

**Title:** Early Cognitive Assessment in Middle-Aged Patients with First-Ever Mild to Moderate Ischemic Stroke: A Cross-Sectional Study

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## Abstract

**Introduction:** Post-stroke cognitive impairment (PSCI) frequently complicates ischemic stroke yet remains underrecognized, particularly in middle-aged populations where early outcome data are limited.

**Methods:** This cross-sectional study enrolled patients aged 40–65 years with first-ever mild-to-moderate ischemic stroke (NIHSS  $\leq 15$ ) from 2023–2025. Diagnosis followed AHA criteria, confirmed by MRI (DWI and 3D FLAIR). Inclusion required literacy and fluency in Azari or Persian. Exclusions comprised prior stroke, major neuropsychiatric disorders, severe systemic disease, aphasia, or dominant hand motor deficits. Screening occurred in three phases: demographic collection, hyperacute assessment ( $\leq 24$  hours: RASS, CAM-ICU, PHQ-2, Mini-MoCA), and acute stroke unit assessment (days 3–7) using MoCA. Mood, functional status, neurological findings, vascular risk factors, and biomarkers (routine profile, IGF-1, IL-6, quantitative CRP) were evaluated.

**Results:** From 1,543 screened patients, 83 comprised the final cohort. PSCI prevalence was 72.3% ( $n=60$ ). Demographics were similar between groups. PSCI patients demonstrated significantly lower MoCA scores ( $22.7 \pm 1.88$  vs.  $26.61 \pm 0.96$ ,  $p < 0.001$ ), with deficits across multiple domains. Combined left-sided limb weakness was more frequent in PSCI patients (50.0% vs. 17.3%,  $p = 0.031$ ). Left hemisphere lesions predominated in the PSCI group ( $p = 0.016$ ). Biomarker levels did not differ between groups; however, correlation analysis showed poor glycemic control negatively associated with MoCA scores, IGF-1 positively associated with cognition/attention, and IL-6 inversely associated with language.

**Conclusions:** PSCI is highly prevalent within the first week post-stroke in middle-aged patients. Lesion topography, particularly left hemisphere involvement, and metabolic-inflammatory markers significantly influence cognitive profiles. Early screening integrating these factors may enhance risk stratification and targeted rehabilitation.

**Keywords:** Cognitive Impairment; Ischemic Stroke; Neuropsychological Tests

## Introduction

Ischemic stroke remains a leading cause of disability and mortality worldwide, with a rising burden in low- and middle-income countries (1),(2). While the majority of stroke-related research and clinical focus has traditionally centered on older adults, a growing body of evidence highlights an increasing incidence of stroke among middle-aged populations (3-5). First-ever ischemic strokes in individuals aged 40 to 65 years often occur in the context of fewer comorbidities, better pre-stroke functional reserves, and higher potential for long-term recovery (3, 6). Consequently, timely and comprehensive assessment of cognitive and mood outcomes in this demographic has critical implications for tailoring early rehabilitation strategies and optimizing functional prognosis.

Cognitive impairment is a frequent but under-recognized sequela of stroke (7). Studies have shown that up to 70% of stroke survivors experience some degree of cognitive impairment, with domains such as attention, memory, language, and executive functioning commonly affected (8, 9). Post-stroke cognitive impairment (PSCI) is associated with increased dependency, reduced quality of life, and elevated risk for depression and recurrent vascular events (10-12). Importantly, early post-stroke cognitive screening particularly within hyperacute and acute care phases can help identify patients at risk and facilitate prompt initiation of neurorehabilitation programs (13). However, the literature remains limited in systematically examining early cognitive trajectories in middle-aged stroke patients, especially during the critical window of hospitalization in specialized stroke units.

Moreover, emerging evidence increasingly underscores the pivotal role of lesion topography in determining the type and severity of PSCI. Beyond overall stroke volume, the anatomical location and network connectivity of an infarct can disproportionately affect cognitive domains such as memory, attention, and executive function. Lesion regions-particularly within the dominant hemisphere-have been shown to exert marked effects on language and memory, while right-hemispheric or distributed network disruptions may more strongly impact visuospatial and executive processes. Recognizing these patterns at an early stage is clinically relevant, as it can guide prognostication, facilitate tailored neurorehabilitation strategies, and improve functional outcomes. Integrating lesion-location analysis alongside conventional severity metrics thus provides a more nuanced understanding of PSCI risk and pathophysiology (14-21).

In recent years, clinical guidelines such as those proposed by the American Heart Association (AHA) have underscored the importance of early cognitive and emotional screening as part of stroke care protocols (22). However, these protocols often require adaptation to suit local contexts, particularly in resource-limited environments or populations with diverse linguistic and educational backgrounds. Middle-aged patients with

literacy and preserved language function represent an ideal subgroup for implementing such assessments during the early phase of stroke care.

Furthermore, there is growing interest in the role of circulating biomarkers in PSCI. Metabolic and inflammatory processes are key pathways in vascular brain injury, and markers such as insulin-like growth factor 1 (IGF-1), interleukin-6 (IL-6), and C-reactive protein (CRP) may offer valuable insights into the pathophysiology of early cognitive decline after stroke. Integrating such biomarkers with clinical and neuroimaging data could enhance risk stratification and identify novel targets for intervention (22, 23).

In this context, the present study aimed to evaluate early cognitive and mood functioning among middle-aged patients with first-ever mild to moderate ischemic stroke, admitted to the stroke care unit (SCU) of a major tertiary hospital.

## **Methods**

This cross-sectional observational study was conducted to evaluate early cognitive functioning in middle-aged patients with first-ever ischemic stroke admitted to the stroke unit of Imam Reza Hospital, a tertiary referral center in Tabriz, Iran. The study was carried out over a two-year period from May 2023 to May 2025 and received ethical approval from the local ethics committee (approval number: [IR.TBZMED.REC.1402.159]). Written informed consent was obtained from all participants or their legal guardians.

