BY; Design: SC, GC; Supervision: BY; Data Collection and/or Processing: SC, GC; Analysis and/or Interpretation: SC, BY, Hİ; Literature Review: SC, GC; Manuscript Preparation: SC, GC, BY; Critical Review: All Authors

REFERENCES

- Hanoğlu L, Ercan FB, Mantar N, et al. Accelerated forgetting and verbal memory consolidation process in idiopathic nondemented Parkinson's disease. *J Clin Neurosci*. 2019;70:208-213. doi:10.1016/j.jocn.2019.08.012
- Aarsland D, Marsh L, Schrag A. Neuropsychiatric symptoms in Parkinson's disease. *Mov Disord*. 2009;24(15):2175-2186. doi:10.1002/MDS.22589
- Goodarzi Z, Mrklas KJ, Roberts DJ, Jette N, Pringsheim T, Holroyd-Leduc J. Detecting depression in Parkinson disease. *Neurology*. 2016; 87(4):426-437. doi:10.1212/WNL.0000000000002898
- Reijnders JSAM, Ehrt U, Weber WEJ, Aarsland D, Leentjens AFG. A systematic review of prevalence studies of depression in Parkinson's disease. *Mov Disord*. 2008;23(2):183-189. doi:10.1002/mds.21803
- Bromet E, Andrade LH, Hwang I, et al. Cross-national epidemiology of DSM-IV major depressive episode. *BMC Med*. 2011;9(1):90. doi:10.1186/1741-7015-9-90
- Dobkin RD, Rubino JT, Friedman J, Allen LA, Gara MA, Menza M. Barriers to mental health care utilization in Parkinson's disease. *J Geriatr Psychiatry Neurol*. 2013;26(2):105-116. doi:10.1177/0891988713481269
- Shulman S, Laursen B. Adolescent perceptions of conflict in interdependent and disengaged friendships. *J Res Adolesc*. 2002;12(3): 353-372. doi:10.1111/1532-7795.00037
- Hughes ME, Waite LJ, Hawkey LC, Cacioppo JT. A short scale for measuring loneliness in large surveys. *Res Aging*. 2004;26(6):655-672. doi:10.1177/0164027504268574
- Müller VI, Cieslik EC, Kellermann TS, Eickhoff SB. Crossmodal emotional integration in major depression. *Soc Cogn Affect Neurosci*. 2014;9(6):839-848. doi:10.1093/scan/nst057
- Ravina B, Camicioli R, Como PG, et al. The impact of depressive symptoms in early Parkinson disease. *Neurology*. 2007;69(4):342-347. doi:10.1212/01.wnl.0000268695.63392.10
- Starkstein SE, Mayberg HS, Leiguarda R, Preziosi TJ, Robinson RG. A prospective longitudinal study of depression, cognitive decline, and physical impairments in patients with Parkinson's disease. *J Neurol Neurosurg Psychiatry*. 1992;55(5):377-382. doi:10.1136/jnnp.55.5.377
- Kazmi H, Walker Z, Booij J, et al. Late onset depression: dopaminergic deficit and clinical features of prodromal Parkinson's disease: a cross-sectional study. *J Neurol Neurosurg Psychiatry*. 2021;92(2):158-164. doi: 10.1136/jnnp-2020-324266
- Nilsson FM, Kessing L V., Bolwig TG. Increased risk of developing Parkinson's disease for patients with major affective disorder: a register study. *Acta Psychiatr Scand*. 2001;104(5):380-386. doi:10.1034/j.1600-0447.2001.00372.x
- Schuurman AG, van den Akker M, Ensink KTJL, et al. Increased risk of Parkinson's disease after depression. *Neurology*. 2002;58(10):1501-1504. doi:10.1212/WNL.58.10.1501
- Leentjens AFG, Verhey FRJ. Depression and Parkinson's disease: a conceptual challenge. *Acta Neuropsychiatr*. 2002;14(3):147-153. doi:10.1034/j.1601-5215.2002.140308.x
- Yulug B. Neuroprotective treatment strategies for poststroke mood disorders: a minireview on atypical neuroleptic drugs and selective serotonin re-uptake inhibitors. *Brain Res Bull*. 2009;80(3):95-99. doi:10.1016/j.brainresbull.2009.06.013
- Mayberg HS, Solomon DH. Depression in Parkinson's disease: a biochemical and organic viewpoint. *Adv Neurol*. 1995;65:49-60.
- Matsui H, Nishinaka K, Oda M, Komatsu K, Kubori T, Udaka F. Minor depression and brain perfusion images in Parkinson's disease. *Mov Disord*. 2006;21(8):1169-1174. doi:10.1002/mds.20923

19. Mayberg HS, Starkstein SE, Sadzot B, et al. Selective hypometabolism in the inferior frontal lobe in depressed patients with Parkinson's disease. *Ann Neurol*. 1990;28(1):57-64. doi:10.1002/ana.410280111
20. Vriend C, Raijmakers P, Veltman DJ, et al. Depressive symptoms in Parkinson's disease are related to reduced. FP-CIT binding in the caudate nucleus. *J Neurol Neurosurg Psychiatry*. 2014;85(2):159-164. doi:10.1136/jnnp-2012-304811
21. Kostić VS, Pekmezović T, Tomić A, et al. Suicide and suicidal ideation in Parkinson's disease. *J Neurol Sci*. 2010;289(1-2):40-43. doi:10.1016/j.jns.2009.08.016
22. Bohnen NI, Frey KA. Imaging of cholinergic and monoaminergic neurochemical changes in neurodegenerative disorders. *Mol Imaging Biol*. 2007;9(4):243-257. doi:10.1007/s11307-007-0083-6
23. Huot P, Fox SH. The serotonergic system in motor and non-motor manifestations of Parkinson's disease. *Exp Brain Res*. 2013;230(4):463-476. doi:10.1007/s00221-013-3621-2
24. Ozansoy M, Ozansoy MB, Yulug B, et al. Melatonin affects the release of exosomes and tau-content in vitro amyloid-beta toxicity model. *J Clin Neurosci*. 2020;73:237-244. doi:10.1016/j.jocn.2019.11.046
25. Meng L, Jin H, Yulug B, et al. Multi-omics analysis reveals the key factors involved in the severity of the Alzheimer's disease. *Alzheimers Res Ther*. 2024;16(1). doi:10.1186/s13195-024-01578-6
26. Kilic U, Elibol B, Uysal O, et al. Specific alterations in the circulating levels of the SIRT1, TLR4, and IL7 proteins in patients with dementia. *Exp Gerontol*. 2018;111:203-209. doi:10.1016/j.exger.2018.07.018
27. Pålhagen SE, Carlsson M, Curman E, Wälinder J, Granérus AK. Depressive illness in Parkinson's disease-indication of a more advanced and widespread neurodegenerative process? *Acta Neurol Scand*. 2008;117(5):295-304. doi:10.1111/j.1600-0404.2007.00986.x
28. Wang H, Chen H, Wu J, et al. Altered resting-state voxel-level whole-brain functional connectivity in depressed Parkinson's disease. *Parkinsonism Relat Disord*. 2018;50:74-80. doi:10.1016/j.parkreldis.2018.02.019
29. Chagas MHN, Linares IMP, Garcia GJ, Hallak JEC, Tumas V, Crippa JAS. Neuroimaging of depression in Parkinson's disease: a review. *Int Psychogeriatr*. 2013;25(12):1953-1961. doi:10.1017/S1041610213001427
30. Prange S, Klinger H, Laurencin C, Danaila T, Thobois S. Depression in patients with Parkinson's disease: current understanding of its neurobiology and implications for treatment. *Drugs Aging*. 2022;39(6):417-439. doi:10.1007/s40266-022-00942-1
31. Aarsland D, Batzu L, Halliday GM, et al. Parkinson disease-associated cognitive impairment. *Nat Rev Dis Primers*. 2021;7(1):47. doi:10.1038/s41572-021-00280-3
32. Grachev ID. Dopamine transporter imaging with FP-CIT (DaTSCAN) in Parkinson's disease with depressive symptoms: a biological marker for causal relationships? *J Neurol Neurosurg Psychiatry*. 2014;85(2):130-131. doi:10.1136/jnnp-2013-305380
33. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12(3):189-198. doi:10.1016/0022-3956(75)90026-6
34. Nasreddine ZS, Phillips NA, Bédirian V, et al. The Montreal cognitive assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc*. 2005;53(4):695-699. doi:10.1111/j.1532-5415.2005.53221.x
35. Kalbe E, Folkerts AK, Witt K, Buhmann C, Liepelt-Scarfone I. German Society of Neurology guidelines for the diagnosis and treatment of cognitive impairment and affective disorders in people with Parkinson's disease: new spotlights on diagnostic procedures and non-pharmacological interventions. *J Neurol*. 2024;271(11):7330-7357. doi:10.1007/s00415-024-12503-0
36. Meng Y, Li X, Wang W, et al. Identification of age and underlying disease characteristics in patients with mild to moderate depression comorbid with Parkinson's disease: a retrospective case-control study. *Actas Esp Psiquiatr*. 2025;53(2):331-339. doi:10.62641/aep.v53i2.1702
37. Meng D, Jin Z, Wang Y, Fang B. Longitudinal cognitive changes in patients with early Parkinson's disease and neuropsychiatric symptoms. *CNS Neurosci Ther*. 2023;29(8):2259-2266. doi:10.1111/cns.14173
38. Cong S, Xiang C, Zhang S, Zhang T, Wang H, Cong S. Prevalence and clinical aspects of depression in Parkinson's disease: a systematic review and meta-analysis of 129 studies. *Neurosci Biobehav Rev*. 2022;141:104749. doi:10.1016/j.neubiorev.2022.104749
39. Backman EA, Luntamo L, Parkkola R, Koikkalainen J, Gardberg M, Kaasinen V. Early cortical atrophy is related to depression in patients with neuropathologically confirmed Parkinson's disease. *J Neurol Sci*. 2023;455:122804. doi:10.1016/j.jns.2023.122804
40. Shi Y, Dobkin R, Weintraub D, et al. Association of baseline depression and anxiety with longitudinal health outcomes in Parkinson's disease. *Mov Disord Clin Pract*. 2024;11(9):1103-1112. doi:10.1002/mdc3.14145
41. Tateno A, Nogami T, Sakayori T, Yamamoto K, Okubo Y. Depression as a prodromal symptom of neurodegenerative diseases. *J Nippon Med Sch*. 2023;90(2):157-164. doi:10.1272/JNMS.JNMS.2023_90-216
42. Urso D, Batzu L, Logroscino G, Ray Chaudhuri K, Pereira JB. Neurofilament light predicts worse nonmotor symptoms and depression in Parkinson's disease. *Neurobiol Dis*. 2023;185:106237. doi:10.1016/j.nbd.2023.106237
43. Ehrh U, Brønneck K, Leentjens AFG, Larsen JP, Aarsland D. Depressive symptom profile in Parkinson's disease: a comparison with depression in elderly patients without Parkinson's disease. *Int J Geriatr Psychiatry*. 2006;21(3):252-258. doi:10.1002/gps.1456
44. Xiang L, Xu R, Zhou X, Ren X, Li Z, Wu IXY. Associations between major depressive disorders and Parkinson's disease and impact of their comorbidity sequence. *J Affect Disord*. 2025;379:639-646. doi:10.1016/j.jad.2025.03.065
45. Magnard R, Vachez Y, Carcenac C, et al. What can rodent models tell us about apathy and associated neuropsychiatric symptoms in Parkinson's disease? *Transl Psychiatry*. 2016;6(3):e753. doi:10.1038/tp.2016.17
46. Burchill E, Watson CJ, Fanshawe JB, et al. The impact of psychiatric comorbidity on Parkinson's disease outcomes: a systematic review and meta-analysis. *Lancet Reg Health Eur*. 2024;39: 100870. doi:10.1016/j.lanepe.2024.100870
47. González-Usigli HA, Ortiz GG, Charles-Niño C, et al. Neurocognitive psychiatric and neuropsychological alterations in Parkinson's disease: a basic and clinical approach. *Brain Sci*. 2023;13(3):508. doi:10.3390/brainsci13030508

Examining the correlation of CRP, MPV, and NLR levels with the severity of stroke in ischemic stroke patients

 Edip Varan*¹,  Serdar Baraklı²,  Serra Ateş Malone²,  Hesna Bektaş²

¹Department of Neurology, Beypazarı State Hospital, Ankara, Türkiye

²Department of Neurology, Ankara Bilkent City Hospital, Ankara, Türkiye

Received: 26/12/2025

Accepted: 04/03/2026

Published: 29/03/2026

Cite this article: Varan E, Baraklı S, Ateş Malone S, Bektaş H. Examining the correlation of CRP, MPV, and NLR levels with the severity of stroke in ischemic stroke patients. *Acad J Neuropsychiatry Neuropsychol.* 2026;3(1):6-12. doi:10.51271/AJNN-0043

*Corresponding Author: Edip Varan, edp1990@hotmail.com

ABSTRACT

Aims: The severity of ischemic stroke may vary depending on the levels of certain biochemical markers. We aimed to investigate the relationship between C-reactive protein (CRP), mean platelet volume (MPV), and neutrophil-to-lymphocyte ratio (NLR) levels and stroke severity in patients presenting to the emergency department with ischemic stroke.

Methods: A total of 159 patients diagnosed with ischemic stroke and 160 healthy volunteers were included in the study. CRP, NLR, and MPV levels were measured in venous blood samples obtained in the emergency department. The relationship between National Institutes of Health Stroke Scale (NIHSS) scores and CRP, MPV, and NLR levels measured at the time of admission to the emergency department was examined.

Results: The mean CRP value of individuals in the control group was 6.19 ± 6.48 , and the mean CRP value of individuals in the patient group was 16.79 ± 18.14 . Patients had higher CRP values. CRP values showed statistically significant differences between the patient and control groups ($p < 0.001$). The mean NLR value of individuals in the control group was 2.50 ± 1.18 , and the mean NLR value of individuals in the patient group was 5.74 ± 5.40 . NLR values were higher in patients. NLR values showed statistically significant differences between the patient and control groups ($p < 0.001$). The mean MPV value of individuals in the control group was 8.15 ± 0.84 , and the mean MPV value of individuals in the patient group was 8.57 ± 1.40 . MPV values were higher in patients. MPV values showed statistically significant differences between the patient and control groups ($p = 0.002$).

Conclusion: The severity of ischemic stroke may vary depending on biochemical markers. Further research is needed to evaluate changes related to multiple biochemical parameters.

Keywords: Ischemic stroke, National Institutes of Health Stroke Scale, C-reactive protein, mean platelet volume, neutrophil-to-lymphocyte ratio

INTRODUCTION

Acute ischemic stroke (AIS) causes irreversible damage to brain tissue due to impaired cerebral blood flow. The incidence of AIS is relatively high; approximately 15 million people experience stroke worldwide each year.¹

It is also the main cause of permanent acquired disability, causing a heavy economic burden on society. AIS is the most common cerebrovascular disease and accounts for about 85% of all strokes.² Stroke risk prediction based on conventional risk factors such as hypertension (HT), diabetes mellitus (DM), and dyslipidemia remains inadequate. Identification of novel predictive biomarkers would contribute to risk prediction in subjects at risk of developing stroke. Inflammation plays an important role in the development of atherosclerosis.^{3,4}

C-reactive protein (CRP), an acute-phase reactant produced by hepatocytes, is considered a biomarker of inflammation. Meanwhile, hs-CRP accurately detects low-grade inflammation.⁵ A high CRP level, measured by hs-CRP, has been proposed as a risk factor for ischemic stroke or total stroke.⁶ A previous meta-analysis conducted by the Emerging Risk Factors Collaboration suggested that a 1-SD increment in CRP was associated with 46% and 39% greater risk of ischemic stroke and all strokes, respectively.⁷

Numerous studies have demonstrated that the neuroinflammatory response plays an essential role in the pathophysiology of ischemic stroke.⁸ Neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and lymphocyte-to-monocyte ratio (LMR) have recently



been reported as potential novel biomarkers of the baseline inflammatory process and could serve as predictors in patients with ischemic stroke.⁹

MPV is an important parameter reflecting platelet size and is considered a marker of platelet activity.¹⁰ Findings have shown that MPV is positively correlated with platelet activity.¹¹ Compared with cerebral infarction, the association between MPV and coronary disease has been more frequently reported. A meta-analysis of MPV in cardiovascular events found that patients with higher MPV had a 12% higher risk of death from cardiovascular events than those with lower MPV.¹² MPV also predicts the risk of ischemic stroke in patients with atrial fibrillation (AF).¹³

Previous studies have evaluated these parameters separately; however, this study is unique in simultaneously evaluating all three parameters. In our study, we aimed to examine the effects of CRP, NLR, and MPV on the severity of ischemic stroke.

METHODS

Ethics

This study was conducted with the approval of the Scientific and Evaluation Ethics Committee for Medical Researches at Ankara Bilkent City Hospital (Date: 05.11.2025, Decision No: TABED 1/1835/2025). Written informed consent was obtained. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The research was conducted as a prospective case-control study.

