Stroke

TOPICAL REVIEW

# Surrogate Molecular Biomarkers for Poststroke Cognitive Impairment: A Narrative Review

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**ABSTRACT:** Cognitive impairment is a clinical condition that frequently occurs after stroke, interfering with patients' functional status and increasing their risk of death. Multiple cognitive domains can be affected, including language, memory, attention, and executive functions. Current research highlights the clinical value of tools for early assessment of cognitive decline risk, enabling implementation of efficient and personalized treatment interventions. In this respect, surrogate molecular biomarkers have been identified as useful predictors of poststroke cognitive decline. After a stroke, the brain undergoes neurochemical alterations, leading to changes in the concentration of several biomarkers, which can be detected in the plasma or serum of patients and have been associated with impaired cognitive performance. However, there is still no consensus on the predictive value of those biomarkers. The present narrative review examines existing research on molecular biomarkers as a prognostic factor for poststroke cognitive deterioration, with a specific focus on the neuropsychological rigor of the methodologies used in these studies. Particularly, data concerning biomarker variations in relation to global cognitive performance and the specifically affected cognitive domains are presented. The aim is to contribute to the establishment of a scientific consensus regarding the management of stroke recovery.

**GRAPHIC ABSTRACT:** A graphic abstract is available for this article.

**Key Words:** biomarkers ■ cognition ■ dementia ■ executive function ■ prevalence





Poststroke cognitive impairment (PSCI) is a subtype of vascular cognitive impairment[1] that occurs in at least 30% of individuals who have suffered a stroke, with a prevalence of up to 70%.[2] The onset of impairment appears to be variable, with studies describing degradation of cognitive functions within 3 months after stroke,[3] although others identify a 6-month time interval.[4] Although the evolution of PSCI is unpredictable, it has been associated with poor functional outcome, increased risk of future stroke, and dementia.[5,6]

PSCI is a complex condition that involves several pathophysiological pathways; however, a universally accepted definition is still lacking.[7] Stroke survivors who suffer from PSCI can have diverse clinical manifestations that involve 1 or more cognitive domains, including orientation, language, memory, visuospatial function, executive functioning (EF), attention, or calculation.[8,9] Given the high incidence of PSCI and its impact on the lives of stroke survivors, identifying early predictors of impairment is essential for designing early and personalized rehabilitation programs. In this respect, the analysis of surrogate molecular biomarkers has been recently identified as a promising tool.[10]

Molecular biomarkers are objectively measurable molecules that can be detected in tissues or fluids, that is, blood, cerebrospinal fluid, or urine, and serve as indicators of normal or pathogenic biological processes.[11] Although neuroimaging and neuropsychological evaluation represent benchmark tools for PSCI diagnosis, their combination with molecular biomarker analysis can facilitate the detection of early changes at the cellular and molecular level, which would not be otherwise detectable.[12] Moreover, the acquisition of molecular biomarkers does not require sophisticated or expensive neuroimaging instruments and has no contraindication for patients. Therefore, biomarker analysis can be easily serialized,

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functioning as a rapid and cost-effective way to predict PSCI.

Current knowledge of molecular biomarkers in PSCI has been guided by neurodegenerative research on diseases, such as Alzheimer disease.[12] However, consensus on their predictive value has not been achieved. Surrogate biomarkers reflect the underlying cerebrovascular pathology and are not notably sensitive to specific patterns of cognitive impairment. An exhaustive evaluation of language and other cognitive functions is, therefore, essential to capture the multidimensional nature of PSCI. Herein, we review research studies investigating the role of molecular biomarkers in PSCI, focusing on cognitive domains and functions that are the object of neuropsychological evaluation, such as language, attention, EF, and memory. We aim to describe the state of the art, to identify potential limitations within the existing literature, and to suggest potential avenues to achieve a better understanding of the diagnostic and prognostic role of blood-based biomarkers in PSCI.

## LITERATURE SEARCH

For this narrative review, 2 complementary searches were conducted. The first was a broader exploration of stroke and PSCI, with particular emphasis on the cognitive domains most affected after stroke. The second search aimed to critically assess existing studies on biomarkers implicated in PSCI. A comprehensive search was then performed across 3 major databases, namely PubMed, Web of Science, and Google Scholar, using a combination of the following keywords: Stroke AND Cognitive Impairment AND Biomarkers. Additionally, Cognitive Decline AND Inflammatory Markers were included as alternative terms to ensure comprehensive coverage of the relevant literature. Titles and abstracts generated from the searches were checked for relevance, duplicates were deleted, and reference lists and article citations were manually reviewed to identify additional relevant articles.