## **Participants and Inclusion Criteria**

The target population comprised individuals aged 40 to 65 years, with a diagnosis of unilateral ischemic stroke in middle cerebral artery (MCA) territory. The diagnosis of acute ischemic stroke was confirmed based on the American Heart Association (AHA), using clinical evaluation and neuroimaging (25). According to the AHA/ASA definition, central nervous system infarction is defined as "brain, spinal cord, or retinal cell death attributable to ischemia, based on neuropathological, neuroimaging, and/or clinical evidence of permanent injury. All patients underwent MRI with Diffusion-Weighted Imaging (DWI) and 3D FLAIR modalities to confirm the diagnosis and lesion location. Only first-ever patients in the acute phase of stroke were included. Additional inclusion criteria required that patients have the ability to read and write, and be fluent in either Azari or Persian. To ensure that cognitive testing would be reliable, only patients with a stroke severity based on National Institutes of Health Stroke Scale (NIHSS) score of 15 or lower (mild to moderate) (22,26), were included.

## **Exclusion Criteria**

Patients were excluded if they had a history of prior stroke, brainstem involvement, or significant neurological, neuropsychological, or psychiatric disorders. Individuals with severe systemic diseases (e.g., hepatic, cardiac, or pulmonary conditions) and major visual or auditory impairments were also excluded. Furthermore, to ensure valid administration of paper-and-pencil and software-based cognitive tests, patients with motor deficits in their dominant hand that would compromise their ability to perform the tasks were not enrolled. Additionally, patients with aphasia or dysarthria that compromised cognitive tasks comprehension or execution were not enrolled. Secondary exclusion was applied to patients whose ischemic stroke later developed into hemorrhagic transformation or whose condition evolved in a manner that precluded continued participation.

## **Screening Procedure and Phases**

The diagnostic criteria and the staging of PSCI assessment were all based on AHA guidelines for assessing PSCI with some modifications (27). Screening for participants was conducted in three structured phases of pre-stroke problems and demographic data gathering, hyperacute and stroke unit (acute) evaluations.

### ***Phase 1: Pre-stroke problems and demographic data gathering***

In the first phase, patients diagnosed with acute ischemic stroke following clinical assessments underwent initial screening. The demographic data were collected using specially designed forms during this stage, collected data were included age, sex, literacy level, pre-stroke independency status, premorbid mRS for pre-stroke functional status and fluency in Azari or Persian. Patients were excluded if they had a prior history of stroke, hemorrhagic transformation, language disorders, cognitive impairment or using cognitive-influencing drugs, neuropsychological disorders, systemic medical conditions, or major hearing or vision disabilities.

### ***Phase 2: Assessments in the hyperacute phase***

During the second phase, comprehensive clinical and cognitive evaluations were performed within 24 hours of hospital admission in the emergency ward. These rapid assessments included the following tools:

- Richmond Agitation-Sedation Scale (RASS): Used to assess the patient's level of agitation or sedation. This is a 10-point scale, ranging from -5 (unarousable) to +4 (combative), with a score of 0 indicating alert and calm. This helped ensure patients were in an appropriate state for initial evaluation (28)
- Confusion Assessment Method for the ICU (CAM-ICU): Administered to detect the presence of delirium. This tool assesses four features: acute change or fluctuating course of mental status, inattention,

disorganized thinking, and altered level of consciousness. Delirium was considered present if features 1 and 2, and either 3 or 4, were positive. Patients with positive CAM-ICU were excluded due to the confounding effect of delirium on cognitive testing (29).

- Patient Health Questionnaire-2 (PHQ-2): Used as an ultra-brief screening tool for depression. It asks about the frequency of depressed mood and anhedonia over the past two weeks, with each item scored from 0 (not at all) to 3 (nearly every day). Total scores range from 0 to 6. Patients with a score of  $\geq 3$  were considered to have positive screens for depressive symptoms and were excluded from the study to avoid the confounding effect of major depression on early cognition (30).

- Mini-MoCA: A brief version of the Montreal Cognitive Assessment, used for a rapid bedside cognitive evaluation in the hyperacute setting when a comprehensive assessment was not feasible. The score range is 0–12. For this phase, patients with severe cognitive impairment, defined as a Mini-MoCA score of less than 9, were excluded, as they would be unable to participate in the full MoCA assessment later. Patients with scores between 9 and 12 (mild to moderate impairment) proceeded to the next phase (31).

- NIHSS: Administered to quantify stroke severity, with scores ranging from 0 to 42 (32, 33). Patients with a score  $>15$  (severe stroke) were excluded.

Patients who demonstrated significant agitation, delirium, severe depression (PHQ-2  $\geq 3$ ), or high stroke severity (NIHSS  $> 15$ ) were excluded.

### ***Phase 3: Assessment in the stroke care unit***

The third phase, which was the main phase of the study, took place between days 3 and 7 of hospitalization in the SCU. At this stage participants underwent a final evaluation for functional independence, mood, and cognitive abilities. The assessments included:

- Barthel Index: This scale was used to assess functional independence in activities of daily living (ADLs). It measures performance in 10 basic activities such as feeding, bathing, grooming, dressing, bowel and bladder control, toilet use, transfers, mobility, and stair climbing (34). Scores range from 0 (total dependence) to 100 (complete independence). This assessment was performed to characterize the functional status of the cohort, but it is not a direct measure of cognition.

- Patient Health Questionnaire-9 (PHQ-9): This questionnaire was used to assess the severity of depressive symptoms. It consists of nine items, each scored from 0 (not at all) to 3 (nearly every day), providing a total score ranging from 0 (normal) to 27 (severe depression). This tool was used to systematically evaluate and account for the potential influence of mood on cognitive performance (35).

•Montreal Cognitive Assessment (MoCA): This was the primary instrument used for cognitive screening and diagnosis of PSCI. The MoCA assesses multiple cognitive domains, including visuospatial/executive function, naming, attention, language, abstraction, delayed recall, and orientation. Total scores range from 0 to 30, with a higher score indicating better cognitive function. Based on the total MoCA score, patients were classified into two groups: those with PSCI (score < 26) and those without cognitive impairment (non-PSCI, score  $\geq$  26) (36, 37).

This structured screening process ensured the accurate selection of patients, allowing a targeted investigation of early cognitive functioning. Additional data collected included demographic variables, clinical stroke scales (NIHSS and mRS) (38, 39), medical history and use of cognition-affecting medications were also documented.