A total of 159 ischemic stroke patients who were admitted to the emergency department and subsequently hospitalized in the neurology inpatient clinic or neurology intensive care unit were included in the study. Additionally, 160 healthy volunteers aged between 18 and 80 years, with no history of stroke, malignancy, dementia, demyelinating disease, infectious disease, or inflammatory disease, participated. Detailed clinical, laboratory, and radiological characteristics of stroke patients were recorded. The presence of DM, HT, coronary artery disease, and AF was assessed.

National Institutes of Health Stroke Scale (NIHSS) was calculated at the time of the patients' admission to the emergency department. Blood samples were obtained from the patients at their initial presentation to the emergency department. CRP, NLR, and MPV values, which were routinely measured in the blood samples collected at admission, were recorded. CRP, MPV, and NLR values of healthy volunteers who applied to the neurology outpatient clinic were also measured, and the results were recorded.

Statistical Analysis

Demographic information, numbers, and percentage values of the individuals participating in the study were calculated. The Shapiro-Wilk test was used to check whether the continuous variables were normally distributed.

There were no differences between the patient and control groups regardless of age and gender. Independent sample t-test and chi-square comparison tests were used. The independent sample t-test was used to determine whether CRP, NLR, and MPV values showed significant differences between patients and controls.

Analysis was performed to determine whether there was a significant relationship between CRP, NLR, and MPV values and NIHSS values based on the patients' data. Pearson correlation coefficients were calculated. The corresponding numbers and percentage values were also calculated.

IBM SPSS Statistics 21.0 (IBM Corp., Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) was used for statistical analyses. G*Power 3.1 software was used for sample size calculation.

Results were considered statistically significant for $p < 0.05$.

RESULTS

The mean age of the individuals in the control group was calculated as 72.41 ± 8.47 , and the mean age of the individuals in the patient group was 71.60 ± 12.53 . No statistically significant difference was found in age values between the patient and control groups (Table 1).

61.3% of the individuals in the control group are female and 38.7% are male. In the patient group, 64.2% of the individuals are female and 35.8% are male. No difference was detected between the patient and control groups in terms of gender (Table 1).

Table 1. Patient and control group demographic information

Demographic information	Control n (%) mean±SD	Patient n (%) mean±SD	p
Age	72.41±8.47	71.60±12.53	0.425
Gender			
Women	92 (61.3)	102(64.2)	0.256
Men	58 (38.7)	57 (35.8)	

SD: Standard deviation

The mean CRP value of individuals in the control group was 6.19 ± 6.48 , and the mean CRP value of individuals in the patient group was 16.79 ± 18.14 . Patient individuals have higher CRP values. CRP values show statistically significant differences between patient and control groups ($p < 0.001$) (Table 2).

Table 2. Comparison of variables based on patient and control groups

Variables	Control mean±SD	Patient mean±SD	p
CRP	6.19±6.48	16.79±18.14	<0.001
NLR	2.50±1.18	5.74±5.40	<0.001
MPV	8.15±0.84	8.57±1.40	0.002

SD: Standard deviation, CRP: C-reactive protein, NLR: Neutrophil-to-lymphocyte ratio, MPV: Mean platelet volume

The mean NLR value of individuals in the control group was determined as 2.50 ± 1.18 , and the mean NLR value of individuals in the patient group was determined as 5.74 ± 5.40 .

NLR values of patient individuals are higher. NLR values show statistically significant differences between patient and control groups ($p < 0.001$) (Table 2).

The mean MPV value of individuals in the control group was 8.15 ± 0.84 , and the mean MPV value of individuals in the patient group was 8.57 ± 1.40 . MPV values of patient individuals are higher. MPV values show statistically significant differences between patient and control groups ($p = 0.002$) (Table 2).

A strong, positive, linear and statistically significant relationship was found between the CRP-NIHSS values of the patients included in the study ($p < 0.001$). As CRP value increase, NIHSS values increase (Table 3, Figure 1).

Variables	Group: patient	Test statistics
	Correlation coefficient	p
CRP-NIHSS	0.722	<0.001
NLR-NIHSS	0.263	0.001
MPV-NIHSS	0.625	<0.001

CRP: C-reactive protein, NIHSS: National Institutes of Health Stroke Scale, NLR: Neutrophil-to-lymphocyte ratio, MPV: Mean platelet volume

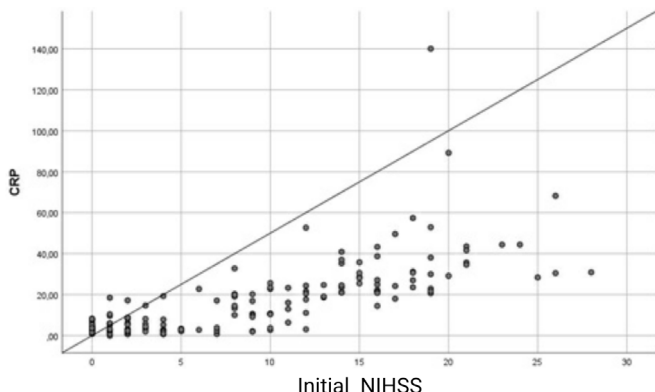


Figure 1. Relationship distribution between C-reactive protein-National Institutes of Health Stroke Scale

A weak, positive, linear and statistically significant relationship was found between the NLR-NIHSS values of the patients included in the study ($p = 0.001$). As NLR value increase, NIHSS values increase (Table 3, Figure 2).

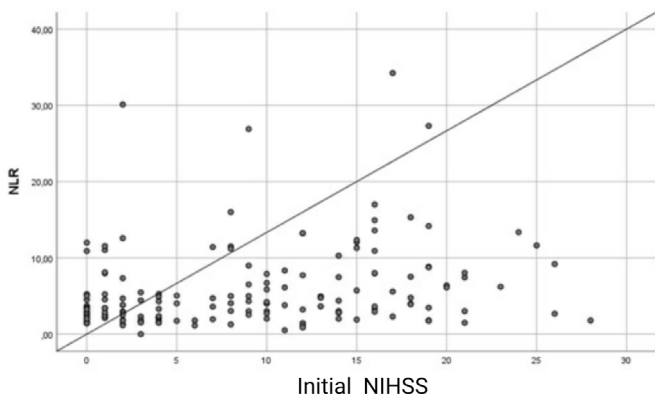


Figure 2. Relationship distribution between neutrophil-to-lymphocyte ratio-National Institutes of Health Stroke Scale

A medium-strength, positive, linear and statistically significant relationship was found between the MPV-NIHSS values of the patients included in the study ($p < 0.001$). As the MPV value increase, NIHSS values increase (Table 3, Figure 3).

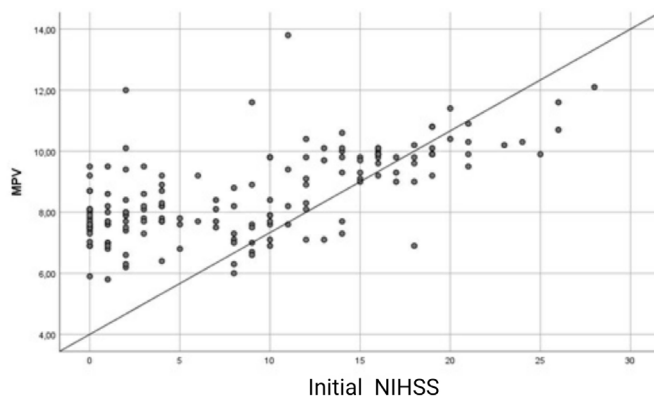


Figure 3. Relationship distribution between mean platelet volume-National Institutes of Health Stroke Scale

We examined the patient and control groups in terms of additional diseases. No significant difference was found between the two groups in terms of the presence of DM, HT, CAD and AF (Table 4).

Additional diseases	Control n (%)	Patient n (%)	p
HT	50 (31.25)	59 (37.11)	0.75
DM	40 (25)	44 (27.68)	0.155
CAD	45 (28.125)	51 (32.08)	0.96
AF	20 (12.5)	26 (16.35)	0.125

HT: Hypertension, DM: Diabetes mellitus, CAD: Coronary artery disease, AF: Atrial fibrillation

There were no statistically significant differences in CRP, MPV, and NLR parameters based on whether individuals had hypertension or not (Table 5).

Variables	Additional medical conditions		Test statistics	
	HT (-) mean±SD	HT (+) mean±SD	t	p
CRP	18.76±32.23	14.21±34.46	0.806	0.421
MPV	7.82±1.13	8.04±1.15	1.122	0.264
NLR	5.48±5.34	5.83±5.44	0.393	0.695

CRP: C-reactive protein, MPV: Mean platelet volume, NLR: Neutrophil-to-lymphocyte ratio, HT: Hypertension, SD: Standard deviation

There were no statistically significant differences in CRP, MPV, and NLR parameters based on whether individuals had diabetes mellitus or not (Table 6).

Variables	Additional medical conditions		Test statistics	
	DM (-) mean±SD	DM (+) mean±SD	t	p
CRP	17.02±37.08	13.42±26.47	0.644	0.521
MPV	7.90±1.12	8.10±1.19	1.058	0.292
NLR	6.03±5.34	5.12±5.49	1.013	0.313

CRP: C-reactive protein, MPV: Mean platelet volume, NLR: Neutrophil-to-lymphocyte ratio, DM: Diabetes mellitus, SD: Standard deviation

There were no statistically significant differences in CRP, MPV, and NLR parameters based on whether individuals had CAD or not (Table 7).

Variables	Additional medical conditions		Test statistics	
	CAD (-) mean±SD	CAD (+) mean±SD	t	p
CRP	17.34±38.65	13.79±25.26	0.642	0.522
MPV	7.94±1.15	8.03±1.15	0.460	0.646
NLR	5.72±5.49	5.84±5.31	0.129	0.897

CRP: C-reactive protein, MPV: Mean platelet volume, NLR: Neutrophil-to-lymphocyte ratio, CAD: Coronary artery disease, SD: Standard deviation

CRP, MPV, and NLR parameters did not show statistically significant differences based on whether individuals had AF or not (Table 8).

Variables	Additional medical conditions		Test statistics	
	AF (-) mean±SD	AF (+) mean±SD	t	p
CRP	14.77±27.89	19.11 ± 48.22	0.689	0.492
MPV	7.91±1.15	8.16 ± 1.14	1.175	0.242
NLR	5.26±4.90	6.35 ± 6.54	1.511	0.186

CRP: C-reactive protein, MPV: Mean platelet volume, NLR: Neutrophil-to-lymphocyte ratio, AF: Atrial fibrillation, SD: Standard deviation

When analyzed according to TOAST classification, the mean CRP level was 14.14±24.29 in the extensive arterial atherosclerosis group, 10.20±15.68 in the cardioembolism group, 27.76 ± 56.07 in the small vessel occlusion group, 13.90±31.05 in the ischemic stroke due to other identified causes group, and 3.60±1.45 in the ischemic stroke of unknown cause group. No statistically significant difference was observed in CRP levels across TOAST subtypes (p=0.236) (Table 9).

Similarly, the mean MPV values were 7.87±1.08 in the extensive arterial atherosclerosis group, 8.01±1.03 in the cardioembolism group, 8.15±1.34 in the small vessel occlusion group, 8.00±1.19 in the ischemic stroke due to other identified causes group, and 7.38±0.84 in the ischemic stroke of unknown cause group. MPV levels did not differ significantly among TOAST subtypes (p=0.636) (Table 9).

The mean NLR values were 5.81±5.26 in the extensive arterial atherosclerosis group, 5.05±4.16 in the cardioembolism group, 6.52±6.50 in the small vessel occlusion group, 5.50±5.60 in the ischemic stroke due to other identified causes group, and 5.06±4.07 in the ischemic stroke of unknown cause group. No

statistically significant differences were detected in NLR levels across TOAST etiological categories (p=0.874) (Table 9).

DISCUSSION

Although the relationship between ischemic stroke and acute-phase reactants (APR) has been reported in previous publications, some studies suggest that APR levels may be normal in stroke patients and may not be determinants of prognosis.¹⁴ CRP, as an APR, may reflect inflammation associated with the etiopathogenesis of ischemic stroke and is a plasma marker for atherothrombotic diseases. CRP most likely recognizes phospholipid components of damaged cells and foreign pathogens and affects the inflammatory process by binding to phosphocholine.¹⁵ CRP may contribute to pathogenesis and a procoagulant state. High CRP levels have been associated with a two-fold increase in AIS in men, a five-fold increase in any vascular event in women, and a seven-fold increase in myocardial infarction or stroke.¹⁶

In the study conducted by Beamer et al.,¹⁷ CRP levels were found to increase in the early period in patients with ischemic stroke. In the study of 151 patients conducted by Montaner et al.,¹⁸ the relationship between CRP levels and mortality in stroke patients treated with tissue plasminogen activator (TPA) was evaluated, and mortality was found to be higher in patients with elevated CRP levels. In the same study, no correlation was found between stroke severity and CRP. In the study conducted by Muir et al.,¹⁹ including 283 patients, CRP levels were found to be higher in patients with ischemic stroke and in those with higher NIHSS values, indicating a relationship between stroke severity and CRP. Similarly, Di Napoli et al.²⁰ demonstrated that CRP levels were elevated in ischemic stroke patients and were positively associated with stroke severity.

In our study, which included 319 individuals, CRP levels were significantly higher in ischemic stroke patients compared with the control group. A positive correlation was observed between admission NIHSS scores and CRP levels, indicating an association between stroke severity and CRP. Based on existing literature and our findings, CRP appears to be an important biochemical marker in ischemic stroke. However, further comprehensive studies are needed.

In recent years, neuroinflammation has attracted increasing attention, and numerous studies have confirmed that inflammatory mechanisms play crucial roles in the pathogenesis and progression of ischemic stroke.²¹ Peripheral leukocytes are recruited by inflammatory cytokines and chemokines released from ischemic tissue. Conversely,

Variables	Toast classification					Test statistics	
	Extensive arterial atherosclerosis (n=52) mean±SD	Cardioembolism (n=26) mean±SD	Small vessel occlusion (n=31) mean±SD	Ischemic stroke due to other identified causes (n=45) mean±SD	Ischemic stroke of unknown cause (n=5) mean±SD	F	p
CRP	14.14±24.29	10.20±15.68	27.76±56.07	13.90±31.05	3.60±1.45	1.401	0.236
MPV	7.87±1.08	8.01±1.03	8.15±1.34	8.00±1.19	7.38±0.84	0.638	0.636
NLR	5.81±5.26	5.05±4.16	6.52±6.50	5.50±5.60	5.06±4.07	0.306	0.874

One-way ANOVA, CRP: C-reactive protein, MPV: Mean platelet volume, NLR: Neutrophil-to-lymphocyte ratio, SD: Standard deviation

peripheral leukocytes may also influence ischemic tissue. Lymphocyte counts have been suggested to exert neuroprotective effects and contribute to neurological recovery.²² Peripheral monocytes and neutrophils may serve as sources of matrix metalloproteinase-9, contributing to hemorrhagic transformation and symptomatic deterioration.^{23,24} Neutrophils may also induce free oxygen radicals, leading to brain injury.²⁵ Furthermore, AIS may result in platelet dysfunction, and excessive platelet activation and aggregation may impair stroke recovery.²⁶

Goyal et al.²⁷ reported that admission NLR may serve as a prognostic biomarker in patients with large vessel occlusion stroke. In a study by Gong et al.²⁸ including 1,060 patients, NLR was found to be higher in patients with early neurological deterioration, and a positive relationship was observed between stroke severity and NLR. Similarly, Zhu et al.²⁹ reported that NLR was elevated in patients with higher NIHSS scores and was positively associated with stroke severity. In our study, NLR levels were significantly higher in ischemic stroke patients, and a positive correlation was found between NLR and NIHSS scores.

In a study conducted by Bath et al.³⁰ involving 3,134 patients with cerebrovascular disease, MPV was identified as an independent determinant of stroke risk. Sadeghi et al.³¹ reported higher MPV levels in ischemic stroke patients, and Sarkar et al.³² demonstrated that platelet indices could predict stroke severity. A meta-analysis by Zheng et al.³³ showed that elevated MPV was associated with unfavorable clinical outcomes in ischemic stroke. Ludhiadch et al.³⁴ also reported increased MPV levels in ischemic stroke patients and suggested its potential use as a biomarker.

Inflammation plays a central role in ischemic stroke pathophysiology beyond the initial vascular occlusion. Increasing evidence characterizes AIS as a thromboinflammatory syndrome rather than a purely hemodynamic event.³⁵⁻³⁷ Following arterial occlusion, damage-associated molecular patterns (DAMPs) released from ischemic tissue activate microglia and endothelial cells, triggering proinflammatory cytokine release (IL-6, TNF- α , IL-1 β), leukocyte recruitment, endothelial dysfunction, blood-brain barrier disruption, and secondary neuronal injury.^{36,37}

CRP should therefore be regarded not only as an acute-phase marker but also as a mediator of vascular inflammation. It contributes to complement activation and procoagulant signaling,^{38,39} and elevated levels have been associated with infarct volume and unfavorable outcomes.⁴⁰ The strong correlation between CRP and NIHSS in our study likely reflects the magnitude of systemic thromboinflammatory activation accompanying more extensive cerebral injury.