From the articles selected in the second search, information about the study sample and its size, stroke location, the biomarkers assessed, the time after stroke at which blood or serum sampling was conducted, as well as the type and timing of neuropsychological assessment, was extracted. Then it was separately tabulated for memory, attention, and EF, as well as for language (Tables 2 and 3). Notably, the reviewed studies predominantly relied on the assessment of global cognitive status using domain-neutral tools, for example, the Montreal Cognitive Assessment (MoCA) and Mini-Mental State Examination (MMSE), whereby global cognition was also discussed separately (Table 1).[28,29] In the following, we discuss the available evidence for global cognition, memory, attention, EF, and language based on the reviewed articles. The authors declare that all supporting data are available within the article (and its Supplemental Materials).

## GLOBAL COGNITION

Evaluation of cognitive deterioration after stroke usually includes the administration of global cognitive screeners such as the MoCA or the MMSE, often along with other tests that address more specific domains (eg, language, attention, memory, and EF). Among the 22 studies reviewed here, 16 exclusively relied on such screening tests (Table 1). In most of these studies, both blood sampling and neuropsychological assessment were conducted uniquely in the acute and subacute stages, with no longitudinal assessment, thereby limiting their implications. Notably, in the case of acute neuropsychological evaluations, there are several non-PSCI related factors that can impact cognitive performance during hospitalization, such as fatigue, sleep disturbances, or emotional stress. So, although these studies have been included because of our interest in analyzing their methodology, their conclusions should be interpreted with caution. By critically assessing their design and limitations, we aim to highlight the importance of incorporating follow-up assessments and propose methodological improvements.

Increased levels of inflammatory biomarkers in the acute stage have been found to predict impaired global cognition in the subacute and chronic stages of recovery from stroke. Alexandrova and Danovska,[13] who used a longitudinal design, revealed that high levels of CRP (C-reactive protein), along with age, were significant predictors of cognitive decline: an increase in serum CRP by 1 mg/L resulted in 18.9% increase in odds of cognitive decline in the first year after stroke. Similarly, using binary logistic regression analyses, Irimie et al[18] found that CRP was associated with poor cognitive outcomes at discharge. Although their study tested a larger sample, cognitive status was assessed only during hospitalization, limiting any definitive conclusion. Consistently, in the study by Rothenburg,[21] serum CRP emerged as the only significant independent predictor of MMSE scores, accounting for 20.8% of the variance. In line with this, Zhu et al[26] also found that higher RF (rheumatoid factor), matrix metallopeptidase 9, and homocysteine were associated with PSCI 3 months following a cerebrovascular accident. Similarly, Zhu et al[25] observed a dose-response association between serum RF levels at baseline and 3-month cognitive impairment. Finally, Qian et al[20] observed that increased levels of endostatin were related to PSCI 3 months after stroke. Although neither study used a longitudinal design, they all collected biomarkers 24 hours after hospital admission and assessed cognitive performance in the subacute phase, making them methodologically robust.