### ***Biomarker Collection and Analysis***

To explore the relationship between circulating biomarkers and cognitive outcomes, blood samples were collected from all participants. Fasting blood samples were drawn on the morning following the main assessment day (between days 4 and 8 of hospitalization) under standardized conditions. Samples were collected in appropriate tubes (e.g., serum separator tubes for IGF-1 and CRP, and EDTA tubes for IL-6). Within 60 minutes of collection, samples were centrifuged at 3000 rpm for 10 minutes at 4°C. The separated serum or plasma was then aliquoted into cryovials and stored at -80°C until the time of analysis. Analysis was performed in batches to minimize inter-assay variability. The following biomarkers were measured: routine profile markers including fasting blood sugar (FBS), HbA1c, lipid profile (total cholesterol, triglycerides, LDL, HDL), as well as specific inflammatory and metabolic markers including high-sensitivity C-reactive protein (hs-CRP), Interleukin-6 (IL-6) using a high-sensitivity ELISA kit, and Insulin-like Growth Factor 1 (IGF-1) using a chemiluminescence immunoassay. All assays were performed according to the manufacturers' instructions by trained laboratory personnel blinded to the patients' cognitive status.

### ***Statistical Analysis***

All statistical analyses were performed using IBM SPSS Statistics version 26. Quantitative data were tested for normality with the Shapiro-Wilk test and summarized as mean  $\pm$  standard deviation (SD) with range. Categorical variables were reported as frequencies and percentages. Comparisons between PSCI and non-PSCI groups were made using the independent samples t-test for normally distributed continuous variables, and the Mann–Whitney U test for non-normally distributed data. Chi-square test or Fisher's exact test was used for categorical variable comparisons. Correlations between MoCA scores (total and domain-specific) and circulating biochemical markers were assessed using Pearson's correlation coefficient for normally

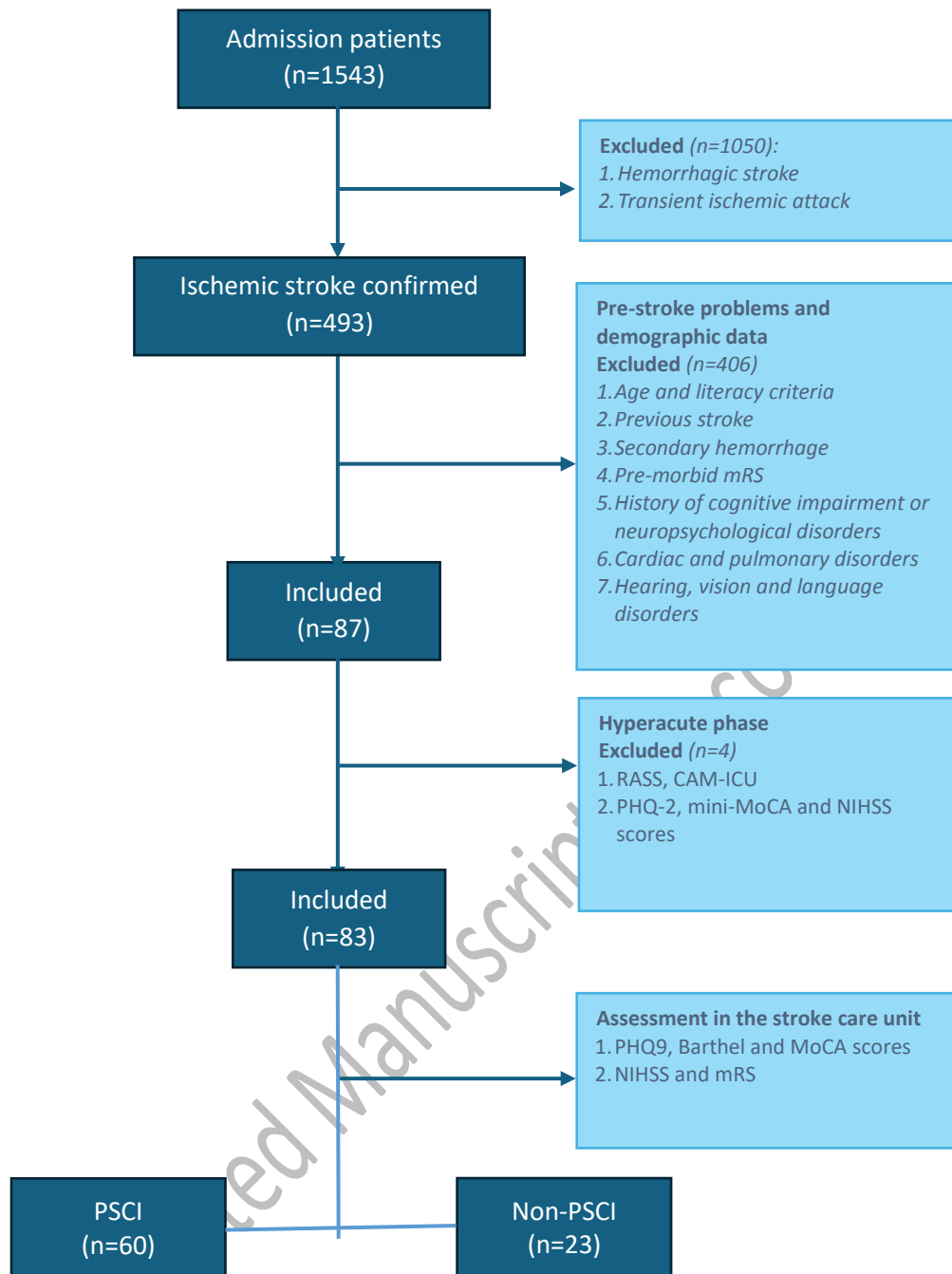
distributed variables and Spearman's rank correlation coefficient otherwise. Results were interpreted using two-tailed tests with a significance threshold of  $p < 0.05$ . This study adhered to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines to ensure transparent and rigorous reporting (40).

## Results

### *Phase 1: Screening and Enrollment (Pre-stroke and Demographic Data Gathering)*

A total of 1543 patients were screened during the study period (Figure 1). After excluding 1050 participants with hemorrhagic stroke or transient ischemic attack, 493 patients with ischemic stroke were assessed for eligibility. Of these, 406 patients were excluded based on preset criteria, including age and literacy limitations, previous stroke, secondary hemorrhage, history of cognitive impairment or neuropsychological disorders, cardiac and pulmonary disorders, or sensory/language deficits.

All participants had a documented pre-morbid modified Rankin Scale (mRS) score of 0, reflecting complete independence in activities of daily living prior to stroke onset. Demographic data collected in this phase are presented in the Demographic and Clinical Characteristics subsection under Phase 3, as they pertain to the final cohort.