NLR integrates innate immune activation and relative adaptive immune suppression. Neutrophils exacerbate ischemic damage through reactive oxygen species and neutrophil extracellular traps (NETs), key mediators of immunothrombosis linking inflammation to thrombus formation.^{41,42} Conversely, post-stroke lymphopenia has been associated with worse outcomes.⁴³ Recent meta-analyses confirm that elevated admission NLR independently predicts

stroke severity,⁴⁴ supporting the biological plausibility of our findings.

Platelets are active mediators of immune-thrombotic crosstalk. Mean platelet volume (MPV) reflects platelet reactivity; larger platelets exhibit enhanced prothrombotic potential and adhesion molecule expression.⁴⁵ Platelet-leukocyte interactions amplify thromboinflammatory responses,^{44,46} and elevated MPV has been linked to greater stroke severity and poorer outcomes.^{34,47} The moderate-to-strong association between MPV and NIHSS in our cohort aligns with this concept.

In this prospective case-control study, we demonstrated that serum CRP, NLR, and MPV levels were significantly higher in patients with AIS compared with healthy controls. All three biomarkers showed positive correlations with stroke severity as assessed by the NIHSS at admission. CRP and MPV exhibited strong correlations, whereas NLR showed a weaker but statistically significant association.

Importantly, the associations between CRP, NLR, and MPV and stroke severity were independent of common vascular comorbidities such as hypertension, diabetes mellitus, coronary artery disease, and atrial fibrillation. Furthermore, no statistically significant differences were detected across TOAST etiological subtypes. These findings suggest that systemic inflammatory and platelet activation responses may represent a shared downstream pathway in AIS, regardless of stroke etiology.

Several methodological strengths reinforce the validity of our findings. The prospective design enhances data reliability and reduces potential bias. The inclusion of a well-matched healthy control group enabled direct comparison of inflammatory biomarker levels. Stroke severity was assessed using the NIHSS, an internationally validated and objective neurological scoring system. Additionally, the total sample size (n=319) provides reasonable statistical power to detect clinically meaningful associations. The performance of TOAST-based subtype analyses further increases the comprehensiveness of the study.

Limitations

Nevertheless, several limitations should be acknowledged. The study was conducted in a single center with a relatively modest sample size. Biomarkers were measured only at admission, precluding evaluation of dynamic temporal changes. Longitudinal measurements and multicenter validation studies are needed to confirm the prognostic value of these parameters and to determine whether modulation of thromboinflammatory pathways translates into improved clinical outcomes.

In conclusion, our findings support the hypothesis that CRP, NLR, and MPV are significantly associated with stroke severity in acute ischemic stroke. These biomarkers likely reflect underlying immune activation and immunothrombotic mechanisms contributing to neurological deficit. Future large-scale, prospective studies are warranted to further clarify their mechanistic role and therapeutic implications in AIS.

CONCLUSION

Ischemic stroke can occur suddenly and may cause physical disability or even death. There is a need for reliable biomarkers to predict ischemic stroke and determine its severity, thereby potentially reducing disability associated with the disease. For this purpose, we examined the relationship between CRP, NLR, and MPV levels and stroke and found positive associations.

The limitations of our study include the relatively small sample size and the lack of serial measurements of biomarkers at regular intervals. We also demonstrated a relationship between CRP, NLR, and MPV levels and stroke severity. Therefore, we suggest that CRP, NLR, and MPV may be useful in predicting ischemic stroke and assessing its severity. However, randomized, double-blind, placebo-controlled clinical trials on this topic are still lacking and are needed to further clarify their predictive value in ischemic stroke and stroke severity.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was conducted with the approval of the Scientific and Evaluation Ethics Committee for Medical Researches at Ankara Bilkent City Hospital (Date: 05.11.2025, Decision No: TABED 1/1835/2025).

Informed Consent

Written informed consent was obtained from all individual participants prior to their inclusion in the study. Participants were fully informed about the study's aims, procedures, potential risks and benefits, and their rights-including the right to withdraw at any time without consequence. All participants voluntarily signed a written informed consent form.

Peer Review Process

This manuscript was subject to external peer review.

Conflict of Interest

The authors declare no conflicts of interest related to this study.

Financial Disclosure

The authors received no financial support for the conduct or publication of this research.

Author Contributions

Conceptualization: EV, SB; Study Design: EV, SB, SAM; Supervision: EV, SB, HB; Data Collection and/or Processing: EV, SAM; Data Analysis and/or Interpretation: EV, SB, SAM, HB; Literature Review: EV, SB; Manuscript Writing: EV, SB; Critical Review: All Authors.

REFERENCES

- Avan A, Digaleh H, Di Napoli M, et al. Socioeconomic status and stroke incidence, prevalence, mortality, and worldwide burden: an ecological analysis from the Global Burden of Disease Study 2017. *BMC Med*. 2019;17(1):191. doi:10.1186/s12916-019-1397-3
- Zhang T, Jiang Y, Zhang S, et al. The association between homocysteine and ischemic stroke subtypes in Chinese: a meta-analysis. *Medicine (Baltimore)*. 2020;99(12):e19467. doi:10.1097/MD.00000000000019467
- Libby P. Inflammation in atherosclerosis. *Nature*. 2002;420(6917):868-874. doi:10.1038/nature01323
- Corrado E, Rizzo M, Coppola G, et al. An update on the role of markers of inflammation in atherosclerosis. *J Atheroscler Thromb*. 2010;17(1):1-11. doi:10.5551/jat.2600
- Musunuru K, Kral BG, Blumenthal RS, et al. The use of high-sensitivity assays for C-reactive protein in clinical practice. *Nat Clin Pract Cardiovasc Med*. 2008;5(10):621-635. doi:10.1038/ncpcardio1322
- Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. *N Engl J Med*. 1997;336(14):973-979. doi:10.1056/NEJM199704033361401
- Emerging Risk Factors Collaboration, Kaptoge S, Di Angelantonio E, et al. C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-analysis. *Lancet*. 2010;375(9709):132-140. doi:10.1016/S0140-6736(09)61717-7
- Dong X, Gao J, Zhang CY, Hayworth C, Frank M, Wang Z. Neutrophil membrane-derived nanovesicles alleviate inflammation to protect mouse brain injury from ischemic stroke. *ACS Nano*. 2019;13(2):1272-1283. doi:10.1021/acsnano.8b0657
- Zhu B, Pan Y, Jing J, et al. Neutrophil counts, neutrophil ratio, and new stroke in minor ischemic stroke or TIA. *Neurology*. 2018;90(21):e1870-e1878. doi:10.1212/WNL.0000000000005554
- Farah R, Samra N. Mean platelets volume and neutrophil to lymphocyte ratio as predictors of stroke. *J Clin Lab Anal*. 2018;32(1):e22189. doi:10.1002/jcla.22189
- Cochran KA, Cavallari LH, Shapiro NL, Bishop JR. Bleeding incidence with concomitant use of antidepressants and warfarin. *Ther Drug Monit*. 2011;33(4):433-438. doi:10.1097/FTD.0b013e318224996e
- Sansanayudh N, Numthavaj P, Muntham D, et al. Prognostic effect of mean platelet volume in patients with coronary artery disease. A systematic review and meta-analysis. *Thromb Haemost*. 2015;114(6):1299-1309. doi:10.1160/TH15-04-0280
- Zheng M, Chen S, Zhu Y, Gu X. Mean platelet volume: a new predictor of ischaemic stroke risk in patients with nonvalvular atrial fibrillation. *BMC Cardiovasc Disord*. 2020;20(1):241. doi:10.1186/s12872-020-01525-x
- Ridker PM, Rifai N, Rose L, Buring JE, Cook NR. Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. *N Engl J Med*. 2002;347(20):1557-1565. doi:10.1056/NEJMoa021993
- Sharp FR, Lu A, Tang Y, Millhorn DE. Multiple molecular penumbras after focal cerebral ischemia. *J Cereb Blood Flow Metab*. 2000;20(7):1011-1032. doi:10.1097/00004647-200007000-00001
- Siesjö BK. Pathophysiology and treatment of focal cerebral ischemia. Part I: Pathophysiology. *J Neurosurg*. 1992;77(2):169-184. doi:10.3171/jns.1992.77.2.0169
- Beamer NB, Coull BM, Clark WM, Briley DP, Wynn M, Sexton G. Persistent inflammatory response in stroke survivors. *Neurology*. 1998;50(6):1722-1728. doi:10.1212/wnl.50.6.1722
- Montaner J, Fernandez-Cadenas I, Molina CA, et al. Poststroke C-reactive protein is a powerful prognostic tool among candidates for thrombolysis. *Stroke*. 2006;37(5):1205-1210. doi:10.1161/01.STR.0000217744.89208.4e
- Muir KW, Weir CJ, Alwan W, Squire IB, Lees KR. C-reactive protein and outcome after ischemic stroke. *Stroke*. 1999;30(5):981-985. doi:10.1161/01.str.30.5.981
- Di Napoli M, Papa F, Bocola V. C-reactive protein in ischemic stroke: an independent prognostic factor. *Stroke*. 2001;32(4):917-924. doi:10.1161/01.str.32.4.917
- Rust R, Grönnert L, Schwab ME. Inflammation after stroke: a local rather than systemic response? *Trends Neurosci*. 2018;41(12):877-879. doi:10.1016/j.tins.2018.09.011
- Macrez R, Ali C, Toutirais O, et al. Stroke and the immune system: from pathophysiology to new therapeutic strategies. *Lancet Neurol*. 2011;10(5):471-480. doi:10.1016/S1474-4422(11)70066-7
- Duan Z, Wang H, Wang Z, et al. Neutrophil-lymphocyte ratio predicts functional and safety outcomes after endovascular treatment for acute ischemic stroke. *Cerebrovasc Dis*. 2018;45(5-6):221-227. doi:10.1159/000489401
- Yamamoto Y, Osanai T, Nishizaki F, et al. Matrix metalloprotein-9 activation under cell-to-cell interaction between endothelial cells and monocytes: possible role of hypoxia and tumor necrosis factor- α . *Heart Vessels*. 2012;27(6):624-633. doi:10.1007/s00380-011-0214-5

25. Ceulemans AG, Zgavc T, Kooijman R, Hachimi-Idrissi S, Sarre S, Michotte Y. The dual role of the neuroinflammatory response after ischemic stroke: modulatory effects of hypothermia. *J Neuroinflammation*. 2010;7:74. doi:10.1186/1742-2094-7-74
26. Xu XR, Zhang D, Oswald BE, et al. Platelets are versatile cells: new discoveries in hemostasis, thrombosis, immune responses, tumor metastasis and beyond. *Crit Rev Clin Lab Sci*. 2016;53(6):409-430. doi:10.1080/10408363.2016.1200008
27. Goyal N, Tsivgoulis G, Chang JJ, et al. Admission neutrophil-to-lymphocyte ratio as a prognostic biomarker of outcomes in large vessel occlusion strokes. *Stroke*. 2018;49(8):1985-1987. doi:10.1161/STROKEAHA.118.021477
28. Gong P, Liu Y, Gong Y, et al. The association of neutrophil to lymphocyte ratio, platelet to lymphocyte ratio, and lymphocyte to monocyte ratio with post-thrombolysis early neurological outcomes in patients with acute ischemic stroke. *J Neuroinflammation*. 2021;18(1):51. doi:10.1186/s12974-021-02090-6
29. Zhu F, Ji Y, Song JH, Huang GX, Zhang YF. Correlations between NLR, NHR, and clinicopathological characteristics, and prognosis of acute ischemic stroke. *Medicine (Baltimore)*. 2023;102(24):e33957. doi:10.1097/MD.00000000000033957
30. Bath P, Algert C, Chapman N, Neal B; PROGRESS Collaborative Group. Association of mean platelet volume with risk of stroke among 3134 individuals with history of cerebrovascular disease. *Stroke*. 2004;35(3):622-626. doi:10.1161/01.STR.0000116105.26237.EC
31. Sadeghi F, Kovács S, Zsóri KS, Csiki Z, Bereczky Z, Shemirani AH. Platelet count and mean volume in acute stroke: a systematic review and meta-analysis. *Platelets*. 2020;31(6):731-739. doi:10.1080/09537104.2019.1680826
32. Sarkar RN, Das CK, Bhattacharjee U, Banerjee M. Platelet indices as a marker of severity in non-diabetic, non-hypertensive acute ischemic stroke patients. *J Assoc Physicians India*. 2018;66(7):40-42.
33. Zheng YY, Wang L, Shi Q. Mean platelet volume (MPV) and platelet distribution width (PDW) predict clinical outcome of acute ischemic stroke: a systematic review and meta-analysis. *J Clin Neurosci*. 2022;101:221-227. doi:10.1016/j.jocn.2022.05.019
34. Ludhiadch A, Sulena, Singh S, et al. Genomic variation affecting MPV and PLT count in association with development of ischemic stroke and its subtypes. *Mol Neurobiol*. 2023;60(11):6424-6440. doi:10.1007/s12035-023-03460-2
35. Iadecola C, Buckwalter MS, Anrather J. Immune responses to stroke: mechanisms, modulation, and therapeutic potential. *J Clin Invest*. 2020;130(6):2777-2788. doi:10.1172/JCI135530
36. Liesz A, Dalpke A, Mracsko E, et al. DAMP signaling in post-ischemic brain inflammation. *Nat Rev Neurol*. 2021;17(3):133-149. doi:10.1523/JNEUROSCI.2439-14.2015
37. Jayaraj RL, Azimullah S, Beiram R, Jalal FY, Rosenberg GA. Neuroinflammation: friend and foe for ischemic stroke. *J Neuroinflammation*. 2019;16(1):142. doi:10.1186/s12974-019-1516-2
38. Sproston NR, Ashworth JJ. Role of C-reactive protein at sites of inflammation and infection. *Front Immunol*. 2018;9:754. doi:10.3389/fimmu.2018.00754
39. Wang L, Song Q, Wang C et al. Neutrophil to lymphocyte ratio predicts poor outcomes after acute ischemic stroke: a cohort study and systematic review. *J Neurol Sci*. 2019;406:116445. doi:10.1016/j.jns.2019.116445
40. Bian J, Guo S, Huang T et al. CRP as a potential predictor of outcome in acute ischemic stroke. *Biomed Rep*. 2023;18(2):17. doi:10.3892/br.2023.1599
41. Laridan E, Denorme F, Desender L, et al. Neutrophil extracellular traps in ischemic stroke thrombi. *Ann Neurol*. 2020;87(2):223-238.
42. Hunkler HJ, Groß S, Thum T, Bär C. Non-coding RNAs: key regulators of reprogramming, pluripotency, and cardiac cell specification with therapeutic perspective for heart regeneration. *Cardiovasc Res*. 2022;118(15):3071-3084. doi:10.1093/cvr/cvab335
43. Lyden P, Raman R, Liu L, Emr M, Warren M, Marler J. National Institutes of Health Stroke Scale certification is reliable across multiple venues. *Stroke*. 2009;40(7):2507-2511. doi:10.1161/STROKEAHA.108.532069
44. Zhang J, Ren Q, Song Y. Prognostic role of neutrophil-lymphocyte ratio in patients with acute ischemic stroke. *Medicine (Baltimore)*. 2017;96(45):e8624. doi:10.1097/MD.00000000000008624
45. Chu SG, Becker RC, Berger PB, et al. Mean platelet volume as a predictor of cardiovascular risk: a systematic review and meta-analysis. *J Thromb Haemost*. 2010;8(1):148-156. doi:10.1111/j.1538-7836.2009.03584.x
46. Zarbock A, Polanowska-Grabowska RK, Ley K. Platelet-neutrophil-interactions: linking hemostasis and inflammation. *Blood Rev*. 2007;21(2):99-111. doi:10.1016/j.blre.2006.06.001
47. Zheng YY, Wang L, Shi Q. MPV predicts clinical outcome of acute ischemic stroke: meta-analysis. *J Clin Neurosci*. 2022;101:221-227.

Disruption of the microbiota-gut-brain-axis in severe traumatic brain injury: implications for novel therapeutic strategies-a narrative review

 Olukorede Olabanji Adekunle*,  Olugbenga Timothy Odebode,  Salamat Ahuoiza Aliu-Ibrahim,  Nurudeen Abiola Adeleke,  Olakunle Michael Adegboye,  Oghenevwoke Isaiah Enaworu,  Hakeem Ayinde Yeqeen

Division of Neurosurgery, Department of Surgery, University of Ilorin Teaching Hospital, Ilorin, Kwara State, Nigeria

Received: 15/02/2026

Accepted: 28/03/2026

Published: 29/03/2026

Cite this article: Adekunle OO, Odebode OT, Aliu-Ibrahim SA, et al. Disruption of the microbiota-gut-brain-axis in severe traumatic brain injury: implications for novel therapeutic strategies-a narrative review. *Acad J Neuropsychiatry Neuropsychol.* 2026;3(1):13-21. doi:10.51271/AJNN-0044

*Corresponding Author: Olukorede Olabanji Adekunle, ooadekunle@rocketmail.com

ABSTRACT

Severe traumatic brain injury (TBI) frequently disturbs the normal balance of intestinal microorganisms, resulting in gut dysbiosis that can exacerbate neuroinflammation and worsen patient outcomes. The microbiota-gut-brain axis (MGBA) represents the integrated signalling pathways connecting the brain and gastrointestinal tract. Following severe TBI, this communication network becomes impaired, contributing to the cascade of secondary injury. As a result, the MGBA has emerged as a promising therapeutic focus.