**Table 1. Reviewed Studies That Assess the Relation Between Global Cognition and Stroke Biomarkers**

| Authors | Sample | Biomarkers | Time of blood sampling | Neuro-psychological assessment | Time of neuro-psychological assessment | Results |
|---|---|---|---|---|---|---|
| Alexandrova and Dan-ovska[13] | 47 patients with ischemic stroke (21 LH, 21 RH, and 5 stem) | Serum: CRP | At hospital admission, 3 MPS, 6 MPS and 12 MPS | MMSE | At discharge, 3 MPS, 6 MPS, and 12 MPS | High levels of CRP on admission were associated with poststroke mild to moderate cognitive impairment |
| Baccaro et al[14] | 103 patients with stroke (ischemic, hemorrhagic, and first-ever episodes). Stroke type: LH, RH, and bilateral | Blood: serotonin, BDNF, IL-6, IL-18 | 1–3 MPS | MMSE, MoCA, and TICS-M | 1–3 MPS. TICS-M repeated at follow-up (6 MPS) | No significant association between biomarkers and cognitive impairment |
| Chen et al[15] | 30 patients with acute stroke and 30 volunteers | Serum: $A\beta_{1\text{-}40}$, cAMP and BDNF | Before and after hospital admission | MMSE and MoCA | Before and after treatment | $A\beta_{1\text{-}40}$ positively correlated with cognitive impairment. Lower levels of BDNF were related to lower MMSE scores. |
| Gold et al[16] | 41 patients with ischemic stroke | Plasma: tryptophan and kynurenine concentrations | 1 MPS | MMSE | 1 MPS | Positive association between elevated K/T ratios and the extent of cognitive impairment |
| Hassan and Yarube[17] | 47 patients with stroke (subtype not specified) and 35 healthy controls | Serum: BDNF | Within the first year after the stroke | MMSE | Within the first year after the stroke | A moderate positive relationship between cognitive performance on MMSE and serum BDNF levels among stroke survivors |
| Irimie et al[18] | 120 patients with acute ischemic stroke | Serum: thyroid-stimulating hormone, CRP, and T3 | <24 h PS | MMSE | At discharge | Poor cognitive prognosis associated with high CRP levels but not with T3 concentrations |
| Kulesh et al[1] | 92 patients with acute ischemic stroke and 14 healthy subjects. | Serum and CSF: IL-1β, IL-6, IL-10, and TNF-α | Between day 4 and 21 PS | MMSE, MoCA, 5 word test | Between the seventh and the 14th days PS | IL-1β, associated with MMSE score. IL-10 expression is associated with global cognition (MMSE and MoCA) IL-6 associated with global cognitive status (MMSE) |
| Liu et al[19] | 193 patients with acute ischemic stroke | Serum: malondialdehyde and 8-Hydroxydeoxyguanosine | 24 h after hospital admission | MMSE | 1 MPS | Compared with the non-PSCI group, markedly increased serum levels of malondialdehyde and 8-hydroxydeoxyguanosine were observed in patients with PSCI |
| Qian et al[20] | 613 patients with ischemic stroke | Plasma: endostatin | 24 h after hospital admission | MoCA | 3 MPS | Increased endostatin levels linearly associated with increased risk of PSCI |
| Rothenburg et al[21] | 48 patients with ischemic stroke (58.3% RH) | Serum: CRP, IL-6, and interferon γ | 5 d–1 mo poststroke | MMSE | 5 d–1 mo post-stroke | IL-6 and CRP negatively correlated with MMSE scores, whereas interferon γ was not |
| Simani et al[22] | 76 patients with acute ischemic stroke and 34 healthy individuals | Serum: coenzyme Q10, malondialdehyde and antioxidant enzyme super-oxide dismutase | 24 h after stroke onset | MMSE | Not specified | Stroke patients showed significantly lower serum levels of coenzyme Q10 and higher levels of malondialdehyde than controls |
| Wang et al[23] | 304 patients with ischemic stroke | Serum: Nfl | 1 MPS | TICS and CDR | 1 MPS and 1 y later | Nfl concentrations at baseline were significantly higher in those with greater PSCI |
| Wang et al[24] | 1694 with first-ever acute ischemic stroke of anterior circulation | Plasma: Nfl | 48 h after stroke onset | MoCA | 3 MPS | Nfl negatively correlated with MoCA |
| Zhu et al[25] | 582 patients with ischemic stroke | Serum: RF | 24 h after hospital admission | MMSE and MoCA | 3 MPS | Patients with higher RF levels had the highest incidence of cognitive impairment |

(*Continued*)

**Table 1. Continued**

| Authors | Sample | Biomarkers | Time of blood sampling | Neuro-psychological assessment | Time of neuro-psychological assessment | Results |
|---|---|---|---|---|---|---|
| Zhu et al[26] | 638 patients with ischemic stroke | Serum: CRP, lipoprotein-associated phospholipase A2, matrix metallopeptidase 9, hepatocyte growth factor, antiphosphatidylserine antibodies, anticardiolipin antibodies, beta (2)-glycoprotein I-dependent anticardiolopin antibodies, N-terminal pro-brain natriuretic peptide, RF, Homocysteine, serum creatinine, and serum uric acid | 24 h after hospital admission | MMSE and MoCA | 3 MPS | RF, matrix metallopeptidase 9, and homocysteine are associated with PSCI |
| Zhu et al[27] | 256 first ever patients with ischemic stroke and 100 healthy controls | Plasma: trimethylamine N-oxide | 24 h after hospital admission | MMSE | 1 y after stroke | Higher trimethylamine N-oxide levels were indicators of cognitive decline |

BDNF indicates brain-derived neurotrophic factor; CRP, C-reactive protein; IL, interleukin; LH, Left hemisphere; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; MPS, months poststroke; Nfl, neurofilament light chain; PS, poststroke; PSCI, poststroke cognitive impairment; RF, rheumatoid factor; RH, right hemisphere; and TNF-α, tumor necrosis factor α.