**Figure 1:** Flow-diagram of the patient recruitment for the study.

### ***Phase 2: Hyperacute Phase Assessment***

Eighty-seven patients proceeded to hyperacute phase assessment (within 24 hours of admission). In this phase, 4 patients were excluded due to severe agitation or delirium, or depressive symptoms ( $\text{PHQ-2} \geq 3$ ). The final study cohort comprised 83 patients, of whom 60 (72.3%) were subsequently diagnosed with Post-

Stroke Cognitive Impairment (PSCI) and 23 (27.7%) were classified as cognitively intact (non-PSCI). Detailed information on excluded patients in each phase is available in Table 1.

**Table 1.** Demographic characteristics, literacy levels, sex distribution, and exclusion criteria of participants across study phases.

|                                                       | Age [Mean $\pm$ SD (Range)] | Literacy [Mean $\pm$ SD (Range)] | Sex Male: Female [Frequency (%)] | Exclusion [Frequency (%)]                                                                                                                                                                                                                                                                                     |
|-------------------------------------------------------|-----------------------------|----------------------------------|----------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Pre-stroke problems and demographic selection (n=493) | 62.3 $\pm$ 13.51 (17-101)   | 6.26 $\pm$ 5.09 (0-20)           | 315 (63.9): 178 (36.1)           | Age and literacy criteria: 92 (18.7)<br>Previous stroke: 89 (18.1)<br>CI History: 19 (3.9)<br>Neuropsychological disorder history: 62 (12.6)<br>Cognition-influencing drugs: 30 (6.1)<br>Aphasia: 53 (10.8)<br>Dysarthria: 49 (9.9)<br>Secondary hemorrhage: 23 (4.7)<br>Systemic medical conditions: 2 (0.4) |
| Assessment in hyperacute phase (n=87)                 | 56.14 $\pm$ 8.19 (40-65)    | 8.25 $\pm$ 3.49 (4-18)           | 56 (64.4): 31 (35.6)             | NIHSS >15: 0 (0)<br>RASS: 4 (4.6)<br>CAM-ICU: 4 (4.6)<br>PHQ-2 $\geq$ 3: 2 (2.3)<br>Mini-MoCA <9: 0 (0)                                                                                                                                                                                                       |
| Assessment in the stroke care unit phase (n=83)       | 56.31 $\pm$ 8.27 (40-65)    | 8.1 $\pm$ 3.54 (4-18)            | 54 (65.1): 29 (34.9)             | PHQ-9 >4: 0 (0)                                                                                                                                                                                                                                                                                               |

Retrospective mini-MoCA results from the hyperacute phase showed significantly lower total scores ( $p < 0.001$ ) and reduced performance in language fluency ( $p = 0.001$ ) and orientation ( $p = 0.026$ ) among patients who would later be diagnosed with PSCI (Table 2).

**Table 2.** Comparisons of demographic and clinical features between patients with and without post-stroke cognitive impairment.

| Phases                     | Variables                          | PSCI                           | Non-PSCI                          | <i>p</i> value | Total                              |
|----------------------------|------------------------------------|--------------------------------|-----------------------------------|----------------|------------------------------------|
| Pre-stroke and demographic | Number (%)                         | 60 (72.3)                      | 23 (27.7)                         | -              | 83 (100)                           |
|                            | Gender (%)                         | Male 39 (65)<br>Female 21 (35) | Male 14 (60.8)<br>Female 9 (39.2) | -              | Male 53 (63.8)<br>Female 30 (36.2) |
|                            | Age (years)                        | 56.15 ± 8.57 (40-65)           | 57.07 ± 6.95 (41-65)              | 0.717          | 56.31 ± 8.27 (40-65)               |
|                            | Education (years)                  | 8.06 ± 3.43 (4-18)             | 8.3 ± 4.13 (4-16)                 | 0.826          | 8.1 ± 3.54 (4-18)                  |
|                            | Duration of Hospitalization (days) | 6.9 ± 3.11 (2-16)              | 6.15 ± 2.67 (3-11)                | 0.425          | 6.76 ± 3.03 (2-16)                 |
|                            | Pre-morbid mRS                     | 0                              | 0                                 | 1              | 0                                  |
| Hyperacute                 | NIHSS in admission                 | 7.78 ± 4.14 (1-15)             | 7.92 ± 4.6 (1-15)                 | 0.914          | 7.8 ± 4.19 (1-15)                  |
|                            | PHQ-2                              | 1.06 ± 0.79 (0-2)              | 0.92 ± 0.64 (0-2)                 | 0.547          | 1.04 ± 0.77 (0-2)                  |
|                            | Mini-MoCA (Total)                  | 10.8 ± 0.98 (9-12)             | 12 ± 0 (12-12)                    | <b>0.000</b>   | 10.98 ± 0.99 (9-12)                |
|                            | Mini-MoCA (Language fluency)       | 2.61 ± 0.66 (1-4)              | 3.3 ± 0.63 (2-4)                  | <b>0.001</b>   | 2.73 ± 0.7 (1-4)                   |
|                            | Mini-MoCA (Orientation)            | 4.93 ± 0.79 (3-6)              | 5.46 ± 0.51 (5-6)                 | <b>0.026</b>   | 5.02 ± 0.78 (3-6)                  |
|                            | Mini-MoCA (Recall)                 | 3.23 ± 0.69 (2-5)              | 3.53 ± 0.66 (3-5)                 | 0.154          | 3.28 ± 0.69 (2-5)                  |
| Stroke care unit           | PHQ-9                              | 1.88 ± 0.97 (0-4)              | 1.54 ± 0.87 (0-3)                 | 0.244          | 1.82 ± 0.96 (0-4)                  |
|                            | Barthel Index                      | 83.33 ± 12.61 (50-100)         | 85.76 ± 11.33 (65-100)            | 0.523          | 83.76 ± 12.35 (50-100)             |
|                            | mRS in discharge                   | 1.28 ± 0.84 (0-3)              | 1.23 ± 0.83 (0-3)                 | 0.839          | 1.27 ± 0.83 (0-3)                  |
|                            | NIHSS in discharge                 | 3.1 ± 2.15 (1-9)               | 2.92 ± 2.13 (0-7)                 | 0.789          | 3.06 ± 2.13 (0-9)                  |
|                            | NIHSS change                       | 4.68 ± 3.61 (-3-13)            | 5 ± 4.6 (0-13)                    | 0.786          | 4.73 ± 3.77 (-3-13)                |
|                            | MoCA (Total)                       | 22.7 ± 1.88 (18-25)            | 26.61 ± 0.96 (26-29)              | <b>0.000</b>   | 23.39 ± 2.3 (18-29)                |
|                            | MoCA (Visuospatial-Executive)      | 3.8 ± 0.75 (2-5)               | 4.77 ± 0.43 (4-5)                 | <b>0.000</b>   | 3.97 ± 0.79 (2-5)                  |
|                            | MoCA (Naming)                      | 2.51 ± 0.53 (1-3)              | 2.76 ± 0.43 (2-3)                 | 0.118          | 2.56 ± 0.52 (1-3)                  |
|                            | MoCA (Attention)                   | 4.16 ± 1.15 (2-6)              | 4.84 ± 0.8 (4-6)                  | <b>0.047</b>   | 4.28 ± 1.12 (2-6)                  |
|                            | MoCA (Language)                    | 2.71 ± 0.49 (1-3)              | 3 ± 0 (3-3)                       | <b>0.042</b>   | 2.76 ± 0.45 (1-3)                  |
|                            | MoCA (Abstraction)                 | 1.06 ± 0.4 (0-2)               | 1.3 ± 0.48 (1-2)                  | 0.065          | 1.1 ± 0.42 (0-2)                   |
|                            | MoCA (Delayed Recall)              | 3.3 ± 0.86 (1-6)               | 3.84 ± 0.37 (3-4)                 | <b>0.03</b>    | 3.39 ± 0.82 (1-6)                  |
|                            | MoCA (Orientation)                 | 5.13 ± 0.7 (3-6)               | 5.84 ± 0.37 (5-6)                 | <b>0.001</b>   | 5.26 ± 0.7                         |