This narrative review examines the workings of the MGBA and highlights evolving therapeutic approaches-including probiotics, prebiotics, postbiotics, prokinetics, and fecal microbiota transplantation (FMT)-that aim to re-establish microbial and neuroimmune balance in patients with severe TBI.

Keywords: Traumatic brain injury, microbiota-gut-brain axis, gut dysbiosis, probiotics, fecal microbiota transplantation

INTRODUCTION

Traumatic brain injury (TBI) results from mechanical trauma to the skull or brain and may lead to disturbances in consciousness and short- or long-term neurological deficits.¹ It remains a significant global health problem, particularly among young adults, where it contributes substantially to disability and death.² The incidence is higher in males, with road traffic crashes constituting the most common aetiology globally.³⁻⁷

Based on severity using the Glasgow Coma Scale (GCS),⁸ TBI is classified as mild (GCS 14-15), moderate (GCS 9-13) and severe (GCS 3-8).⁹ While mild and moderate TBI generally have favourable outcomes, severe TBI remains a major cause of disability and death despite advances in neurosurgical and critical care.¹⁰

Although the injury occurs within the cranial vault, its physiological influence extends systemically due to the brain's regulatory role over multiple organ systems.¹¹ The central nervous system (CNS) maintains a bidirectional relationship with the gastrointestinal tract (GIT) through the activities of the gut microflora.¹²

The GIT hosts a vast array of microorganisms that support digestion, immunity, and neural function.¹³⁻¹⁵ This microbial ecosystem communicates with the CNS through neural, endocrine, and immunological pathways collectively termed the microbiota-gut-brain axis (MGBA).¹² Under normal conditions, this system maintains intestinal stability and contributes to metabolic and neuromodulatory processes.¹⁶ Conversely, the gut microbiota produce some neuroactive compounds- including bacterial metabolites and neurotransmitters-that influence the activity of the enteric nervous system (ENS), and modulate vagal output signaling.¹⁶ Severe TBI, however, disrupts these interactions, promoting dysbiosis and systemic inflammation, which in turn may aggravate secondary brain injury.^{11,17} Consequently, the MGBA has become a potential therapeutic target in TBI management. Growing evidence suggests that modulating gut microbial composition through targeted interventions- such as probiotics, prebiotics, postbiotics, prokinetic drugs, and FMT- may help mitigate complications and improve recovery. This narrative review evaluates the MGBA and explores therapeutic strategies that may be incorporated into the management of severe TBI.^{18,19}



METHODOLOGY

A comprehensive literature search was performed using ClinicalTrials.gov, the European Union Clinical Trials Register, PubMed, and Google Scholar. The search focused on studies examining the relationship between severe TBI and the gut microbiome and included both animal and human research from 1990 up to 2025. Keywords included combinations of “traumatic brain injury,” “brain injury,” “head injury,” “gut,” “gastrointestinal,” “intestinal,” “gut-brain axis,” “microbiome,” “microbiota,” “probiotics,” “prebiotics,” “postbiotics,” “prokinetics,” “fecal microbiota transplantation,” “human” and “animal.” Boolean operators deployed were AND, OR and NOT while search strings included “microbiota” OR “microbiome” AND “gastrointestinal” OR “gut” OR “intestinal” AND “traumatic brain injury,” OR “brain injury” OR “head injury” AND “gut-brain axis” AND “human” OR “animal” AND “probiotics,” OR “prebiotics,” OR “postbiotics,” OR “prokinetics,” OR “fecal microbiota transplantation.” Priority was given to randomized controlled trials (RCTs), systematic reviews, and meta-analyses. Where these were unavailable, relevant narrative reviews and preclinical studies were included to provide mechanistic insights. The selection of literature for this review is summarized in **Table 1**, which categorizes the included evidence by study design and thematic focus.

Table 1. Summary of evidence and study characteristics

Evidence category	Included (n)	Primary thematic focus
Meta-analyses & systematic reviews	12	Clinical efficacy of prokinetics ^{7,79} & probiotics ⁵⁷
Randomized controlled trials	8	Direct human outcomes in TBI cohorts ^{61,64,76,78}
Preclinical (animal) studies	15	MGBA mechanisms, FMT pathways ⁸⁹ , & dysbiosis ^{33,34}
Observational & prospective studies	10	Infection rates & feeding tolerance ^{6,58,62}
Narrative reviews & consensus	25	Theoretical frameworks ^{47,48} & postbiotic definitions ⁸⁵
Foundational pathophysiology	15	TBI classification ^{8,9} & HPA axis disruption ³⁵

TBI: Traumatic brain injury, MGBA: Microbiota-gut-brain axis, FMT: Fecal microbiota transplantation, HPA: Hypothalamic-pituitary-adrenal axis

Exclusion Criteria

During the literature screening process, records were excluded based on the following pre-defined criteria: (1) studies focused exclusively on mild TBI without relevance to the severe injury cascade; (2) microbiome studies related to chronic metabolic or skin conditions with no CNS implications; and (3) sources published prior to 1990 (except for critical historical definitions) or those lacking full-text availability/peer-review status.

THE MICROBIOTA-GUT-BRAIN AXIS

The MGBA is a dynamic communication network linking gastrointestinal (GI) microorganisms with the CNS.²⁰ It serves as a conduit between the brain and the bowel, facilitating continuous physiological interaction. Signalling occurs through immune mediators, autonomic pathways-including the vagus nerve-and the ENS,^{20,21} as depicted in **Figure 22** below.

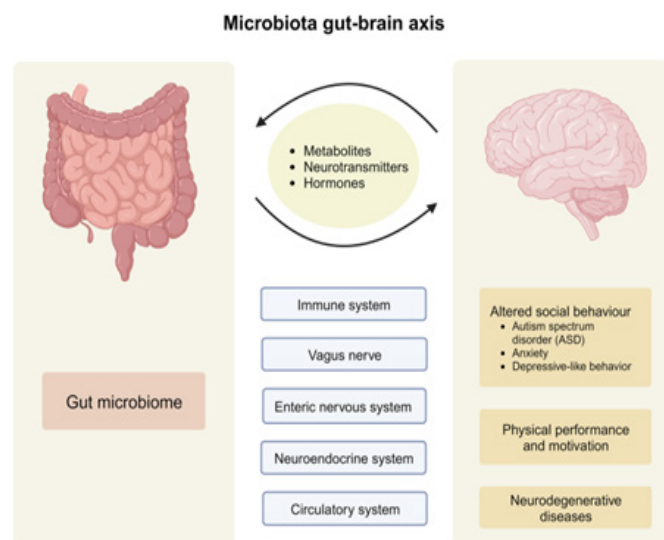


Figure. The microbiota-gut-brain axis-the bidirectional communication between the brain and the bowel. Adapted from Microbiota-gut-brain axis and its therapeutic applications in neurodegenerative diseases¹²

Autonomic fibers connect the GIT to the CNS via the vagus nerve and spinal afferent fibers associated with the gut’s extrinsic innervation.²⁰ Through these routes, the brain regulates intestinal activities such as motility and secretion, while gut microbes generate metabolites and neurotransmitter-like substances capable of influencing neural function.^{21,23}

Conversely, the gut microbiota can influence CNS functions through a number of mechanisms. Gut microbes produce neurotransmitters and organic compounds such as serotonin, gamma-aminobutyric acid (GABA), and short-chain fatty acids (SCFAs) which can control brain activity.^{24,25} SCFAs, for example, can cross the blood-brain barrier and modulate neuroimmune responses.^{24,26}

DYSFUNCTION OF THE MICROBIOTA-GUT-BRAIN-AXIS

Disruption of gut microbial composition can influence neurological processes in several ways. The MGBA plays an important role in mediating this relationship.^{27,28} Disruption of this axis due to dysbiosis has been associated with various neurological disorders and poorer outcomes in patients with severe TBI.²⁷

One major pathway involves the production and regulation of neurotransmitters. The gut microbiota produces neurotransmitters like serotonin and GABA which are essential for brain function.^{23,29} Altered microbial diversity may impair the production of neuroactive substances, promoting mood disturbances and cognitive dysfunction. Furthermore, dysbiosis can compromise the integrity of the gut barrier, resulting in increased gut permeability.³⁰⁻³² Increased intestinal permeability allows inflammatory molecules and bacterial metabolites to enter systemic circulation, potentially crossing the blood-brain barrier and provoking neuroinflammation.^{31,32}

The MGBA disruption and dysfunction following severe TBI involves several interconnected factors which include:

- **Catecholamine surge:** TBI causes sympathetic nervous system hyperactivity, leading to a “sympathetic storm” and a surge in circulating catecholamines (epinephrine and norepinephrine).³³ This surge redirects blood flow away from the GI tract, causing enteric ischemia and contributing to gut dysmotility.³³ The presence of high norepinephrine levels in the gut also directly favors the overgrowth of opportunistic pathogens like *Escherichia coli*, driving dysbiosis.³⁴
- **Cortisol/HPA axis:** The brain injury activates the hypothalamic-pituitary-adrenal (HPA) axis, leading to elevated cortisol levels.³⁵ High cortisol compromises the integrity of the intestinal epithelial barrier by reducing tight junction proteins, creating a “leaky gut”.³⁶ This increased permeability allows bacteria and their inflammatory components, such as lipopolysaccharides (LPS), to translocate from the gut lumen into the systemic circulation.³⁷
- **Enteric ischemia & ileus/feeding interruptions:** The sympathetic hyperactivity leads to reduced blood flow (ischemia) in the gut.³⁸ This, combined with damage to the ENS, results in decreased intestinal motility (ileus or gastroparesis).³⁸ Impaired motility and feeding interruptions exacerbate gut dysbiosis by creating an environment that favors pathogenic overgrowth and reduces the production of beneficial, anti-inflammatory SCFAs by commensal bacteria.³¹
- **Opioid/Sedation effects:** Opioids, commonly used for pain management and sedation in severe TBI patients, significantly disrupt the gut microbiome and physiology.³⁹ They further slow GI motility, contributing to constipation and ileus.³⁹ Opioids can decrease beneficial bacteria (e.g., *Lactobacillus*, *Ruminococcaceae*) and increase pathogenic microbes (e.g., *Enterococcus*, *Staphylococcus*), while also promoting bacterial virulence.⁴⁰ This enhances gut barrier disruption and systemic inflammation.
- **Antimicrobial exposure:** The common use of broad-spectrum antibiotics to treat or prevent infections in severe TBI patients, while necessary, further compounds gut dysbiosis by depleting diverse microbial populations, including beneficial commensals.⁴¹ This “extinction of the microbiota” can worsen outcomes, including increased neuronal loss and altered immune responses, by removing the protective effects of a healthy microbiome.²²
- **Nosocomial infection pressures:** The combination of compromised gut barrier function, systemic immunosuppression (initially induced by HPA axis activation), dysbiosis, and the presence of more virulent pathogenic bacteria creates a conducive milieu for nosocomial infections, such as pneumonia and sepsis.⁴² The translocation of gut bacteria into the bloodstream is a major pathway for these infections, which significantly increase morbidity and mortality in TBI patients.⁴³

These mechanisms underscore the importance of maintaining microbial balance and suggest that modulating gut flora may have therapeutic value in severe TBI.^{44,45} Therapeutic strategies including probiotics, prebiotics, prokinetics, and fecal microbiota transplantation (FMT) aim to restore microbial balance, reduce inflammation, and potentially improve clinical outcomes in patients with severe TBI.^{32,45,46}

PROBIOTICS

Probiotics consist of viable microorganisms that, when administered in sufficient amounts, exert beneficial effects on host physiology.^{47,48} They are widely used to stabilize intestinal flora, enhance mucosal barrier integrity, and modulate immune responses thus, helping to prevent infectious complications in various clinical conditions, including severe TBI.⁴⁸ They were discovered by the Russian scientist Elie Metchnikoff about a hundred years ago.⁴⁹ The term “probiotic” was, however, first used in 1965 by Lilly and Stillwell. It was derived from a Greek word which means “for life.”^{48,50,51}

Probiotics may be composed of either gram-positive or gram-negative bacteria. Common probiotic strains include *Lactobacillus*, *Bifidobacterium*, *Streptococcus* species, and the non-pathogenic *Escherichia coli* Nissle. Formulations are available as capsules, powders, and fermented foods.⁵¹

MECHANISM OF ACTION OF PROBIOTICS

The precise mechanisms of actions of probiotics are not fully understood. However, different mechanisms have been suggested, including:

- Competing with pathogenic organisms for mucosal binding sites,
- Producing antimicrobial substances such as bacteriocins,
- Enhancing innate and adaptive immune responses
- Strengthening the intestinal epithelial barrier,
- Contributing essential metabolites that support microbial diversity.⁵²⁻⁵⁵

Through these mechanisms, probiotics mitigate gut dysbiosis not only in severe TBI but also in conditions such as Crohn’s disease and ulcerative colitis.^{14,48,54,56-58} Important properties needed for a probiotic to be effective therapeutically include ability to colonize the gut, capacity to adhere to the gut mucosa as well as resistance to gastric acid and bile.^{59,60}

POTENTIAL ROLE OF PROBIOTICS IN THE MANAGEMENT OF SEVERE TRAUMATIC BRAIN INJURY

Studies have suggested that probiotic administration may reduce intensive care unit (ICU) stay, lower infection rates, and improve GI function in critically ill patients, including those with severe TBI.^{61,63,64} While mortality outcomes remain inconsistent, the overall trend indicates that probiotics may provide supportive benefits when added to standard care. Wan et al.,⁶¹ in a prospective study, reported that probiotic administration significantly reduced hospital stay and pulmonary infection rates in severe TBI patients compared with controls. There was however no significant difference in one-month mortality or incidence of sepsis between the two groups. Similarly, Rijkers⁵⁶ observed that probiotics significantly reduced the length of ICU stay in patients with severe trauma, while the observed reductions in ventilator-associated pneumonia and mortality in the probiotic group did not reach statistical significance. Falcao et al.⁵⁸ also noted a shorter ICU stay and lower infection rates among patients who had probiotics.

Likewise, Tzikos et al.⁶² in a study involving multiple-trauma patients with concomitant head injury, found that a probiotic mixture significantly reduced the incidence of surgical site infections. In a randomized controlled trial (RCT), involving 52 severe TBI patients,⁶³ those treated with probiotics had lower rates of nosocomial infections and shorter ICU stays compared with those who had placebo.^{63,64}

The observed inconsistencies in clinical outcomes across probiotic studies in severe TBI likely stem from significant methodological heterogeneity. While early prospective trials, such as those by Wan et al.,⁶¹ reported significant reductions in hospital stays and pulmonary infections, subsequent larger-scale observations have struggled to replicate these 'hard' clinical benefits consistently- for example, Tan et al.⁶⁴ noted no difference in 28-day mortality among probiotic treated patients compared to the placebo group. A primary confounding factor is the variability in probiotic strains-ranging from single-strain *Lactobacillus* to multi-strain cocktails-and disparate dosage concentrations-**Table 2**. Furthermore, the timing of administration is critical; some protocols initiate therapy within 24 hours of injury, while others delay until the sub-acute phase, potentially missing the peak of the sympathetic storm where gut-derived neuroinflammation is most potent. This lack of standardization makes it difficult to discern whether a failed trial is a result of an ineffective intervention or a suboptimal delivery window.

Consequently, while probiotics show promise in reducing secondary infectious complications, their direct impact on long-term neurological recovery remains an area of significant uncertainty.^{63,64}

PROKINETICS

Prokinetic drugs enhance GI motility and are widely used for disorders such as gastroparesis.⁶⁵ They are useful in the treatment of motility disorders associated with medical conditions such as diabetic gastroparesis and ileus secondary to severe TBI.⁶⁶ They function by promoting coordinated contraction of intestinal smooth muscle and accelerating gastric emptying.⁶⁷ Besides this pro-motility effects, they are also anti-inflammatory and immunomodulatory.⁶⁸

Prokinetic agents act through several mechanisms: i. they facilitate gastric emptying; ii. they promote peristaltic esophageal contractions; and iii. they increase synchronized gastric contractions.^{65,69-71}

Classes of prokinetics include:

- Cholinergic agonists-such as bethanechol, neostigmine, and pyridostigmine,^{70,72-74}
- Dopamine receptor antagonists-including metoclopramide, levosulpiride, itopride and domperidone^{70,75}
- Serotonergic agents-such as cisapride, tegaserod, and prucalopride⁷⁰ and
- Macrolide-based motility enhancers-including azithromycin, clarithromycin, roxithromycin, and erythromycin.⁷⁰

Beyond improving GI motility, macrolide prokinetics also possess antimicrobial properties that may help prevent or treat infectious complications such as pneumonia, which can contribute to secondary brain injury in patients with severe TBI.^{68,70,76}

EFFECTS OF PROKINETICS ON OUTCOME IN SEVERE TRAUMATIC BRAIN INJURY

By enhancing gut motility, prokinetics help preserve intestinal barrier integrity and reduce gut dysbiosis frequently observed in patients with severe TBI. TBI-associated dysmotility may lead to feeding intolerance and increased risk of infection. Clinical studies show mixed results: some report improved gastric emptying and reduced stasis with agents such as erythromycin, while others found no significant differences between treatment and placebo groups. Meta-analyses indicate benefits in feeding tolerance but limited evidence for reductions in mortality or length of hospital stay.