Oxidative stress has also been characterized as a pathological mechanism involved in cerebral ischemia. In this regard, Liu et al[19] found that malondialdehyde and 8-hydroxydeoxyguanosine have good prognostic accuracy for PSCI 1 month poststroke. Their results showed that greater amounts of both serum biomarkers were correlated with decreased cognitive performance in the MMSE. One year later, these findings were replicated by Simani et al.[22] Their study included a smaller sample compared with the previous one, but incorporated a control group. However, a notable limitation is the lack of reporting on the timing of cognitive assessment. In the same line, Zhu et al[27] reported higher levels of trimethylamine N-oxide to be associated with PSCI 1 year after stroke.

Findings regarding the role of other oxidative stress biomarkers, such as IL-6 (interleukin-6), diverge across studies. Although Baccaro et al[14] reported no significant association between IL-6 and cognitive impairment 1 to 3 months after stroke, Kulesh et al[1] and Rothenburg et al[21] showed significant correlations between higher levels of IL-6 and worse cognitive performance in the subacute stage after stroke. The discrepancy within these studies suggests that the timing of biomarker measurements can be highly relevant for detecting potential associations between IL-6 and cognitive impairment.

Biomarkers associated with neuronal damage have also been associated with impaired global cognition. Nfl (neurofilament light chain), whose elevated concentration in plasma can be detected 48 hours after stroke, correlated with poorer scores on the MoCA 3 months after a cerebrovascular event.[24] Similarly, Wang et al[23] found that circulating Nfl above 79.31 pg/mL could distinguish patients with longitudinal cognitive decline from those with normal cognition after stroke. Chen et al[15] and Hassan and Yarube[17] focused on BDNF (brain-derived neurotrophic factor). This biomarker plays a critical role in mediating the synaptic transmission and plasticity underlying learning and memory, and its expression in the brain appears to be reduced after stroke.[30] Interestingly, although Chen et al[15] found higher levels of BDNF to be associated with cognitive impairment, Hassan and Yarube[17] reported the opposite. The observed discrepancy may, in part, be due to the timing of blood sample collection, as later sampling could have affected biomarker concentration in Hassan and Yarube.[17]

Overall, the studies reported in Table 1 show that abnormal levels of diverse biomarkers, such as CRP, Nfl, or RF among others, can be used as predictors of global cognition at different times poststroke, from the acute (ie, during the first week) to the subacute (between 1 and 6 months) and chronic stage (>6 months).

## MEMORY, ATTENTION, AND EF

Of the 22 studies reviewed here, 7 focused on more specific cognitive domains, such as memory (short-term memory and working memory), attention, or EF (Tables 2 and 3). Short-term memory refers to the ability to temporarily maintain and retrieve information, normally in serial order. Conversely, working memory is a more complex cognitive construct that goes beyond the temporary maintenance of information, supporting its mental manipulation, including shifting attentional control between tasks, updating and monitoring working memory representations, inhibiting dominant or automatic responses, and