### Phase 3: Stroke Care Unit Assessment

The main assessments were conducted between days 3 and 7 of hospitalization in the stroke unit.

#### Demographic and Clinical Characteristics

The mean age of the cohort was  $56.31 \pm 8.27$  years (range: 40–65), with no significant difference between PSCI ( $56.15 \pm 8.57$  years) and non-PSCI ( $57.07 \pm 6.95$  years) groups ( $p = 0.717$ ). The overall male-to-female ratio was 63.8% to 36.2%, with no significant group difference. Years of education were comparable between PSCI ( $8.06 \pm 3.43$ ) and non-PSCI ( $8.3 \pm 4.13$ ) patients ( $p = 0.826$ ). Duration of hospitalization did not differ significantly (PSCI:  $6.9 \pm 3.11$  days vs. non-PSCI:  $6.15 \pm 2.67$ ,  $p = 0.425$ ) (Table 2).

#### *Functional Status Outcomes*

Baseline stroke severity, measured by the NIHSS at admission, was similar between groups (PSCI:  $7.78 \pm 4.14$  vs. non-PSCI:  $7.92 \pm 4.6$ ;  $p = 0.914$ ). The mRS score at discharge also showed no significant difference between the groups ( $p = 0.839$ ).

Regarding functional status assessed in the stroke unit, the Barthel Index did not differ significantly between the PSCI ( $83.33 \pm 12.61$ ) and non-PSCI ( $85.76 \pm 11.33$ ) groups ( $p = 0.523$ ). This indicates that despite differences in cognition, both groups had similar levels of independence in basic daily activities during the acute phase.

#### *Cognitive Outcomes*

The primary cognitive assessment in the stroke unit, the Montreal Cognitive Assessment (MoCA), demonstrated widespread deficits in the PSCI group across multiple domains. The mean total MoCA score was significantly lower in PSCI patients ( $22.7 \pm 1.88$ ) compared with the non-PSCI group ( $26.61 \pm 0.96$ ;  $p < 0.001$ ). Domain-specific analysis revealed that visuospatial/executive function, attention, language, delayed recall, and orientation were significantly reduced in PSCI patients ( $p$  values ranging from  $< 0.001$  to  $0.047$ ), while naming and abstraction showed no statistically significant difference (Table 2).

#### *Neurological and Radiological Findings*

Laterality of stroke, vascular territory involvement, and weakness patterns were assessed. Combined upper and lower limb weakness on the left side was more prevalent in the PSCI group (50.0% vs. 17.3%,  $p = 0.031$ ) (Table 3). Other motor deficits, language disorders, facial deformities, and balance issues showed no significant differences.

**Table 3.** Neurological signs in patients with and without PSCI.

| Variables                             | PSCI (%)<br>[n=60] | Non-PSCI (%)<br>[n=23] | <i>p</i> value | Total (%) |
|---------------------------------------|--------------------|------------------------|----------------|-----------|
| Upper side weakness (Left)            | 3 (5)              | 4 (17.3)               | 0.214          | 7 (8.4)   |
| Upper side weakness (Right)           | 2 (3.3)            | 2 (8.6)                | 0.450          | 4 (4.8)   |
| Upper and lower side weakness (Left)  | 30 (50)            | 4 (17.3)               | <b>0.031</b>   | 34 (40.9) |
| Upper and lower side weakness (Right) | 21 (35)            | 11 (47.8)              | 0.532          | 32 (38.6) |
| Language disorder                     | 40 (66.7)          | 11 (47.8)              | 0.210          | 51 (61.4) |
| Facial deformity (Right)              | 8 (13.3)           | 4 (17.3)               | 1              | 12 (14.4) |
| Facial deformity (Left)               | 13 (21.7)          | 2 (8.6)                | 0.440          | 15 (18)   |
| Balance                               | 4 (6.7)            | 5 (21.7)               | 0.102          | 9 (10.8)  |
| Falling                               | 0 (0)              | 2 (8.6)                | 0.178          | 2 (2.4)   |

Analysis of lesion characteristics demonstrated that patients with PSCI were more likely to have lesions involving the left hemisphere, compared with those without cognitive impairment ( $p = 0.016$ ). Lesions confined to the right hemisphere were less commonly associated with significant cognitive deficits. Across cognitive domains, left hemisphere lesions showed stronger associations with impairments in language, memory, abstraction, and attention scores, whereas right-sided lesions were more variably linked to visuospatial and executive functions (Table 4).