Makkar et al.⁷⁶ in a RCT, demonstrated that the macrolide prokinetic-erythromycin improved gut motility significantly compared with placebo in TBI patients. In this study, gastric aspirate volume (GAV) served as a surrogate marker of gut motility. The incidence of high GAV was 60.5% in the placebo group and 28.9% in the erythromycin group ($p=0.006$), indicating that prokinetics caused a significant reduction in gastric stasis.

Table 2. Clinical parameters and protocols of probiotic interventions in severe TBI

Study (author, year)	Probiotic strains used	Formulation/delivery	Daily dosage	Duration	Primary clinical outcomes
Tan et al. (2011) ⁶⁴	<i>Bifidobacterium. longum</i> , <i>Lactobacillus bulgaricus</i> , <i>Streptococcus thermophilus</i>	Sachets (7 sachets 3 times daily)	0.5 X 10 ⁸ to 0.5 X10 ⁷ CFU	21 days	Reduced incidence of nosocomial infections and shorter ICU stay. 28-day mortality rate was unaffected.
Wan et al. (2019) ⁶¹	<i>Bifidobacterium longum</i> , <i>Lactobacillus bulgaricus</i> , <i>Enterococcus faecalis</i>	Tablets (6 tabs two times daily) via gastric tube	≥1.0 X 10 ⁷ CFU	15 days	Lower inflammatory markers (IL-6, IL-10, TNFα & CRP); reduced pulmonary infection rates and shorter length of hospital stay.
Falcao et al. (2004) ⁵⁸	<i>Lactobacillus johnsonii</i>	Fermented milk	240mls	5 to 14 days	Reduced incidence of infection rate, and shorter length of ICU stay.
Tzikos et al (2022) ⁶²	<i>Lactobacillus acidophilus</i> , <i>Lactiplantibacillus plantarum</i> , <i>Bifidobacterium animalis</i> , & <i>Saccharomyces boulardii</i>	Sachets (2 two times daily) via enteral route	(0.5×10 ⁸ to 1.75 x 10 ⁹ CFU)	15 days	Reduced incidence of surgical site infection

TBI: Traumatic brain injury, ICU: Intensive care unit, CFU: Colony-forming unit TNFα: Tumor necrosis factor-alpha, CRP: C-reactive protein

Similarly, Lewis et al.,⁷⁷ in a systematic review and meta-analysis, concluded that in critically ill patients evidence supports the use of prokinetic agents in mitigating poor feed tolerance compared to placebo; even though the effects of prokinetics on other outcome measures such as length of ICU stay, pneumonia and mortality were inconclusive.

In contrast, Nursal et al.⁷⁸ in another RCT, observed no significant advantage of prokinetics over placebo in TBI patients. Complication rates and feeding intolerance were comparable in both groups ($p=0.543$ and $p=0.930$, respectively).

In another systematic review and meta-analysis, Peng et al.⁷⁹ concluded that prokinetic therapy may improve tolerance to gastric feeding in critically ill adults.

Critical analysis of prokinetic therapy in severe TBI reveals a disconnect between physiological markers and clinical endpoints. Studies such as those by Makkar et al.⁷⁶ demonstrate that macrolide prokinetics significantly improve gut motility, using GAV as a successful surrogate marker for reduced stasis. However, these improvements in gastric emptying do not consistently translate to improved patient outcomes, such as 28-day mortality or improved GCS scores.^{78,79} This discrepancy suggests that while prokinetics are effective at mitigating feed intolerance, the sheer complexity and severity of the primary and secondary brain injury cascade may overshadow the incremental benefits of improved gut motility. Furthermore, the reliance on meta-analyses in this field is hampered by 'low' evidence quality regarding hospital stay duration, as most trials are not sufficiently powered to detect subtle neurological improvements. Future research must move beyond motility markers to investigate whether prokinetic-led gut stabilization actually reduces the systemic translocation of inflammatory mediators.

PREBIOTICS

Prebiotics are non-digestible substrates fermented by gut bacteria, resulting in growth of beneficial microbial species and production of SCFAs.⁸⁰ According to the International Scientific Association of Probiotics and Prebiotics (ISAPP), prebiotics are fermented ingredients that cause changes in the composition and/or activity of the gut microflora thereby promoting the host's health.⁸⁰ Examples include fructans, pectin, galacto-oligosaccharides, and flavanol-rich fibres.^{80,81}

EFFECTS OF PREBIOTICS ON GUT MICROBIOTA

Prebiotics are energy sources for beneficial gut microbials, thereby modulating both their activity and composition.⁸² They also influence the gut milieu by altering the physicochemical profile of the gut. Prebiotic fermentation produces acidic metabolites, mainly SCFAs, which lower luminal pH.⁸² Significant alteration in the gut microflora can occur with a drop in gut pH by one unit. This change may reduce acid-sensitive species like *Bacteroides* while promoting Firmicutes to produce butyrate -the so called butyrogenic effect.⁸⁰

SCFAs are small molecules and are able to traverse enterocytes into the bloodstream and can also traverse

the blood-brain barrier.^{82,83} Therefore, prebiotics not only influence gut function but also have effects on distant organs, like the brain.

PREBIOTICS AND THE CENTRAL NERVOUS SYSTEM

The effects of prebiotics on the CNS are not fully understood yet.

A search through major clinical trial registries and academic literature databases including ClinicalTrials.gov, European Union clinical trials register, Pubmed and Google Scholar showed that no RCTs have yet investigated the role of prebiotics specifically in severe TBI. Although no clinical trials have directly assessed prebiotics in severe TBI, their known effects on immune modulation, microbial composition, and SCFA production suggest potential relevance.⁸⁴ However, some review articles have suggested that prebiotics, either alone or as synbiotic formulations (prebiotics combined with probiotics) may offer enhanced therapeutic benefit.^{46,84}

Currently, the absence of RCTs specifically evaluating prebiotics in severe TBI constitutes a significant barrier to evidence-based clinical practice. While animal models suggest that prebiotics may modulate the gut dysbiosis associated with neurotrauma,⁸⁴ the lack of human data prevents the establishment of standardized enteral protocols. This gap forces clinicians to rely on 'clinical extrapolation' from general ICU populations, which may not account for the unique TBI-driven catecholamine surge that acutely alters intestinal motility. Without RCTs to define the optimal 'dose-response' relationship for prebiotic-induced fermentation, there remains a risk that early administration in the hyper-acute phase could exacerbate GI intolerance or bloating in patients already suffering from gastroparesis. Future research must prioritize trials that combine prebiotics with specific probiotic strains (synbiotics) to determine if synergistic effects can more effectively mitigate the systemic inflammatory response in the first 72 hours post-injury

POSTBIOTICS

Postbiotics consist of microbial-derived compounds produced during fermentation.⁸⁵ These include SCFAs, cell fragments, extracellular polysaccharides, and proteins.⁸⁵ They may exert anti-inflammatory and immunomodulatory effects without requiring live bacteria.

Similar to prebiotics, a search through major clinical trial registries and academic literature databases also showed that there are currently no RCTs investigating the role of postbiotics in the management of severe TBI. Nevertheless, some review articles have suggested that postbiotics may have therapeutic potentials in this context.^{46,86} Thus, current evidence in TBI is theoretical, based on extrapolation from other inflammatory and metabolic conditions.

The observation that no RCTs currently exist for postbiotic therapy in TBI patients highlights a critical 'translational gap' in neuro-gastroenterology. Postbiotics, such as SCFAs like butyrate, represent a potentially safer alternative to live

probiotics in immunocompromised patients in the ICU settings; however, their clinical utility remains speculative without human efficacy data. The implications of this vacuum are twofold: first, the therapeutic window for modulating the blood-brain barrier (BBB) via microbial metabolites remains undefined; and second, the potential for postbiotics to serve as 'adjunct neuroprotectants' cannot be realized. Until rigorous trials are conducted to monitor the 'butyrogenic effect' in real-time-using fecal or serum metabolite markers-the transition from bench-to-bedside for postbiotic interventions will remain stalled, leaving a significant portion of the MGBA therapeutically unaddressed.

FECAL MICROBIOTA TRANSPLANTATION

FMT involves the administration of processed stool from a healthy donor to restore microbial diversity in a recipient's gut. It represents a novel method for modulating the MGBA.⁸⁷ Even though the exact mechanisms and therapeutic effects of FMT in TBI remain unclear, evidence suggests that FMT can improve gut and blood-brain barrier integrity and lessen microglial activation, thus offering potential routes for clinical intervention.⁸⁶ While widely used for recurrent *Clostridioides difficile* infection, its role in neurological conditions is still experimental, and its safety, efficacy, and long-term outcomes are all still being debated.⁸⁸

Preclinical studies in TBI models demonstrate reduced microglial activation, improved white-matter integrity, and decreased ventricular enlargement. In an experimental animal study, Davis et al.⁸⁹ demonstrated that FMT led to a marked reduction in ventriculomegaly and maintenance of white matter circuitry up till 59 days post-TBI. These findings suggest that restitution of gut microflora via FMT may attenuate microglial activation and reduce neuropathological changes following TBI, representing a potential novel therapeutic strategy in its management. However, safety considerations and lack of clinical trials limit current application in TBI patients.

BARRIERS TO CLINICAL TRANSLATION OF MGBA-TARGETED THERAPIES

Despite the therapeutic potential of modulating the MGBA, several critical barriers hinder its integration into standard clinical protocols for severe TBI:

- **Individualized microbiome vs. standardized protocols:** A significant challenge is the one-size-fits-all approach to treatment. While current TBI management is highly standardized, the human gut microbiome is intensely

individualized, influenced by genetics, diet, and pre-existing health status.^{13,31} The absence of baseline pre-injury microbiome data makes it difficult for clinicians to determine the specific degree of dysbiosis in an individual patient or to identify a precise target for microbial restoration.⁴⁵

- **Safety concerns in the critically ill:** In the context of severe TBI, the compromise of the intestinal epithelial barrier-often referred to as "leaky gut"-presents a significant safety risk.^{36,37} There is a theoretical but serious concern regarding the translocation of live probiotic microorganisms from the gut lumen into the systemic circulation, which could potentially lead to iatrogenic sepsis in already immunocompromised, critically ill patients.^{42,63}
- **Logistical and regulatory hurdles of FMT:** While preclinical models show that FMT can reduce neuroinflammation and lesion size, translating this to the ICU remains challenging.⁸⁹ Barriers include the lack of standardized donor screening protocols, the risk of transferring multi-drug-resistant organisms, and the significant aesthetic and logistical challenges of processing and administering stool in a sterile critical care environment.^{87,88}
- **Confounding effects of standard care:** The mandatory use of broad-spectrum antibiotics to prevent nosocomial infections and opioids for sedation in TBI patients creates a "moving target" for microbial restoration.^{40,41} These essential treatments often act as major disruptors of the microbiota, potentially neutralizing the beneficial effects of concurrently administered probiotics or prebiotics.^{39,41} This creates a clinical paradox where the treatments required to save a patient's life simultaneously undermine the therapies intended to restore their microbial balance.

While the individual therapies discussed-probiotics, prokinetics, prebiotics, and FMT-each offer unique mechanistic advantages, they also face distinct clinical and logistical hurdles. To provide a clear overview for clinicians and researchers, **Table 3** presents a comparative analysis of these MGBA-targeted interventions, weighing the strengths of current clinical evidence against the remaining uncertainties and experimental barriers.

FUTURE RESEARCH DIRECTIONS AND HYPOTHESES

To bridge the gap between the experimental findings summarized in **Table 3** and actual clinical utility, future research should transition from broad, non-specific outcome

Table 3. Comparative analysis of clinical evidence, strengths, and translational uncertainties for MGBA-targeted interventions in severe TBI

Intervention	Strengths of current evidence	Weaknesses and uncertainties
Probiotics	Strong clinical evidence for reducing ICU-acquired infections, such as pneumonia. ^{51,63}	High strain variability and dosage inconsistency; "optimal" strain for TBI remains unknown; potential risk of translocation in the critically ill.
Prokinetics	Consistently demonstrates improvement in enteral feeding tolerance and significant reduction in gastric stasis. ^{76,79}	Limited and inconsistent evidence regarding reductions in ICU/hospital length of stay or long-term neurological recovery.
Prebiotics	Favorable safety profile; promotes endogenous production of neuroprotective SCFAs and stabilizes gut pH. ^{40,82}	Evidence is currently theoretical in the context of TBI; lacks human RCTs to determine clinical efficacy and standardized dosing.
FMT	Restores the entire microbial ecosystem rather than isolated strains; addresses deep-seated dysbiosis. ⁸⁷	Experimental status in TBI; significant safety concerns regarding the transfer of resistant pathogens; lack of standardized protocols for the acute phase.

MGBA: Microbiota-gut-brain axis, TBI: Traumatic brain injury, ICU: Intensive care unit, RCTs: Randomized controlled trials, FMT: Fecal microbiota transplantation

measures toward a precision medicine framework. Based on the evidence synthesized in this review, we propose the following hypotheses to guide subsequent clinical investigations:

- **Metabolomic-targeted restoration:** It is hypothesized that the targeted restoration of specific short-chain fatty acid (SCFA) levels-particularly butyrate-may correlate more strongly with reduced neuroinflammation and blood-brain barrier stability than interventions aimed solely at increasing overall microbial diversity.
- **Temporal synergy in intervention:** We propose that MGBA-targeted therapies initiated during the hyperacute sympathetic storm (within the first 24-48 hours post-injury) potentially offer superior neuroprotective outcomes compared to sub-acute administration, by preemptively mitigating gut-derived systemic inflammatory cascades.
- **Synbiotic efficacy in hostile environments:** It is hypothesized that synbiotic formulations (combined prebiotics and probiotics) may demonstrate enhanced clinical efficacy over monotherapies by facilitating the survival and colonization of beneficial bacteria within the physiologically altered GIT following severe TBI.

CONCLUSION

The MGBA represents a crucial intersection between gut microbial activity and CNS function. Severe TBI disrupts this axis, promoting dysbiosis, neuroinflammation, and systemic complications. Interventions that modulate gut microbiota-such as probiotics, prebiotics, postbiotics, prokinetics, and FMT show potential to mitigate secondary injury mechanisms.

Nevertheless, robust clinical evidence remains scarce, and large, well-designed trials are required to clarify efficacy, safety, and implementation strategies before these approaches can be widely adopted in TBI management.

ETHICAL DECLARATIONS

Peer Review Process

This review was externally peer-reviewed.

Conflict of Interest

The authors declare no conflicts of interest.

Financial Disclosure

No financial support was received for the preparation or publication of this article.

Author Contributions

Concept: OA; Design: OA, OO; Supervision: OO, SA-I, NA; Literature Review: OA; Manuscript Preparation: OA, OO; Critical Review: All Authors.