**Table 2. Reviewed Studies That Included Tests Assessing Attention, EF, and Memory Functions**

| Authors | Sample | Biomarkers | Time of blood sampling | Behavioral assessment | Time of neuro-psychological assessment | Results |
|---|---|---|---|---|---|---|
| Cogo et al[31]* | 23 patients with ischemic stroke | Blood: tryptophan-derived kynurenine | Acute phase of stroke | Attention and EF: frontal assessment battery, trail making test A/B, Rey figure, Stroop Victoria | 3 MPS | Patients with poststroke with cognitive decline present higher levels of serum kynurenin, indolamine-2,3-dioxygenase activity, quinolinic acid concentrations and quinolinic acid/kynurenic acid ratio |
| El Husseini et al[32] | 24 patients with small vessel ischemic stroke | Serum: IFN-γ, vascular cell adhesion molecule 1, IL-1, IL-6, IL-8, IL-10, thrombin-antithrombin | On the day of cognitive testing | Memory: Hopkins verbal learning test II and brief visuo-spatial memory test-revised<br>Attention and EF: Digit-symbol substitution, symbol search, stroop test, trail making test B | >6 WPS (8 patients examined within 6 MPS) | Negative correlation between vascular cell adhesion molecule 1 and performance in memory tests |
| Hagberg et al[33]* | 164 patients with first-ever ischemic stroke, 28 with transient ischemic attack and 16 with hemorrhagic stroke (a total of 208 patients) | CSF: $A\beta_{42}$, T-tau and P-tau | 1- and 7-y poststroke | Memory: Word memory test<br>Attention and EF: Clock drawing test, trail making test part A and B | 1- and 7-y poststroke | No relation between amyloid positivity and worse cognitive performance was found |
| Ihle-Hansen et al[34]* | 210 patients with first-ever ischemic stroke or transient ischemic attack | CSF: T-tau | 1 y poststroke | Memory: Word memory test<br>Attention and EF: Clock drawing test, TMT A and B | 1 WPS and 1 y poststroke | Relationship between change in cognitive variables from baseline to 1 y follow-up and CSF T-tau was not examined |
| Kulesh et al[1]* | 92 patients with acute ischemic stroke and 14 healthy subjects | Serum and CSF: IL-1β, IL-6, IL-10 and TNF-α | Between day 4 and 21 PS | Attention and EF: FAB, clock drawing test, and Schulte test | Between the seventh and the 14th days PS | Patients in the dysexecutive group had high levels of IL-1β and IL-10 in cerebro-spinal fluid and IL-6 in serum compared with the no cognitive decline group. No significant difference was observed in cytokine levels between dysexecutive patients and mixed cognitive impairment groups |
| Narasimhalu et al[35] | 243 patients with ischemic stroke | Serum: CRP, IL-1β, IL-6, IL-8, IL-12, IL-10 or TNF-α | At a median of 47 d after the index stroke | Memory: Word list recall, story recall, picture recall, and WMS-R visual reproduction<br>Attention and EF: Digit span,† visual span,† auditory detection, symbol digit modality test, digit cancellation, maze task, clock drawing test | 3–4 MPS and followed annually for 5 y | Higher levels of IL-8 were associated with baseline PSCI. IL-12 predicted subsequent cognitive decline |
| Qian et al[36]* | 152 patients with first-ever acute ischemic stroke<br>40 healthy control subjects | Serum: Beta-secretase 1, soluble receptor for advanced glycation end-products,, and NEP | 1 h after admission (6–72 h after the onset of symptoms) | Memory: Word memory test<br>Attention and EF: Clock drawing test, digit-symbol coding (WAIS), and EDI | 2WPS | Soluble receptor for advanced glycation end-products was significantly decreased in the vascular cognitive impairment with no dementia group and mixed dementia group compared with the no cognitive deficit group. Beta-secretase 1 was increased in the vascular no dementia group. NEP increased in the vascular dementia group |

CSF indicates cerebrospinal fluid; EF, executive functions; IL, left ventricle, MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; MPS, months poststroke; NEP, neprilysin; PS, poststroke; PSCI, poststroke cognitive impairment; TNF-α, tumor necrosis factor α; and WPS, weeks poststroke.

*These studies also include global screening tests such as the MoCA or the MMSE.

†These tests are indicated here as measures for attention following the article classification, even though in other studies these instruments are used as measures of memory.





suppressing different types of interference.[37,38] Finally, attention refers to a series of mechanisms aimed at selecting relevant stimuli to achieve specific objectives. It is responsible for conscious cognitive processing as well as for filtering environmental information.[39] Attention is part of the broader category of top-down mental

**Table 3. Reviewed Studies That Assess Language Performance**

| Authors | Sample | Biomarkers | Time of blood sampling | Neuro-psychological assessment | Time of neuro-psychological assessment | Results |
|---|---|---|---|---|---|---|
| Hagberg et al[33] | 164 patients with first-ever ischemic stroke, 28 with transient ischemic attack and 16 with hemorrhagic stroke (a total of 208 patients) | CSF: $A\beta_{42}$, T-tau and P-tau | 1- and 7-years poststroke | COWAT | 1–7 y PS | No information about language performance after stroke and biomarkers was presented |
| Kulesh et al[1] | 92 patients with acute ischemic stroke and 14 healthy subjects | Serum and CSF: IL-1β, IL-6, IL-10, and TNF-α | Between day 4 and 21 PS | Semantic verbal fluency test | Between the seventh and the 14th days PS | No information about language performance and biomarkers concentration was reported. |
| Narasimhalu et al[35] | 243 patients with ischemic stroke | Serum: CRP, IL-1β, IL-6, IL-8, IL-12, IL-10, or TNF-α | At a median of 47 d after stroke | Modified Boston naming category fluency (animals and food subtasks) | 3–4 MPS and followed annually for 5 y | No information about the relation between language impairment and biomarkers was reported. |

COWAT indicates Controlled Oral Word Association Test; CRP, C-reactive protein; CSF, cerebrospinal fluid; IL, interleukin; MPS, months poststroke; PS, poststroke; and TNF-α, tumor necrosis factor α.