**Table 4.** Radiological findings and comorbid conditions among patients with and without PSCI.

| Radiological Variables | PSCI (%)<br>[n=60] | Non-PSCI (%)<br>[n=23] | <i>p</i> value | Total (%) |
|------------------------|--------------------|------------------------|----------------|-----------|
| MCA (Right)            | 17 (28.3)          | 11 (47.8)              | 0.108          | 28 (33.7) |
| MCA (Left)             | 36 (60)            | 5 (21.7)               | <b>0.016</b>   | 41 (49.3) |
| Cortical               | 28 (46.6)          | 11 (47.8)              | 1              | 39 (46.9) |
| Subcortical            | 32 (53.3)          | 12 (52.1)              | 1              | 44 (53)   |
| Lacunar MCA (Right)    | 4 (6.6)            | 5 (21.7)               | 0.106          | 9 (10.8)  |
| Lacunar MCA (Left)     | 3 (5)              | 0 (0)                  | 0.630          | 3 (3.6)   |

#### *Comorbidities and Risk Factors*

Hypertension, diabetes mellitus, cardiovascular disease, smoking, alcohol abuse, rheumatologic disease, hyperlipidemia, COPD, and CKD frequencies were similar between groups. Snoring was observed in the cohort and was significantly more common among non-PSCI patients (39.1% vs. 13.3%,  $p = 0.047$ ) (Table 5).

**Table 5.** Comorbidity findings and comorbid conditions among patients with and without PSCI.

| <b>Comorbid Variables</b>                    | <b>PSCI (%)<br/>[n=60]</b> | <b>Non-PSCI (%)<br/>[n=23]</b> | <b><i>p</i> value</b> | <b>Total (%)</b> |
|----------------------------------------------|----------------------------|--------------------------------|-----------------------|------------------|
| <b>Hypertension</b>                          | 39 (65)                    | 16 (69.5)                      | 1                     | 55 (66.2)        |
| <b>Diabetes mellitus</b>                     | 17 (28.3)                  | 4 (17.3)                       | 0.492                 | 21 (25.3)        |
| <b>Cardiovascular disease</b>                | 16 (26.7)                  | 5 (21.7)                       | 1                     | 21 (25.3)        |
| <b>Smoking</b>                               | 20 (33.3)                  | 9 (39.1)                       | 0.754                 | 29 (34.9)        |
| <b>Alcohol abuse</b>                         | 4 (6.7)                    | 0 (0)                          | 1                     | 4 (4.8)          |
| <b>Rheumatologic disease</b>                 | 3 (5)                      | 0 (0)                          | 1                     | 3 (3.6)          |
| <b>Hyperlipidemia</b>                        | 6 (10)                     | 2 (8.6)                        | 1                     | 8 (9.6)          |
| <b>Snoring</b>                               | 8 (13.3)                   | 9 (39.1)                       | <b>0.047</b>          | 17 (20.4)        |
| <b>Chronic obstructive pulmonary disease</b> | 3 (5)                      | 0 (0)                          | 1                     | 3 (3.6)          |
| <b>Chronic Kidney disease</b>                | 1 (1.7)                    | 2 (8.6)                        | 0.326                 | 3 (3.6)          |

#### *Laboratory and Circulating Biomarkers*

There were no significant between-group differences in hemoglobin, hematocrit, fasting blood sugar (FBS), cholesterol, triglycerides, LDL, HDL, random blood sugar, HbA1c, BMI, blood pressure, IGF-1, IL-6, or CRP levels (Table 6).

**Table 6.** Laboratory, metabolic, and inflammatory biomarker profiles of patients with and without PSCI.

| Variable                                          | PSCI<br>[n=60]           | Non-PSCI<br>[n=23]       | <i>p</i><br>value | Total                    |
|---------------------------------------------------|--------------------------|--------------------------|-------------------|--------------------------|
| <b>Hemoglobin (Hb) mg/dl</b>                      | 14.36 ± 1.89 (9-19)      | 13.96 ± 1.57 (10-17)     | 0.497             | 14.29 ± 1.83 (9-19)      |
| <b>Hematocrit (Hct) %</b>                         | 43.83 ± 4.26 (33-54)     | 42.43 ± 3.77 (35-51)     | 0.277             | 43.58 ± 4.19 (33-54)     |
| <b>Fasting Blood Sugar (FBS) mg/dl</b>            | 144.88 ± 74.37 (75-400)  | 126.54 ± 33.28 (84-180)  | 0.389             | 141.62 ± 69.04 (75-400)  |
| <b>Blood Sugar (BS) mg/dl</b>                     | 165.95 ± 87.77 (75-500)  | 142.69 ± 51.52 (89-261)  | 0.361             | 161.81 ± 82.68 (75-500)  |
| <b>HbA1c %</b>                                    | 6.95 ± 2.32 (5-14)       | 6.21 ± 1.22 (5-9)        | 0.269             | 6.82 ± 2.18 (5-14)       |
| <b>Total Cholesterol mg/dl</b>                    | 174.62 ± 36.67 (106-249) | 178.38 ± 47.59 (117-255) | 0.751             | 175.29 ± 38.49 (106-255) |
| <b>Triglyceride mg/dl</b>                         | 157.65 ± 88.2 (38-440)   | 159.69 ± 68.26 (83-278)  | 0.938             | 158.01 ± 84.56 (38-440)  |
| <b>LDL mg/dl</b>                                  | 100.80 ± 32.36 (27-164)  | 101.85 ± 37 (61-169)     | 0.918             | 100.99 ± 32.96 (27-169)  |
| <b>HDL mg/dl</b>                                  | 37.73 ± 11.63 (18-65)    | 40.31 ± 15.72 (21-70)    | 0.5               | 38.19 ± 12.37 (18-70)    |
| <b>Body Mass Index (BMI)</b>                      | 28.46 ± 3.91 (20-38)     | 28.04 ± 2.64 (24-33)     | 0.714             | 28.38 ± 3.7 (20-38)      |
| <b>Systolic blood pressure mmHg</b>               | 142.63 ± 20.86 (100-198) | 150.77 ± 18.45 (120-180) | 0.198             | 144.08 ± 20.57 (100-198) |
| <b>Diastolic blood pressure mmHg</b>              | 86.75 ± 11.91 (62-130)   | 89 ± 12.72 (70-122)      | 0.544             | 87.15 ± 12 (62-130)      |
| <b>Insulin-like Growth Factor-1 (IGF-1) ng/ml</b> | 136.79 ± 60.34 (37-297)  | 142.73 ± 21.10 (101-192) | 0.728             | 137.85 ± 55.34 (37-297)  |
| <b>Interleukin-6 (IL-6) pg/ml</b>                 | 7.79 ± 5.12 (2-25)       | 6.36 ± 2.9 (3-11)        | 0.335             | 7.53 ± 4.81 (2-25)       |
| <b>C-reactive protein (CRP) mg/L</b>              | 12.35 ± 15.08 (2-83)     | 12.74 ± 7.79 (2-24)      | 0.929             | 12.42 ± 14.02 (2-83)     |

Correlation analyses across the whole cohort revealed notable associations between metabolic/circulatory biomarkers and cognitive performance: elevated FBS, BS, and HbA1c were negatively associated with MoCA total scores and specific domains; IGF-1 was positively associated with total MoCA and attention sub-score; BMI was positively associated with visuospatial-executive and delayed recall scores; and IL-6 was inversely related to language performance (Table 7).