REFERENCES

1. Syed AT, Lone NA, Wani MA, Bhat AS. Clinical management of patients with minor head injuries. *Int J Health Sci (Qassim)*. 2007;1(1):131-140.
2. Goldstein M. Traumatic brain injury: a silent epidemic. *Ann Neurol*. 1990;27(3):327. doi:10.1002/ana.410270315
3. Yusuf AS, Odebo TO, Adeniran JO, et al. Pattern and outcome of motorcyclists head injury in Ilorin, Nigeria. *Niger J Basic Clin Sci*. 2014; 11(2):80-84. doi:10.4103/0331-8540.140340
4. Emejulu JKC, Isiguzo CM, Agbasoga CE, Ogbuagu CE. Traumatic brain injury in the accident and emergency department of a tertiary hospital in Nigeria. *East Cent Africa J Surg*. 2010;15(2):28-38.
5. Adeleye AO. Pattern of referrals of head injury to the University College Hospital, Ibadan. *Ann Ibadan Postgrad Med*. 2017;15(1):34-40.
6. Adeolu AA, Malomo AO, Shokunbi MT, Komolafe EO, Abiona TC. Etiology of head injuries in southwestern Nigeria: a public health perspective. *Internet J Epidemiol*. 2004;2(2):10-13. doi:10.5580/21d2
7. Ismail NJ, Lasseini A. Management of intracranial epidural haematoma. *J Dent Med Sci*. 2020;19(3):51-55. doi:10.9790/0853-1903165155
8. Mattei TA, Teasdale GM. The story of the development and adoption of the Glasgow Coma Scale: part I, the early years. *World Neurosurg*. 2020; 134:311-322. doi:10.1016/j.wneu.2019.10.193
9. Galgano M, Toshkezi G, Qiu X, Russell T, Chin L, Zhao LR. Traumatic brain injury: current treatment strategies and future endeavors. *Cell Transplant*. 2017;26(7):1118-1130. doi:10.1177/0963689717714102
10. Opondo EA, Mwangombe NJM. Outcome of severe traumatic brain injury at a critical care unit: a review of 87 patients. *Ann African Surg*. 2009;1(1):3-9. doi:10.4314/aas.v1i1.45788
11. Gaddam SSK, Buell T, Robertson CS. Systemic manifestations of traumatic brain injury. *Handb Clin Neurol*. 2015;127:205-218. doi:10.1016/B978-0-444-52892-6.00014-3
12. Ma Q, Xing C, Long W, Wang HY, Liu Q, Wang R-F. Impact of microbiota on central nervous system and neurological diseases: the gut-brain axis. *J Neuroinflammation*. 2019;16(1):53. doi:10.1186/s12974-019-1434-3
13. Zhu CS, Grandhi R, Patterson TT, Nicholson SE. A review of traumatic brain injury and the gut microbiome: insights into novel mechanisms of secondary brain injury and promising targets for neuroprotection. *Brain Sci*. 2018;8(6):1-13. doi:10.3390/brainsci8060113
14. Rice MW, Pandya JD, Shear DA. Gut microbiota as a therapeutic target to ameliorate the biochemical, neuroanatomical, and behavioral effects of traumatic brain injuries. *Front Neurol*. 2019;10(8):1-8. doi:10.3389/fneur.2019.00875
15. Kaur P, Sharma S. Recent advances in pathophysiology of traumatic brain injury. *Curr Neuropharmacol*. 2017;16(8):1224-1238. doi:10.2174/1570159x15666170613083606
16. Han Y, Wang B, Gao H, et al. Vagus nerve and underlying impact on the gut microbiota-brain axis in behavior and neurodegenerative diseases. *J Inflamm Res*. 2022;15:6213-6230. doi:10.2147/JIR.S384949
17. Galland L. The gut microbiome and the brain. *J Med Food*. 2014;17(12): 1261-1272. doi:10.1089/jmf.2014.7000
18. Dickerson RN, Mitchell JN, Morgan LM, et al. Disparate response to metoclopramide therapy for gastric feeding intolerance in trauma patients with and without traumatic brain injury. *JPEN J Parenter Enteral Nutr*. 2009;33(6):646-655. doi:10.1177/0148607109335307
19. Lin D, Howard A, Raihane AS, et al. Traumatic brain injury and gut microbiome: the role of the gut-brain axis in neurodegenerative processes. *Curr Neurol Neurosci Rep*. 2025;25(1):23. doi:10.1007/s11910-025-01410-0
20. Zheng Y, Bonfilii L, Wei T, Eleuteri AM. Understanding the gut-brain axis and its therapeutic implications for neurodegenerative disorders. *Nutrients*. 2023;15:4631. doi:10.3390/nu15214631
21. Jamerlan AM, An SSA, Hulme JP. Microbial diversity and fitness in the gut-brain axis: influences on developmental risk for Alzheimer's disease. *Gut Microbes*. 2025;17(1):2486518. doi:10.1080/19490976.2025.2486518
22. Loh JS, Mak WQ, Tan LKS, et al. Microbiota-gut-brain axis and its therapeutic applications in neurodegenerative diseases. *Signal Transduct Target Ther*. 2024;9(1):37. doi:10.1038/s41392-024-01743-1
23. Ashique S, Mohanto S, Ahmed MG, et al. Gut-brain axis: a cutting-edge approach to target neurological disorders and potential synbiotic application. *Heliyon*. 2024;10(13):e34092. doi:10.1016/j.heliyon.2024. e34092
24. Dicks LMT. Gut bacteria and neurotransmitters. *Microorganisms*. 2022;10:1838. doi:10.3390/microorganisms10091838
25. Xu J, Lu Y. The microbiota-gut-brain axis and central nervous system diseases: from mechanisms of pathogenesis to therapeutic strategies. *Front Microbiol*. 2025;16:1583562. doi:10.3389/fmicb.2025.1583562
26. Alavian F, Safaeian M. How the gut microbiome shapes learning and memory: a comprehensive review. *IBRO Neurosci Reports*. 2025;19:491-506. doi:10.1016/j.ibneur.2025.08.005

27. Kandpal M, Indari O, Baral B, et al. Dysbiosis of gut microbiota from the perspective of the gut-brain axis: role in the provocation of neurological disorders. *Metabolites*. 2022;12:1064. doi:10.3390/metabo12111064
28. Lu S, Zhao Q, Guan Y, et al. The communication mechanism of the gut-brain axis and its effect on central nervous system diseases: a systematic review. *Biomed Pharmacother*. 2024;178:117207. doi:10.1016/j.biopha.2024.117207
29. Ullah H, Arbab S, Tian Y, et al. The gut microbiota-brain axis in neurological disorder. *Front Neurosci*. 2023;17:1225875. doi:10.3389/fnins.2023.1225875
30. Mitra S, Dash R, Nishan A Al, Habiba SU, Moon IS. Brain modulation by the gut microbiota: from disease to therapy. *J Adv Res*. 2023;53:153-173. doi:10.1016/j.jare.2022.12.001
31. Shen Y, Fan N, Ma SX, Cheng X, Yang X, Wang G. Gut microbiota dysbiosis: pathogenesis, diseases, prevention, and therapy. *MedComm*. 2025;6:e70168. doi:10.1002/mco2.70168
32. Camberos-Barraza J, Guadrón-Llanos AM, De la Herrán-Arita AK. The gut microbiome-neuroglia axis: implications for brain health, inflammation, and disease. *Neuroglia*. 2024;5:254-273. doi:10.3390/neuroglia5030018
33. Baassiri E, Baassiri MG El, Raouf Z, et al. Dysregulated brain-gut axis in the setting of traumatic brain injury: review of mechanisms and anti-inflammatory pharmacotherapies. *J Neuroinflammation*. 2024;21(124):1-31. doi:10.1186/s12974-024-03118-3
34. Lingdi N, Mingchun G, Yifan L, et al. Effects of the stress hormone norepinephrine on the probiotic properties of *Levilactobacillus*: antibacterial colonization, anti-inflammation, and antioxidation. *Front Microbiol*. 2025;16:1526362. doi:10.3389/fmicb.2025.1526362
35. Li D, Chen J, Weng C, Huang X. Impact of the severity of brain injury on secondary adrenal insufficiency in traumatic brain injury patients and the influence of HPA axis dysfunction on prognosis. *Int J Neurosci*. 2024;134(11):1414-1423. doi:10.1080/00207454.2023.2280450
36. Yao H, Yu J, Yang X, Xu J. Ecotoxicology and Environmental Safety Mechanisms of disruption of the gut-brain axis by environmental endocrine disruptors. *Ecotoxicol Environ Saf*. 2025;304:119124. doi:10.1016/j.ecoenv.2025.119124
37. Dmytriv TR, Storey KB, Lushchak VI. Intestinal barrier permeability: the influence of gut microbiota, nutrition, and exercise. *Front Physiol*. 2024;15:1380713. doi:10.3389/fphys.2024.1380713
38. Agrawal H, Agarwal N, Gupta N. Enteric nervous system as a therapeutic target in gastrointestinal disorders. *World J Gastrointest Pharmacol Ther*. 2025;16(4):110843. doi:10.4292/wjgpt.v16.i4.110843
39. Yu B, Hua B. The interplay between the microbiota and opioid in the treatment of neuropathic pain. *Front Microbiol*. 2024;15:1390046. doi:10.3389/fmicb.2024.1390046
40. Zádori ZS, Király K, Al-khrasani M, Gyires K. Interactions between NSAIDs, opioids and the gut microbiota-future perspectives in the management of inflammation and pain. *Pharmacol Ther*. 2023;241:108327. doi:10.1016/j.pharmthera.2022.108327
41. Ramirez J, Guarner F, Fernandez LB, Maruy A, Sdepanian VL, Cohen H. Antibiotics as major disruptors of gut microbiota. *Front Cell Infect Microbiol*. 2020;10:572912. doi:10.3389/fcimb.2020.572912
42. Ling Z, Ding W, Liu X, et al. Gut microbiota dysbiosis and systemic immune dysfunction in critical ill patients with multidrug-resistant bacterial colonization and infection. *J Transl Med*. 2025;23:981. doi:10.1186/s12967-025-07049-2
43. Yang W, Yuan Q, Li Z, et al. Translocation and dissemination of gut bacteria after severe traumatic brain injury. *Microorganisms*. 2022;10(10):2082. doi:10.3390/microorganisms10102082
44. Kearns R. Gut-brain axis and neuroinflammation: the role of gut permeability and the kynurenine pathway in neurological disorders. *Cell Mol Neurobiol*. 2024;44:64. doi:10.1007/s10571-024-01496-z
45. Krakowski MA, Arora N, Jain S, et al. Diet-microbiome-gut-brain nexus in acute and chronic brain injury. *Front Neurosci*. 2022;16:1002266. doi:10.3389/fnins.2022.1002266
46. Albert V, Kedia S, Subramanian A. A comprehensive review of the brain-gut microbiota system in traumatic brain injury: mechanisms, outcomes, and emerging interventions. *Indian J Neurosurg*. 2025;14:103-110. doi:10.1055/s-0045-1806842
47. Hill C, Guarner F, Reid G, et al. Expert consensus document: the international scientific association for probiotics and prebiotics consensus statement on the scope and appropriate use of the term probiotic. *Nat Rev Gastroenterol Hepatol*. 2014;11:506-514. doi:10.1038/nrgastro.2014.66
48. Sanders ME. Probiotics: definition, sources, selection, and uses. *Clin Infect Dis*. 2008;46(Suppl 2):S58-S151. doi:10.1086/523341
49. McFarland L V. From yaks to yogurt: the history, development, and current use of probiotics. *Clin Infect Dis*. 2015;60(S2):S85-S90. doi:10.1093/cid/civ054
50. Gogineni VK, Morrow LE, Gregory PJ, Malesker MA. Probiotics: history and evolution. *J Anc Dis Prev Remedies*. 2013;1:107. doi:10.4172/2329-8731.1000107
51. Behnsen J, Deriu E, Sassone-Corsi M, Raffatellu M. Probiotics: properties, examples, and specific applications. *Cold Spring Harb Perspect Biol*. 2013;5(2):a010074. doi:10.1101/cshperspect.a010074
52. Hemaiswarya S, Raja R, Ravikumar R, Carvalho IS. Mechanism of action of probiotics. *Brazilian Arch Biol Technol*. 2013;56(1):113-119. doi:10.1590/S1516-89132013000100015
53. Plaza-Diaz J, Ruiz-Ojeda FJ, Gil-Campos M, Gil A. Mechanisms of action of probiotics. *Adv Nutr*. 2019;10(suppl 1):S49-S66. doi:10.1093/advances/nmy063
54. O'Hara AM, Shanahan F. Mechanisms of action of probiotics in intestinal diseases. *ScientificWorldJournal*. 2007;7:31-46. doi:10.1100/tsw.2007.26
55. Gogineni VK, Morrow LE. Probiotics: mechanisms of action and clinical applications. *J Probiotics Health*. 2013;1(1):1-11. doi:10.4172/2329-8901.1000101
56. Rijkers GT. Probiotics for severe trauma patients. *Crit Care*. 2011;15:1022. doi:10.1186/cc10589
57. McFarland LV. Use of probiotics to correct dysbiosis of normal microbiota following disease or disruptive events: a systematic review. *Br Med J Open*. 2014;4(8):e005047. doi:10.1136/bmjopen-2014-005047
58. Falcão De Arruda IS, De Aguiar-Nascimento JE. Benefits of early enteral nutrition with glutamine and probiotics in brain injury patients. *Clin Sci (Lond)*. 2004;106(3):287-292. doi:10.1042/CS20030251
59. Somashekaraiah R, Shruthi B, Deepthi BV, Sreenivasa MY. Probiotic properties of lactic acid bacteria isolated from neera: a naturally fermenting coconut palm nectar. *Front Microbiol*. 2019;10:1382. doi:10.3389/fmicb.2019.01382
60. Kim JA, Bayo J, Cha J, et al. Investigating the probiotic characteristics of four microbial strains with potential application in feed industry. *PLoS One*. 2019;14(6):e0218922. doi:10.1371/journal.pone.0218922
61. Wan G, Wang L, Zhang G, et al. Effects of probiotics combined with early enteral nutrition on endothelin-1 and C-reactive protein levels and prognosis in patients with severe traumatic brain injury. *J Int Med Res*. 2019;48(3):1-9. doi:10.1177/0300060519888112
62. Tzikos G, Tsalkatidou D, Stavrou G, et al. A four-probiotic regime to reduce surgical site infections in multi-trauma patients. *Nutrients*. 2022;14(13):2620. doi:10.3390/nu14132620
63. Pagkou D, Kogias E, Foroglou N, Kotzampassi K. Probiotics in traumatic brain injury: new insights into mechanisms and future perspectives. *J Clin Med*. 2024;13(15):4546. doi:10.3390/jcm13154546
64. Tan M, Zhu JC, Du J, Zhang LM, Yin HH. Effects of probiotics on serum levels of Th1/Th2 cytokine and clinical outcomes in severe traumatic brain-injured patients: a prospective randomized pilot study. *Crit Care*. 2011;15(6):R290. doi:10.1186/cc10579
65. Usai-Satta P, Lai M, Oppia F, Cabras F. Effects of prokinetics on the digestive tract. *Curr Rev Clin Exp Pharmacol*. 2022;17(3):161-165. doi:10.2174/2772432816666210805125813
66. Camilleri M, Atieh J. New developments in prokinetic therapy for gastric motility disorders. *Front Pharmacol*. 2021;12:711500. doi:10.3389/fphar.2021.711500
67. Roe NA, Sakaan S, Swanson H, Twilla JD. Evaluation of prokinetic agents used in the treatment of gastroparesis. *J Drug Assess*. 2017;6(1):6-9. doi:10.1080/21556660.2016.1278546
68. Hawkyard C V, Koerner RJ. The use of erythromycin as a gastrointestinal prokinetic agent in adult critical care: benefits versus risks. *J Antimicrob Chemother*. 2007;59(3):347-358. doi:10.1093/jac/dkl1537
69. Yang YJ, Bang CS, Baik GH, et al. Prokinetics for the treatment of functional dyspepsia: Bayesian network meta-analysis. *BMC Gastroenterol*. 2017;17(1):83. doi:10.1186/s12876-017-0639-0
70. Quigley EMM. Prokinetics in the management of functional gastrointestinal disorders. *J Neurogastroenterol Motil*. 2015;21(3):330-336. doi:10.1007/s11894-017-0593-6
71. Hiyama T, Yoshihara M, Tanaka S, Haruma K, Chayama K. Effectiveness of prokinetic agents against diseases external to the gastrointestinal tract. *J Gastroenterol Hepatol*. 2009;24(4):537-546. doi:10.1111/j.1440-1746.2009.05780.x
72. Baradari AG, Khajavi MR, Firouzian A, et al. Effects of combined prokinetic administration on gastric emptying in critically ill patients. *Arab J Gastroenterol*. 2017;18(1):30-34. doi:10.1016/j.ajg.2017.01.007
73. Parthasarathy G, Ravi K, Camilleri M, et al. Effect of neostigmine on gastrooduodenal motility in patients with suspected gastrointestinal motility disorders. *Neurogastroenterol Motil*. 2015;27(12):1736-1746. doi:10.1111/nmo.12669