processes known as executive functions,[40] an umbrella term that encompasses a set of higher-order cognitive abilities essential for effective goal-directed actions and for the regulation of attentional resources.[41]

Qian et al[36] investigated whether levels of soluble receptor for advanced glycation end products correlated with composite scores derived from the administration of verbal memory, visuo-spatial, and sustained attention tests in patients with subacute-stage ischemic. They classified patients into vascular dementia, vascular cognitive impairment with no dementia, and no-cognitive impairment groups based on their performance in neuropsychological assessment. Results showed that 2 weeks after stroke, significantly lower levels of soluble receptor for advanced glycation end products were found in patients affected by vascular dementia compared with those with no cognitive deficit. Moreover, higher levels of beta-secretase 1 and neprilysin enzymes were observed in the vascular dementia group compared with patients with no cognitive deficits. The latter finding contradicts previous studies that report lower levels of neprilysin in patients with dementia,[42] which is expected considering that neprilysin is an amyloid-β degrading enzyme.[43] A later follow-up would have strengthened these conclusions.

Aβ-42 (amyloid-β peptide) and the microtubule-associated tau protein are established biomarkers of neurodegeneration in Alzheimer disease,[44] a disease in which memory is the most prominently affected domain. However, findings from studies testing PSCI report mixed evidence on the relationship between these biomarkers of neurodegeneration and cognitive impairment. Ihle-Hansen et al[34] reported a significant positive correlation between increased τ protein deposition and brain atrophy after 1 year. However, the relationship between change in cognitive variables from baseline to 1-year follow-up and cerebrospinal fluid T-tau was not examined. More recently, Hagberg et al[33] reported that amyloid binding was uncommon in 7-year poststroke survivors diagnosed with cognitive impairment, thus indicating amyloid pathology is not a mediator of neurodegeneration and memory impairment 7 years poststroke. This finding contradicts Chen et al,[15] who despite using only global screening tools to measure cognition, did find that $A\beta_{1\text{-}40}$ positively correlated with cognitive impairment. However, it should be noted that in Hagberg et al,[33] delayed measurement of biomarker concentration and the inclusion of patients suffering from transient ischemic attack could explain the lack of significant correlations, since these patients, by definition, do not develop PSCI.[45] Moreover, the conclusions drawn by Chen et al[15] should also be interpreted with caution, as cognitive variables were assessed exclusively during the acute phase.

El Husseini et al[32] tested memory functions in relation to biomarkers of blood and vascular function, such as vascular cell adhesion molecule 1, in a small group of patients who suffered from small-vessel ischemic stroke. The results showed that high concentrations of this protein correlated with poor performance in verbal learning and visuo-spatial memory tests, independent of patients' age and education levels. However, as suggested by the authors, these results should be validated with a larger sample and include other types of strokes, as well as, nonstroke patients with memory impairment.

As for attention and EF, Kulesh et al[1] reported high interleukin levels (eg, IL-1β, IL-6, IL-10, IL-12) in patients with stroke with dysexecutive syndromes in the acute stage poststroke. Although these results may not be fully representative due to cognitive assessment being limited to the acute stage, during the subacute stage Narasimhalu et al[35] also showed dissociation between IL-8, associated with baseline impairment, and IL-12, which was found to be a strong predictor of performance at 5-year follow-up tests. Critically, these results are at odds with findings from El Husseini et al,[32] who did not

report any significant relationship between interleukins and EF in the subacute stage poststroke (and also with Baccaro et al,[14] who did not find any significant relation between interleukins and global cognition; Table 1). Notably, neither Kulesh et al,[1] nor Narasimhalu et al[35] reported significant correlations between TNF-α (tumor necrosis factor α) and cognitive performance following stroke. As a possible explanation, neither study obtained blood samples in the first 48 hours after stroke, thus leading to a probable bias of nonrepresentative level of biomarkers in patients' blood. Moreover, it has been suggested that IL-6 can exert a suppressive effect on TNF-α production.[46]

Finally, the tryptophan metabolic pathway, including kynurenin, kynurenic acid, and 3-hydroxynurenin, has also been proposed as a predictor for the underlying pathophysiology of inattention and EF impairment. Cogo et al[31] found evidence suggesting that initial serum kynurenin and quinolinic acid levels, quinolinic acid/kynurenic acid ratio, and indolamine-2,3-dioxygenase activity are significantly higher in patients showing impairment in a series of attention and EF tests compared with unimpaired patients. Similarly, Gold et al[16] demonstrated a significant association between elevated kynurenin/tryptophan ratios and the extent of cognitive impairment among patients with acute ischemic stroke (Table 1).