**Table 7.** Significant correlations between MoCA task scores and circulating biochemical factors among all participants.

| Variables                                         | MoCA (Total)                | Visuospatial-Executive      | Attention                   | Language                    | Delayed Recall             |
|---------------------------------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|----------------------------|
| <b>Hemoglobin (Hb) mg/dl</b>                      | -                           | -                           | $r = 0.273$<br>$p = 0.019$  | -                           | -                          |
| <b>Hematocrit (Hct) %</b>                         | -                           | -                           | $r = 0.254$<br>$p = 0.029$  | -                           | -                          |
| <b>Fasting Blood Sugar (FBS) mg/dl</b>            | $r = -0.239$<br>$p = 0.042$ | $r = -0.285$<br>$p = 0.015$ | -                           | -                           | -                          |
| <b>Blood Sugar (BS) mg/dl</b>                     | $r = -0.249$<br>$p = 0.033$ | -                           | $r = -0.235$<br>$p = 0.045$ | -                           | -                          |
| <b>HbA1c %</b>                                    | $r = -0.279$<br>$p = 0.017$ | $r = -0.245$<br>$p = 0.037$ | $r = -0.28$<br>$p = 0.016$  | -                           | -                          |
| <b>Body Mass Index (BMI)</b>                      | -                           | $r = 0.231$<br>$p = 0.048$  | -                           | -                           | $r = 0.310$<br>$p = 0.007$ |
| <b>Insulin-like Growth Factor-1 (IGF-1) ng/ml</b> | $r = 0.311$<br>$p = 0.007$  | -                           | $r = 0.351$<br>$p = 0.002$  | -                           | -                          |
| <b>Interleukin-6 (IL-6) pg/ml</b>                 | -                           | -                           | -                           | $r = -0.332$<br>$p = 0.004$ | -                          |

## Discussion

This study provides updated insights into the prevalence, domain-specific patterns, and associated factors of PSCI in a middle-aged unilateral MCA ischemic stroke cohort, using standardized assessment tools including the Mini-MoCA, MoCA, and PHQ questionnaires. Our results revealed a remarkably high PSCI prevalence of 72.3% within the first week post-stroke, despite similar demographic and stroke severity profiles between cognitively impaired and non-impaired patients. The reason for including only unilateral MCA strokes in this study was due to their higher prevalence and the need for a more homogeneous study group (41).

The observed prevalence exceeds both the 66.4% reported by Kaddumukasa et al. in Ugandan post-stroke patients (mean MoCA 11.7) (42) and the 52.38% early rate reported by Liao et al. at 2 weeks post-stroke, which declined to 34.16% by one year (43). This disparity may reflect methodological differences-our study exclusively included acute and subacute cases-and limited availability of early rehabilitation in our setting. The persistence of such high early deficits strengthens the argument for standardized inpatient cognitive screening as part of acute care protocols.

In our study, all patients demonstrated a premorbid mRS score of 0, indicating complete independence prior to the index ischemic stroke. This uniform baseline functional status supports the interpretation that post-stroke cognitive deficits were unlikely to be influenced by pre-existing neurological or functional limitations. Moreover, discharge mRS scores did not differ significantly between patients with and without PSCI, suggesting that early cognitive impairment in this population may occur independently of measurable differences in global physical disability at hospital discharge. These observations highlight that functional recovery, as captured by the mRS, may not fully reflect the cognitive sequelae of stroke, underscoring the need for dedicated cognitive screening alongside routine functional assessments.

Notably, despite the fact that all participants in our cohort experienced only mild to moderate ischemic stroke by NIHSS criteria, the majority nonetheless exhibited measurable cognitive impairment during the acute phase. This underscores that even relatively preserved motor and functional status does not preclude substantial neurocognitive sequelae. Such findings challenge the common clinical tendency to focus rehabilitation resources primarily on patients with overt neurological disability, risking under-recognition of cognitive deficits in those with milder presentations. The data highlight the importance of systematic cognitive screening for all stroke severities, as undetected impairments may impede return to work, social reintegration, and long-term quality of life.

In our study, no significant correlation was observed between NIHSS scores at admission and the severity of cognitive impairment as measured by MoCA. This suggests that stroke severity as captured by standard neurological scales may not fully reflect the cognitive burden, particularly in mild-to-moderate cases. The NIHSS is weighted toward motor, sensory, and language deficits, with relatively limited sensitivity to higher-order cognitive domains such as executive function, memory, or attention. Consequently, patients with strategically located infarcts—especially in cortical or subcortical regions critical to cognition—may score low on NIHSS yet experience substantial neuropsychological deficits. This pattern aligns with prior evidence that cognitive impairment after stroke is more strongly influenced by lesion location, network disruption, and hemispheric involvement than by overall stroke severity scores. Our findings reinforce the need for routine cognitive screening even in patients with relatively low NIHSS scores, as neurological “mildness” does not preclude significant cognitive morbidity (14-21).