74. Jayarajah U, Yapa K, Ranaweera K, Rahuman A, Perera P, Weerasekara D. Successful use of neostigmine for resistant gastroparesis following distal gastrectomy: a case report. *Int J Surg Case Rep.* 2023;106:108166. doi:10.1016/j.ijscr.2023.108166
75. Tonini M, Cipollina L, Poluzzi E, Crema F, Corazza GR, De Ponti F. Review article: clinical implications of enteric and central D2 receptor blockade by antidopaminergic gastrointestinal prokinetics. *Aliment Pharmacol Ther.* 2004;19(4):379-390. doi:10.1111/j.1365-2036.2004.01867.x
76. Makkar JK, Gauhi B, Jain K, Jain D, Batra YK. Comparison of erythromycin versus metoclopramide for gastric feeding intolerance in patients with traumatic brain injury: a randomized double-blind study. *Saudi J Anaesth.* 2016;10:308-313. doi:10.4103/1658-354X.174902
77. Lewis K, Alqahtani Z, Mcintyre L, et al. The efficacy and safety of prokinetic agents in critically ill patients receiving enteral nutrition: a systematic review and meta-analysis of randomized trials. *Crit Care.* 2016;20(1):259. doi:10.1186/s13054-016-1441-z
78. Nursal T, Erdogan B, Noyan T, Cekinmez M, Gülşen B, Bilgin N. The effect of metoclopramide on gastric emptying in traumatic brain injury. *J Clin Neurosci.* 2007;14(5):344-348. doi:10.1016/j.jocn.2005.11.011
79. Peng R, Li H, Yang L, et al. The efficacy and safety of prokinetics in critically ill adults receiving gastric feeding tubes: a systematic review and meta-analysis. *PLoS One.* 2021;16(1):e0245317. doi:10.1371/journal.pone.0245317
80. Davani-Davari D, Negahdaripour M, Karimzadeh I, et al. Prebiotics: definition, types, sources, mechanisms, and clinical applications. *Foods.* 2019;8(3):92. doi:10.3390/foods8030092
81. Bamigbade GB, Subhash AJ, Kamal-Eldin A, Nyström L, Ayyash M. An updated review on prebiotics: insights on potentials of food seeds waste as source of potential prebiotics. *Molecules.* 2022;27:5947. doi:10.3390/molecules27185947
82. Bedu-Ferrari C, Biscarrat P, Langella P, Cherbuy C. Prebiotics and the human gut microbiota: from breakdown mechanisms to the impact on metabolic health. *Nutrients.* 2022;14:2096. doi:10.3390/nu14102096
83. Sankarganesh P, Bhunia A, Kumar AG, Babu S, Gopukumar ST, Lokesh E. Short-chain fatty acids (SCFAs) in gut health: implications for drug metabolism and therapeutics. *Med Microecol.* 2025;25:100139. doi:10.1016/j.medmic.2025.100139
84. Markowiak P, Ślizewska K. Effects of probiotics, prebiotics, and synbiotics on human health. *Nutrients.* 2017;9(9):1021. doi:10.3390/nu9091021
85. Meena KK, Joshi M, Gupta L, Meena S. Comprehensive insights into postbiotics: bridging the gap to real-world application. *Food Nutr.* 2025; 1(2):100024. doi:10.1016/j.fnutr.2025.100024
86. Luo C, Li S, Chen T. Editorial: The role of probiotics, postbiotics, and microbial metabolites in preventing and treating chronic diseases, volume II. *Front Cell Infect Microbiol.* 2024;14:1442855. doi:10.3389/fcimb.2024.1442855
87. Kim KO, Gluck M. Fecal microbiota transplantation: an update on clinical practice. *Clin Endosc.* 2019;52:137-143. doi:10.5946/CE.2019.009
88. Yu J, Chen YX, Wang JW, Wu HT. Research progress on the relationship between traumatic brain injury and brain-gut-microbial axis. *Ibrain.* 2024;10:477-487. doi:10.1002/ibra.12153
89. Davis BT, Chen Z, Islam MBAR, Timken ME, Procissi D, Schwulst SJ. Post-injury fecal microbiome transplant decreases lesion size and neuroinflammation in traumatic brain injury. *Shock.* 2022;58(4):287-294. doi:10.1097/SHK.0000000000001979

Lateral meningocele syndrome in a Nigerian child: a case report and literature review

 **Ayodeji Salman Yusuf**^{1,2},  **Mansur Mohammed Idris**²,  **Olukorede Olabanji Adekunle**^{*3},
 **Nenkimun Dirting Bakwa**⁴,  **Aliyu Saliyu Muhammed**²

¹Department of Surgery, University of Abuja, Gwagwalada, Federal Capital Territory, Nigeria

²Department of Neurosurgery, National Hospital Abuja, Federal Capital Territory, Nigeria

³Division of Neurosurgery, Department of Surgery, University of Ilorin Teaching Hospital, Ilorin, Kwara State, Nigeria

⁴Division of Neurosurgery, Department of Surgery, Jos University Teaching Hospital, Jos, Plateau State, Nigeria

Received: 05/01/2026

Accepted: 19/03/2026

Published: 29/03/2026

Cite this article: Yusuf AS, Idris MM, Adekunle OO, Bakwa ND, Muhammed AS. Lateral meningocele syndrome in a Nigerian child: a case report and literature review. *Acad J Neuropsychiatry Neuropsychol.* 2026;3(1):22-24. doi:10.51271/AJNN-0045

*Corresponding Author: Olukorede Olabanji Adekunle, ooadekunle@rocketmail.com

ABSTRACT

Lateral meningocele syndrome is a very rare neurosurgical disorder characterized by the presence of multiple lateral thoracolumbar spinal meningoceles. Very few cases have been reported in literature and as such there are no standard management protocols and treatment is still fraught with several controversies. We present a 2-year-old girl with a 16-month history of progressive abdominal distention associated with occasional abdominal pain. Thoracoabdominal magnetic resonance imaging showed a huge left-sided cystic intra-abdominal mass lesion with a fistulous connection to the spinal subarachnoid space at the level of the third lumbar (L3) vertebra and other smaller cystic thoracolumbar lateral meningoceles. She had L3, L4 left hemi-laminectomy, decompression of the cyst and obliteration duroplasty to close the fistulous connection. Post-operative period was however complicated by cyst re-accumulation, pseudomeningocele and meningitis. Follow-up neuroimaging revealed hydrocephalus necessitating ventriculoperitoneal shunt insertion. This case highlights a very rare congenital anomaly and the attendant diagnostic and management challenges.

Keywords: Lateral meningocele syndrome, obliteration duroplasty, pseudomeningocele, cerebrospinal fluid

INTRODUCTION

Lateral meningocele syndrome (LMS) is a rare neurosurgical disorder.¹ It has been described as a genetic connective tissue disorder with morphological changes similar to those seen in other connective tissue disorders.^{1,2} Its morphological hallmarks are multiple bilateral, large lateral meningoceles herniating through the spinal foramina.³ These lateral meningoceles can occur primarily as seen in Lehman syndrome, also known as LMS or as a component of other connective tissue disorders like Marfan syndrome, Nevo syndrome, Hajdu-Cheney syndrome as well as Neurofibromatosis type 1 (NF1).³ These meningoceles may remain small and asymptomatic but can also become large and symptomatic.⁴ In such cases, the patient may present with axial or radicular back pain, discomfort and motor weakness due to direct compression of the spinal nerve root exiting the foramen; there may also be abdominal distention and respiratory embarrassment from mass effect on retroperitoneal and intrathoracic structures.⁵⁻⁷ Lateral meningoceles often distort the cerebrospinal fluid (CSF) flow dynamics and tend to co-exist with concurrent Chiari malformation thus creating unique management challenges.^{3,8}

We present a 2-year-old female toddler with multiple lateral meningoceles with a symptomatic giant lateral lumbar meningocele who developed hydrocephalus necessitating CSF diversion following surgical repair of the lumbar intra-abdominal lesion.

CASE

A 2-year-old female toddler presented to us with a history of progressive abdominal distention since the 8th month of life. There was occasional history of abdominal pain. However, there was no vomiting, early satiety, constipation or lower urinary tract symptoms. There was no history of chest pain, cough, breathlessness or weight loss. She had no limb weakness or sphincter dysfunction. She was a product of an uneventful term gestation delivered via spontaneous vaginal delivery. Physical examination revealed a fully conscious child with dysmorphic facies (arched eyebrows, flattened midface, and angulated eyes and ears). Neurological examination was essentially normal. The abdomen was grossly distended without any palpably enlarged organs.



Percussion note was dull and bowel sound was normoactive. She had normal female external genitalia and no stigmata of a neurocutaneous syndrome. Her laboratory tests revealed no abnormal findings.

Thoracoabdominal magnetic resonance imaging (MRI) showed multilevel bilateral thoraco-lumbar lateral paraspinous outpouchings one of which was huge and dominant—a left-sided cystic lesion communicating with the spinal subarachnoid space at the L3 level which extended into the retroperitoneum with displacement of bowel loops superiorly and inferiorly. The cyst was hypointense on T1-weighted and hyperintense on T2-weighted images (Figures 1-4).

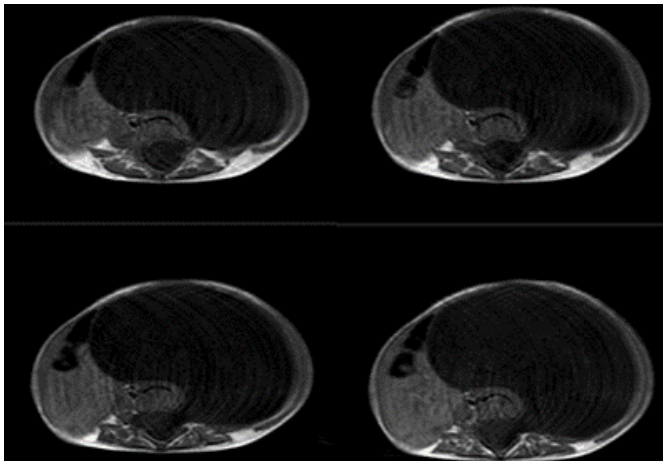


Figure 1. Axial T1-weighted images showing a left-sided hypointense cystic lesion communicating with the spinal subarachnoid space

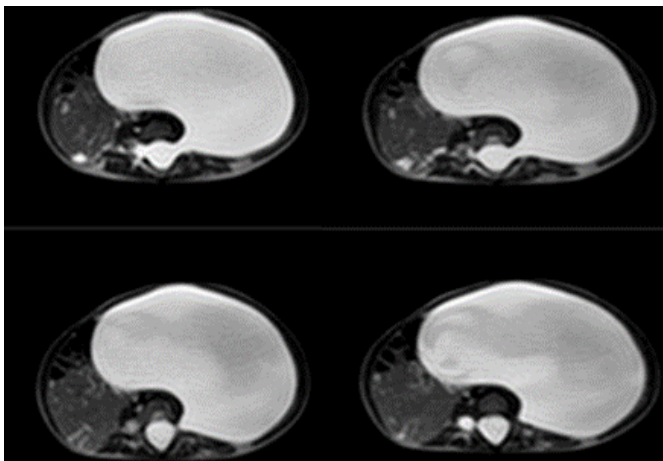


Figure 2. Axial T2-weighted images showing a left-sided hyperintense cystic lesion communicating with the spinal subarachnoid space

The patient had no clinical features of an intracranial pathology or elevated intracranial pressure; hence a cranial imaging was not done at this time. She had L3, L4 left hemilaminectomy and durotomy with intraoperative findings of egress of clear CSF under marked pressure from the dominant meningocele via a 4cm wide fistula between the cyst and the spinal subarachnoid space. The fistula was located at the lateral aspect of the L3 vertebra. The meningocele was decompressed by manual pressure on the abdomen till there was no longer egress of CSF via the fistula. About 1000mls of CSF was drained. An obliterative duroplasty was done to close the CSF fistula followed by a water-tight duroplasty. Multiple blind ending outpouchings of the dura were also noted intraoperatively. Immediate

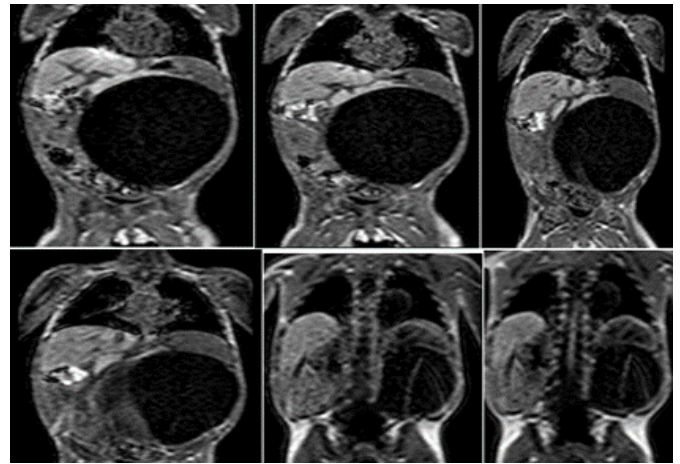


Figure 3. Coronal T1-weighted images showing the same lesion communicating with the spinal subarachnoid space at the L3 level

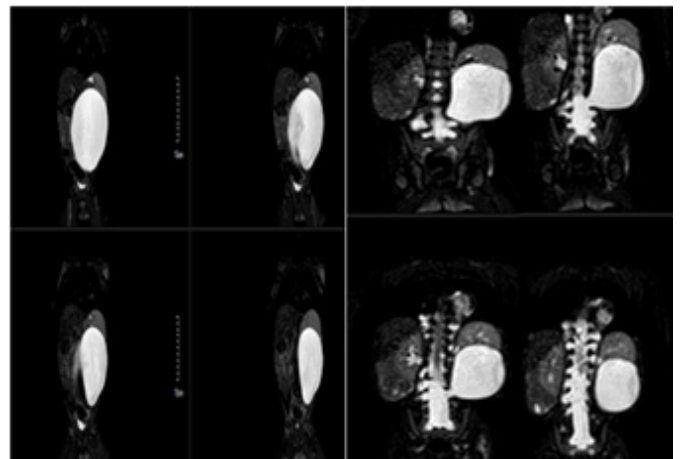


Figure 4. Coronal T2-weighted images showing the same lesion communicating with the spinal subarachnoid space at the L3 level

post-operative period was uneventful, bowel sound was normoactive on the first post-operative day and feeding was commenced. One week post-operatively, she had a re-accumulation of the cyst with progressive abdominal expansion necessitating wound exploration, cyst drainage and a reinforcement of the obliteration duroplasty. Following the re-do surgery, the abdominal swelling never recurred. She subsequently developed pseudomeningocele, which resolved with aseptic aspiration and firm dressing. After resolution of the pseudomeningocele, she developed meningitic features i.e. fever, nuchal rigidity and seizures. The diagnosis of bacterial meningitis was confirmed via CSF culture and she was managed with appropriate antibiotics by the Pediatricians. She subsequently developed increased seizure frequency with subsequent status epilepticus in spite of combination anti-seizure medications necessitating cranial computed tomographic (CT) scan and admission into the Intensive Care Unit. The cranial CT scan revealed communicating hydrocephalus. She had CSF diversion via an initial external ventricular drain and a definitive ventriculo-peritoneal shunt insertion after serial negative CSF cultures. Fever and seizures however persisted, her clinical condition continued to deteriorate until she died about 8 weeks after the first surgery. Parents declined autopsy.

DISCUSSION

LMS is characterized by lateral meningoceles herniating through the intervertebral foramina and associated scalloping

of the posterior vertebral bodies.^{5,7} The meningoceles are mostly dependent, occurring in the lower thoracic and lumbar spine, unlike in NF1 where they mostly occur in the thoracic spine.^{3,9} Lateral meningoceles can occur in isolation or as a component of other connective tissue disorders or syndromes. Such syndromes include Loeys-Dietz syndrome, Marfan syndrome, Ehler Danlos syndrome, Hajdu-Cheney syndrome, Nevo syndrome and Lehman syndrome.^{9,10} Our patient had some dysmorphic facial features which suggested that the lateral meningocele was likely syndromic. Confirmation of syndromic association is usually done via genetic tests which are not readily available in our setting. For example heterozygous, de novo 2-nucleotide deletion in exon 33 on the NOTCH3 gene is diagnostic of LMS.^{11,12} While many lateral meningoceles may be asymptomatic, some may become large enough and cause symptoms via mass effect on nerve roots, the spinal cord or adjoining structures manifesting as abdominal distention and/or respiratory distress.^{3,13,14} Our patient had progressive abdominal distention and abdominal pain. LMS though congenital may become symptomatic for the first time in adult life.^{6,8} The likely diagnosis of LMS is usually suggested following neuroimaging like thoracolumbar MRI as seen in our patient. Some authors recommend imaging the entire neuroaxis because of other possible co-existent pathologies which may not be symptomatic at initial presentation but may impact on management.^{4,10} Such pathologies include hydrocephalus, Chiari 1 malformation, kyphoscoliosis and syringomyelia among others.^{4,10} Our patient had recurrent pseudomeningocele following surgical intervention and subsequently developed features of raised intracranial pressure. Cranial CT scan done at this time showed active hydrocephalus warranting CSF diversion. Even though there was no preoperative cranial imaging, we think the hydrocephalus may have been present but latent prior to surgery but subsequently became active after surgical intervention. It was thought that ligating a huge lateral meningocele like the one in this patient may disrupt the CSF dynamics causing active hydrocephalus.³

What constitutes optimal neurosurgical management in these patients is still poorly defined largely due to the rarity and variable clinical presentation.⁹ The various interventions that have been reported in literature include laminectomy, decompression and ligation/obliteration as seen in this patient, ventriculoperitoneal shunt insertion, lumboperitoneal shunt and suboccipital craniectomy for foramen magnum decompression in co-existent chiari 1 malformation.^{2,3,9} Patients with multilevel bilateral symptomatic meningoceles which may preclude laminectomy and ligation have been shown to improve with CSF diversion alone.²

Complications associated with treatment include pseudomeningocele as seen in our patient and spine destabilization needing instrumented spine fusions, due to the presence of bony changes of the spine such as scoliosis and scalloped vertebrae.^{3,9}

CONCLUSION

This case highlights a neurosurgical rarity-LMS and the attendant management challenges due to the absence of standard treatment protocols. It is hoped that that more clarity is gained with each reported case.

ETHICAL DECLARATIONS

Informed Consent

Written informed consent was obtained from the parents of the patient included in this report. Signed consent forms are retained by the authors and are available upon request.

Peer Review Process

This report underwent external peer review.

Conflict of Interest

The authors declare no conflicts of interest.

Financial Disclosure

This case report did not receive any financial support.

Author Contributions

Concept: ASY, OOA; Design: ASY, OOA; Supervision: ASY; Literature Review: ASY, MMI, OOA; Manuscript Preparation: All authors; Critical Review: All Authors.