Taken together, the studies reviewed in this section suggest that increased biomarkers of inflammation and neurodegeneration can be associated with poor memory, EF, and attention performance. However, these results should be taken with caution due to small sample sizes, the lack of biomarker measurement during the acute phase after stroke, and the absence of a longitudinal follow-up in most of the presented studies.

## LANGUAGE

According to Pal et al,[47] language is the most affected cognitive domain after stroke. Approximately 40% of left-hemispheric stroke survivors are diagnosed with poststroke aphasia. This condition can impact diverse language functions, including spontaneous speech, repetition, naming, auditory comprehension, reading, and writing[48] and can remain chronic in almost 50% of the cases.[49] Besides affecting patients' autonomy and quality of life, poststroke aphasia has also been related to higher mortality.[50]

To date, the relationship between poststroke language abilities and biomarker concentrations has received very scarce attention. As illustrated in Table 3, only 3 studies (Kulesh et al[1]; Narasimhalu et al[35]; Hagberg et al[33]) report the use of tasks that assess language functions (eg, verbal fluency and naming). In the remaining studies that we reviewed, language assessment was included either in comprehensive cognitive assessment batteries (eg, WAIS) or comprised within the limited scope of global cognitive screeners like the MMSE and MoCA. Moreover, aphasia was often listed as an exclusion criterion in these studies (eg, Baccaro et al[14]; Gold et al[16]; Wang et al[23]; see review in Kosgallana et al[7]), due to the difficult administration of cognitive tests to patients with language impairment.

Unlike PSCI, the link between surrogate biomarkers and language functions has been widely investigated in primary progressive aphasia, a neurodegenerative condition that is characterized by isolated language impairment during the first stages of disease progression. This clinical syndrome has heterogeneous neuropathological causes, falling within both the frontotemporal dementia spectrum and Alzheimer disease pathology.[51] Molecular biomarkers, such as plasma t-tau,[52,53] the RNA-binding protein TDP-43,[54] glial fibrillary acidic protein, or plasma Nfl, have been suggested as potential predictors for primary progressive aphasia onset and progression.[55]

In the studies analyzed in this article (Table 3), although specific tests were used to assess the language domain, none reported data on language performance in relation to biomarker concentration. Instead, language scores were incorporated into overall cognitive performance together with other assessments, and only global scores were considered for analysis.

## CONCLUSIONS

Clinical research on stroke is currently focused on oxidative stress pathways, including vascular inflammation, neurodegeneration, and blood-brain barrier dysfunction.[19] This review summarizes current evidence regarding the relationship between biomarkers and cognitive decline after stroke, focusing on 5 domains that are the object of poststroke neuropsychological assessment, namely global cognition, language, memory, attention, and EF (Figure). Two main conclusions can be drawn from the present review.

First, existing evidence suggests that the disruptive functioning of some biomarkers may mediate PSCI. This is indicative that dysregulation of neuronal function, inflammatory processes, or blood-brain barrier dysfunction after stroke (which enables the release of biomarkers from the brain to the vascular system) may determine increased concentrations of biomarkers and subsequent cognitive decline, as evidenced by significant negative correlations with impaired global cognition. The main conclusions of this review suggest that elevated levels of Nfl[23,24] and CRP[13,18,21] may be associated with PSCI, as these biomarkers demonstrate the greatest consistency across different studies. Although some studies have also proposed a link between interleukins and poststroke cognitive decline, findings remain inconsistent. Similarly, increased levels of kynurenine, tryptophan,[16,31] MDA,[19,22] endostatin,[20] or RF,[25,26] among others appear to be implicated in PSCI. However,