Our study revealed a significant association between lesion location and specific cognitive deficits, with patients harboring left hemisphere lesions, particularly those involving both upper and lower limb motor areas, demonstrating a higher prevalence and severity of PSCI. This pattern aligns with prior studies showing that cortical involvement, especially in the dominant hemisphere, exerts a disproportionate impact on cognition. Nys et al. reported that left cortical strokes were associated with more pronounced deficits in executive functioning, language, and verbal memory compared with right-sided lesions, and that cortical

location was an independent predictor of acute cognitive impairment (21). Using multivariate lesion-symptom mapping in over 400 patients, Zhao et al. further identified the left angular gyrus, basal ganglia structures, and surrounding white matter as strategic hubs for post-stroke cognitive impairment across multiple domains (20). Similarly, Sagnier et al. demonstrated that language, abstraction, and delayed recall were closely tied to left-hemispheric lesions, while visuospatial, executive, and attention deficits often resulted from bilateral or distributed lesions (14). Together, these findings underscore the role of lesion topography-not merely volume-in shaping early post-stroke cognitive outcomes. Our results add to this evidence by demonstrating that even in a middle-aged cohort with mild-to-moderate stroke severity, early lesion location mapping can provide clinically relevant prognostic information, suggesting that targeted neurorehabilitation strategies should incorporate location-based risk profiling alongside traditional clinical predictors.

Domain-specific analysis indicated that visuospatial/executive function, attention, delayed recall, orientation, and language were significantly impaired in the PSCI group, while abstraction and naming showed no significant group differences. This pattern closely mirrors Liao et al., who found delayed recall and visuospatial/executive function to be the most frequently affected cognitive domains (43). Our findings reaffirm MoCA's value in detecting subtle deficits, which might be underdetected with broader cognitive screening tools such as MMSE (44).

The mean MoCA score of  $22.7 \pm 1.88$  observed in our PSCI group was lower than the 24/25 optimal cut-off reported by Potocnik et al. in the Slovenian MoCA validation (45), underlining the importance of culture- and education-adjusted thresholds. Zhu et al. similarly found MoCA to be a reliable PSCI predictor, equivalent to MMSE (46).

Beyond neuropsychological testing, left-sided combined upper and lower limb weakness was observed more frequently in PSCI patients, suggesting potential hemispheric influence on cognition. While vascular risk factor prevalence-most notably hypertension and diabetes-was consistent with findings by Rost et al. (47), an observation regarding snoring was noted in the cohort, but as it was not a primary focus and its role is ambiguous in the literature it is reported without emphasis (48,49). Since snoring finding in this study is controversial and the significance is marginal, the finding risks being misleading and should either be analysed more rigorously, and considered with caution.

Biochemical analyses revealed notable correlations: poor glycemic control (higher FBS, BS, HbA1c) was linked to lower total MoCA and domain scores, aligning with previous work linking metabolic dysregulation to cognitive decline (47, 50). Higher IGF-1 associated positively with total cognition and attention, while elevated IL-6 was negatively associated with language scores supporting inflammatory

pathways as possible contributors to PSCI pathophysiology. Integrating biomarker analysis into PSCI risk stratification could enhance early detection and targeted intervention.

Functional outcomes showed universal improvement in NIHSS from admission to discharge, consistent with Salvadori et al., who emphasized early recovery despite cognitive limitations (51). However, as Quinn et al. discuss, cognitive rehabilitation remains a critical determinant for regaining independence (52).

Overall, our findings align with Liao et al.'s observation that recovery is domain-dependent, with orientation showing relatively greater preservation (43). Future care models should thus consider domain-specific rehabilitation, coupled with vascular risk factor control, metabolic optimization, and anti-inflammatory strategies. Tools like MoCA and potentially Cognitive Assessment Scale for Stroke Patients (CASP) (53) should be integrated into early hospital-based screening to capture domain deficits and guide interventions.

An important methodological consideration is the two-step cognitive assessment process utilized in our study. In the hyperacute phase (emergency ward), we incorporated the Mini-MoCA with a cut-off scores between 9 and 12 solely as a rapid bedside tool to assess patients with marked cognitive impairment when immediate and comprehensive evaluation was not feasible. This approach allowed us to perform efficient screening within the <24-hour window while minimizing patient burden in the acute triage context. However, our primary cognitive assessment was deliberately deferred to the acute stage (days 3-7) in the SCU, using the MoCA as a more comprehensive and domain-sensitive instrument to define PSCI status. Accordingly, the Mini-MoCA functioned strictly as a preliminary inclusion criterion and did not determine cognitive classification in the final analysis. This strategy ensured both rapid patient flow in emergency care and methodological robustness for the main cognitive outcome, while reducing potential confounding from acute delirium, hemodynamic instability, or severe fatigue, which are common in the hyperacute post-stroke period.

This study has several limitations. First, its cross-sectional design precludes causal inference or assessment of long-term cognitive trajectories. Second, the sample size-while sufficient for primary comparisons-limits power for detecting smaller effect sizes, especially for less prevalent risk factors. Third, the single-center setting may limit generalizability, particularly to healthcare systems with different rehabilitation resources. Fourth, exclusion of patients with severe stroke, significant language deficits, or impaired consciousness may underestimate the true burden of PSCI. Fifth, also some studies use a +1 correction for education <12 years for MoCA threshold, but we used of <26 (according regional guidelines) that may inflate the prevalence figure. Finally, while we identified co-occurrence with metabolic and inflammatory markers, these findings are exploratory and require validation in larger, longitudinal biomarker studies.

Incorporating a broader range of cognitive assessment tools including those suitable for aphasic patients such as CASP could capture deficits currently missed by MoCA. Additionally, exploring sleep-related variables, such as polysomnographic data, may clarify the intriguing snoring association.

## **Conclusions**

In this study a high proportion of middle-aged patients with first-ever mild-to-moderate ischemic stroke developed PSCI in the acute phase, predominantly affecting visuospatial-executive function, attention, language, and delayed recall. While demographic and general clinical variables showed no significant differences between PSCI and non-PSCI groups, combined upper and lower limb weakness, and specific biochemical markers related to glycemic control, BMI, IGF-1, and inflammation were significantly associated with cognitive outcomes. These findings suggest that combining targeted neurological assessment with metabolic–inflammatory profiling may enhance early identification of patients at risk for PSCI.

## **Declaration of competing interest**

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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## **Authors’ contributions**

ME and SSE designed the study. ME and SA collected and analyzed the data. ME and SSE prepared the tables and figures. ME drafted the initial manuscript, and SSE, YS, ESH, and MF contributed to subsequent revisions. All authors critically revised the manuscript, approved the final version, and agreed to be accountable for all aspects of the work.

## **Availability of data and materials**

All data generated or analyzed in this work are included in the published version.

**Ethics approval and consent to participate**

The study received ethical approval from the local ethics committee (approval number: [IR.TBZMED.REC.1402.159]). Written informed consent was obtained from all participants or their legal guardians.

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