REFERENCES

- Alves D, Sampaio M, Figueiredo R, Leão M. Lateral meningocele syndrome: additional report and further evidence supporting a connective tissue basis. *Am J Med Genet A*. 2013;161A(7):1768-1772. doi:10.1002/ajmg.a.35968
- Han Y, Chen M, Wang H. Management of lateral meningocele syndrome in a child without neurological symptoms and literature review. *Childs Nerv Syst*. 2022;38(5):903-907. doi:10.1007/s00381-022-05466-y
- Brown EC, Gupta K, Sayama C. Neurosurgical management in lateral meningocele syndrome: case report. *J Neurosurg Pediatr*. 2017;19(2):232-238. doi:10.3171/2016.9.PEDS16311
- Cappuccio G, Apuzzo D, Alagia M, et al. Expansion of the phenotype of lateral meningocele syndrome. *Am J Med Genet A*. 2020;182(5):1259-1262. doi:10.1002/ajmg.a.61536
- Panil Kumar BE, Hegde K, Kumari G, Agrawal A. Bilateral multiple level lateral meningocele. *J Clin Imaging Sci*. 2013;3(1):1-3. doi:10.4103/2156-7514.106613
- Mushtaq G, Hussain I, Khan JA, Kamal MA. Lateral meningocele with asymmetric canal stenosis: a case study. *Saudi J Biol Sci*. 2015;22(1):102-105. doi:10.1016/j.sjbs.2014.09.001
- Seddighi A, Seddighi AS. Lateral sacral meningocele presenting as a gluteal mass: a case report. *J Med Case Rep*. 2010;4:2-7. doi:10.1186/1752-1947-4-81
- Reis C, Carneiro E, Fonseca J, et al. Epithelioid hemangioendothelioma and multiple thoraco-lumbar lateral meningoceles: two rare pathological entities in a patient with NF-1. *Neuroradiology*. 2005;47(2):165-169. doi:10.1007/s00234-004-1321-0
- Cuoco JA, Klein BJ, Busch CM, et al. Neurosurgical management of lateral meningocele syndrome: a clinical update for the pediatric neurosurgeon. *Pediatr Neurosurg*. 2020;55(1):2-11. doi:10.1159/000504060
- Amuthabarathi M, Harshith K, Nagarajan K. Infantile presentation of Lehman syndrome with multiple lateral meningoceles, dural ectasias, and herniation of conus: a rare case report. *J Pediatr Neurosci*. 2020;15(2):111-115. doi:10.4103/jpn.JPN_152_18
- Canalis E, Yu J, Schilling L, Yee SP, Zanotti S. The lateral meningocele syndrome mutation causes marked osteopenia in mice. *J Biol Chem*. 2018;293(36):14165-14177. doi:10.1074/jbc.RA118.004242
- Rubadeux D, Owens JW, Shillington A. A Case of Lateral Meningocele Syndrome without Lateral Meningocele. *Mol Syndromol*. 2024;15(4):328-332. doi:10.1159/000536632
- Velho V, Guthe S, Survashe P, Darade P. Symptomatic multiple level lateral meningoceles with intraspinal meningocele: a case study and its surgical management. *Indian J Neurosurg*. 2017;06(01):15-19. doi:10.1055/s-0037-1598093
- Ndlovu SM, Gaur B, Sureshkumar A, Saha S, Sidhu R. Isolated Large Lateral Thoracic Meningocele. *Cureus*. 2024;16(11):e73041. doi:10.7759/cureus.73041

Seizure-related head injury with rare etiology-Fahr's syndrome: a case report

 Ketut Yoga Wira Nugraha

Department of Neurosurgery, Faculty of Medicine, Udayana University, Bali, Indonesia

Received: 02/03/2026

Accepted: 19/03/2026

Published: 29/03/2026

Cite this article: Nugraha KYW. Seizure-related head injury with rare etiology-Fahr's syndrome: a case report. *Acad J Neuropsychiatry Neuropsychol.* 2026;3(1):25-27. doi:10.51271/AJNN-0046

Corresponding Author: Ketut Yoga Wira Nugraha, ketutyogawira8@gmail.com

ABSTRACT

A 49-year-old woman presented with scalp laceration following an unsupervised generalized tonic-clonic seizure. Non-contrast head computed tomography performed for mild traumatic brain injury revealed incidental finding of bilateral symmetric striopallidodentate calcifications consistent with Fahr's syndrome. Clinical findings include positive Trousseau's sign, prolonged QT interval, bradykinesia, and shuffling gait. Laboratory evaluation confirmed hypoparathyroidism, hypocalcemia, and hyperphosphatemia. A history of total thyroidectomy 30 years earlier suggested chronic postoperative hypoparathyroidism as the underlying etiology. The patient was managed with antiseizure medication, wound care, and supportive treatment, with good short-term outcome. This case highlights Fahr's syndrome as an under-recognized metabolic cause of seizures and emphasizes the importance of neuroimaging and biochemical evaluation in seizure patients, particularly when head trauma or atypical neurological features are present.

Keywords: Seizure, craniocerebral trauma, brain calcification, hypoparathyroidism, hypocalcemia

INTRODUCTION

Head injuries are common in seizure-related falls, especially in unsupervised patients.¹ Seizure etiologies can vary from idiopathic, metabolic, to structural brain lesions. Fahr's syndrome (FS) is a secondary bilateral calcification of striatum, basal ganglia, and dentate nucleus, with most common etiology from hypoparathyroidism.^{2,3}

FS is a rare disease with prevalence of less than 1 in 1,000,000 people.³ Manifestation of FS includes cognitive disorders, movement disorders, psychiatric symptoms, and seizure.^{2,3} FS can be asymptomatic and often an incidental finding on a brain computed tomography (CT) scan for other indication.³

This case report aims to highlight FS as an under-recognized etiology of seizures and to highlight the importance of neuroimaging in seizure patients, especially when head injury is involved.

CASE

A 49-year-old woman presented to our hospital's emergency room (ER) with scalp laceration after an episode of seizure 30 minutes before. She was unsupervised when the seizure started, hence she fell and hit her head on the floor. Seizure described as generalized tonic-clonic. The patient was aware during the seizure but could not control her body. After the

seizure, patient had postictal headache with slight confusion, initially unaware of the scalp laceration. Upon arrival at the ER, seizure had already stopped and patient was able to walk, complained of headache, scalp laceration, and mild cramps in both arms and legs.

She had her first tonic-clonic seizure in 2020, hospitalized for several days at a local hospital and discharged with daily medications of oral Carbamazepine 200 mg, Vitamin B6, and Folic Acid 400 mcg. From 2020 to 2025, seizure was controlled with medication. In the last 3 months prior to this episode, patient took her medication inconsistently and started to have seizures about 3 times per month, and increased to about 3 times per week. Each seizure resolved spontaneously without medication. In 1996, patient was diagnosed for thyroid gland hypertrophy with airway obstruction. Total thyroidectomy surgery was performed and she was discharged without hormone therapy.

During initial assessment, she showed no disorientation, and was able to follow instruction. Vital signs are normal, but during blood pressure examination, she exhibited a positive Trousseau's Sign (**Figure. 1**). We noticed that she had a shuffling gait. We conducted further neurological exam and found spasticity and bradykinesia. On physical examination, there was scalp laceration measuring 3 cm by 1 cm with





Figure 1. Positive Trousseau's sign

active bleeding in left parietooccipital region (Figure 2). The wound was stitched, covered with sterile gauze and pressure bandage.



Figure 2. Scalp laceration in left parietooccipital region

Due to suspicion of skull fractures and intracranial bleeding, we performed non-contrast head CT-Scan. The results were unexpected: abnormal, bilateral, symmetric strio-pallido-dentate calcification (Figure 3). Electrocardiography (ECG) showed a prolonged QT Interval of 0.56 second (Figure 4). Complete blood count (CBC) and renal function test showed normocytic anaemia (Haemoglobin of 84 g/L, normal range 120-160 g/dl), elevated serum ureum (7.3 mmol/L, normal range 2.5-7.1 mmol/L), high serum creatinine (164 μ mol/L, normal range 49-90 μ mol/L).

Patient was admitted to regular ward, with medication of IV Ketorolac 30 mg every 8 hours, IV Ranitidine 50 mg every 12

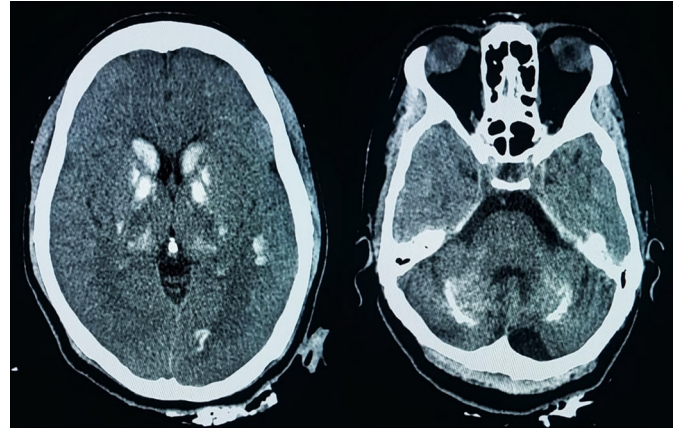


Figure 3. Bilateral and symmetric strio-pallido-dentate calcification

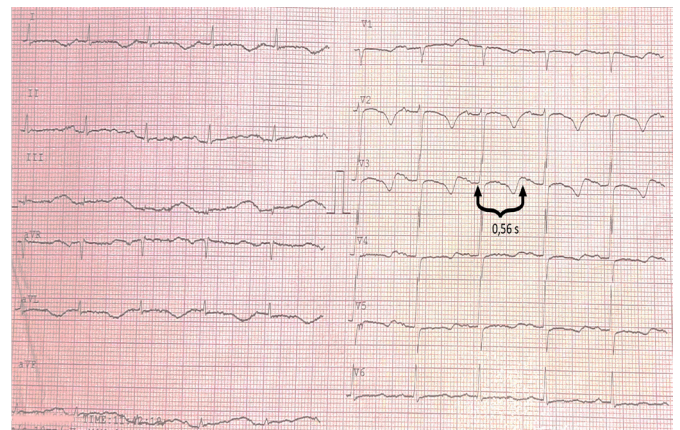


Figure 4. ECG showing prolonged QT interval (0.56 s)

hours, oral Phenytoin 100 mg every 8 hours, oral Piracetam 1200 mg every 8 hours, and 2 bags packed red blood cell (PRBC) transfusion. On daily follow up, there were no further episode of seizure, pain was managed with medication, and wound were clean. The only complain left was about mild cramps. After 2 bags of PRBC transfusion, haemoglobin increased to 94 g/L.

Patient was discharged on day 3 of care with take-home medications of oral Phenytoin 100 mg every 8 hours, oral Piracetam 1200 mg every 8 hours, and Flunarizine 5 mg every 12 hours. Patient returned to Neurosurgery Clinic after 10 days, there were no seizure, headache resolved, and stitches were removed. On follow up, patient returned with laboratory result of low PTH (0.4 pmol/L, normal range 1.6-6.9 pmol/L), low serum calcium (1.55 mmol/L, normal range 2.1-2.60 mmol/L) and high serum phosphate (2.20 mmol/L, normal range 0.8-1.50 mmol/L) and referred to Internal Medicine for hypoparathyroidism, managed with oral calcium carbonate 500 mg every 8 hours and calcitriol 0.5 μ g/day.

DISCUSSION

Unsupervised seizure patient is at high risk of physical injury. After upper extremity fracture, head injury is the second most common injuries in seizure-related injury.¹ Our patient presented with mTBI after an unsupervised seizure. Performing a CT-Scan in mTBI is mandatory when CCTHR indications are met, regardless of the preceding event that causes the injury.⁴ In our institution, neuroimaging is not a

routine procedure in seizure without neurological deficit. We referred to CCTHR to perform CT-Scan in this case, with unexpected finding of bilateral symmetric brain calcifications (Figure 3).

There are various etiologies of brain calcification such as infections and calcified brain tumors, but these calcifications are not bilaterally nor symmetrically configured in striopallidodentate structures.³ Asymptomatic bilateral symmetric basal ganglia calcification are common incidental findings in head CT-Scan of middle-aged patient, but most are confined in globus pallidus in small configuration.⁵ Fahr's Disease (FD) has the same neuroimaging finding as FS. The difference between FS and FD is in the etiology, where FD is associated with idiopathic hereditary conditions such as gene mutations, in the absence of secondary metabolic causes.⁶

Fahr's Syndrome refers to secondary bilateral calcification of striatum, basal ganglia, and dentate nucleus due to metabolic causes.^{2,3} Common etiology of FS in adulthood includes hypoparathyroidism.^{2,6} Parathyroid hormone promotes the release of calcium from bones into bloodstream, increases kidney calcium reabsorption, and increases intestinal absorption.⁶ Seizures are a common clinical manifestation in FS.^{2,3} Cramps, positive Trousseau's sign (carpopedal spasm), and prolonged QT intervals on ECG that are the signs of hypocalcemia.^{2,6} Our patient presented with extensive bilateral and symmetric calcifications on striatum, globus pallidus, and dentate nucleus, with findings of hypoparathyroidism, hypocalcemia, and history of total thyroidectomy, highly supporting diagnosis of FS.

Hypoparathyroidism is common after total thyroidectomy procedure, due to accidental damage in parathyroid gland or its vasculature.^{2,6} This disrupts the calcium-phosphate homeostasis, causing hypocalcemia and pathological calcium deposition in vascular and perivascular of metabolically active regions such as the striopallidodentate structures, which could impair tissue perfusion and impairs neuronal circuit.^{7,8}

After parathyroid gland removal, untreated patient started to develop asymptomatic basal ganglia calcification in a median of 17 years, and hypoparathyroidism diagnosis in a mean of 30 years.^{2,5} In our case, symptoms appear 24 years and full diagnosis was made 30 years after total thyroidectomy. Removal of the micro-calcification is impossible, and treatments are focused on seizure control with ASM while limiting the disease progression by treating the underlying cause.⁶ In postoperative hypoparathyroidism with PTH levels below 10-15 pg/ml, oral supplementation of calcium and calcitriol are recommended.⁷ This patient had a good short-term outcome and seizure was successfully managed with ASM.

CONCLUSION

This case illustrates a clinical cascade from total thyroidectomy leading to unrecognized chronic hypoparathyroidism, hypocalcemia, and subsequent striopallidodentate calcification consistent with FS, ultimately manifesting as recurrent seizures and seizure-related head injury. Because the clinical manifestations of Fahr's syndrome are often nonspecific, the diagnosis may be overlooked. This report emphasizes that

neuroimaging and appropriate biochemical evaluation should be considered in seizure patients, particularly when trauma or atypical neurological signs are present. Management of FS is symptomatic and underlying metabolic disorder should be addressed. Additionally, patients with recurrent seizures require constant supervision to reduce the risk of preventable physical injuries.

ETHICAL DECLARATIONS

Informed Consent

Written informed consent was obtained from the patient(s) included in this report. Signed consent forms are retained by the authors and are available upon request.

Peer Review Process

This report underwent external peer review.

Conflict of Interest

The author declare no conflicts of interest.

Financial Disclosure

This case report did not receive any financial support.

Author Contributions

The author is solely responsible for the conception, data collection, analysis, and writing of this manuscript.

REFERENCES

- Mühlenfeld N, Störmann P, Marzi I, et al. Seizure related injuries- Frequent injury patterns, hospitalization and therapeutic aspects. *Chin J Traumatol.* 2022;25(5):272-276. doi:10.1016/j.cjtee.2021.10.003
- Marinković DM, Dragović T, Kiković S, Kuzmić-Janković S, Đuran Z, Hajduković Z. Fahr's syndrome and idiopathic hypoparathyroidism: a case report. *Vojnosanitetski Pregled.* 2026;74(2):184-188. doi:10.2298/VSP150916109M
- Berrabeh S, Messaoudi N, Elmehraoui O, et al. Hypoparathyroidism and Fahr's syndrome: a case series. *Cureus.* 2023;15(6):e40502. doi:10.7759/cureus.40502
- Piwowarczyk S, Oblój P, Janicki Ł, Kowalik K, Łukaszuk A, Siemiński M. Seizure-related head injuries: a narrative review. *Brain Sci.* 2024; 14(5):473. doi:10.3390/brainsci14050473
- Kalampokini S, Georgouli D, Dadouli K, et al. Fahr's syndrome due to hypoparathyroidism revisited: a case of parkinsonism and a review of all published cases. *Clin Neurol Neurosurg.* 2021;202:106514. doi:10.1016/j.clineuro.2021.106514
- Donzuso G, Mostile G, Nicoletti A, Zappia M. Basal ganglia calcifications (Fahr's syndrome): related conditions and clinical features. *Neurol Sci.* 2019;40(11):2251-2263. doi:10.1007/s10072-019-03998-x.
- Shoback DM, Bilezikian JP, Costa AG, et al. Presentation of hypoparathyroidism: etiologies and clinical features. *J Clin Endocrinol Metab.* 2016;101(6):2300-2312. doi:10.1210/jc.2015-3909
- Kaygisiz S. Our cases of Fahr's disease and review of the literature. *Med Sci | Int Med J.* 2025;14(2):325. doi:10.5455/medscience.2025.03.077