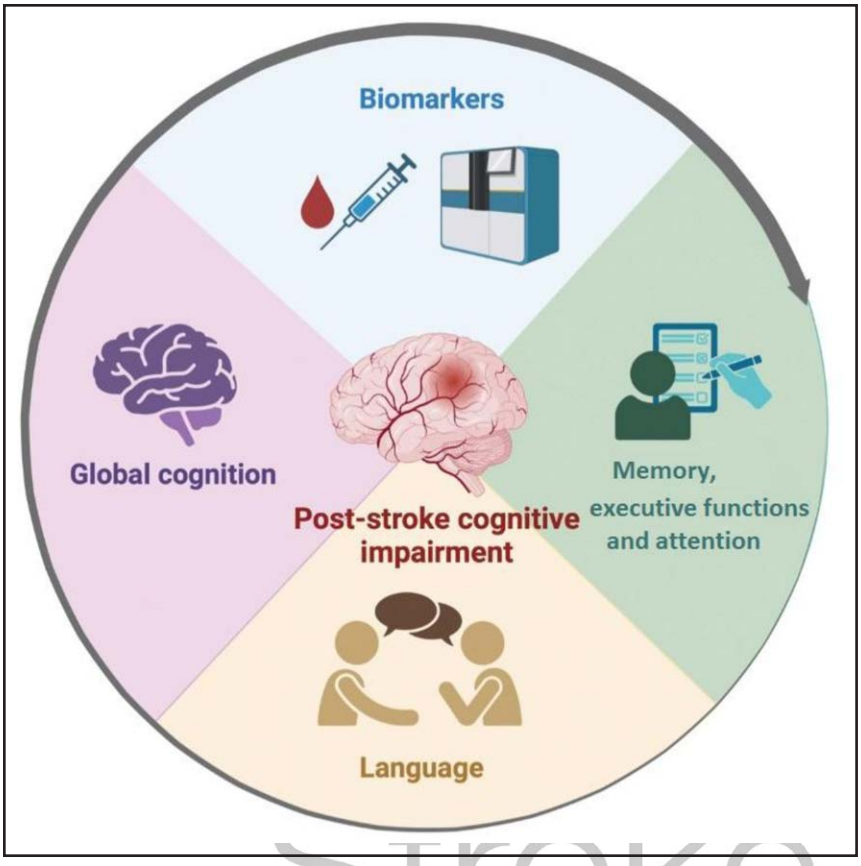


**Figure. Multifactorial dimension of poststroke cognitive impairment.**





further external validation is needed to support the utility of these key biomarkers for both general cognition and specific domains, given the small number of investigations and the methodological limitations that characterize existing studies, which will be discussed below.

A notable limitation of the prior research is the varied sample sizes across different studies, which range from as few as 23 up to 1964 participants. Moreover, low statistical power in smaller-sample studies may contribute to both the lack and presence of significant correlations. Another limitation is the lack of representativeness among the stroke populations tested. This weakness is common in studies conducted within a single laboratory, making it difficult to generalize the results to different populations. Consistently, many of the analyzed studies included patients with transient ischemic attack, whose association with cognitive function and inflammatory markers may differ,[35] as well as patients with hemorrhagic stroke. Furthermore, the inclusion of individuals with a history of previous stroke represents a significant limitation, as it precludes determining whether cognitive impairment is attributable to the current stroke event. Additionally, most reviewed studies excluded aphasic patients from their samples, thus losing information about language disabilities in PSCI and their relation to biomarkers. It is worth noting that collecting data through international consortia can address both issues of sample size and representativeness.

The type of design adopted is also greatly relevant as only 6 studies included in this review measured biomarkers and conducted neuropsychological assessments at multiple time points, so that temporal evolution could be tracked.[13,14,23,33–35] Likewise, the conclusions drawn from studies that assessed cognition only in the acute phase[1,15,18,36] after stroke should be validated through longitudinal studies, as cognitive performance in the acute phase may be influenced by external factors, such as hospitalization itself. This oversight crucially limits our understanding of the prognostic value of molecular biomarkers in poststroke recovery. Moreover, the time point at which blood samples were obtained is also of critical importance. In fact, differences across studies can be mostly explained by the time after an acute event in which biomarkers are collected. Longer postevent windows of time exhibited lower levels of biomarkers, as the concentration of biomarkers decreases progressively after the vascular event.

Second, this review reveals the absence of studies that include (basic) language among the cognitive domains tested, despite being one of the most affected domains after stroke. Although molecular biomarkers are unlikely to predict dissociations in language and cognitive impairment, an exhaustive neuropsychological examination that explores all domains is important for identifying altered functions and plan rehabilitation programs more rigorously. There is accumulating evidence

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concerning the limited sensitivity of the MoCA and MMSE to detect PSCI and many have noted that these tools have no unanimous cut-off scores for stroke.[7,56,57] This obfuscates the reliability of the impairment (or lack thereof) detected by these 2 domain-neutral tools. PSCI is a complex condition, and patients with stroke differ in their degree of impairment across cognitive domains. Multiple cognitive functions should, therefore, be assessed separately, especially if the goal is to identify prognostic biomarkers for the design of more efficient intervention programs.

To conclude, PSCI is a complex condition that affects a vast portion of stroke survivors, often with devastating impact on their lives. The detection of biomarkers associated with this condition may provide new avenues in their clinical management.

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### Disclosures

None.

### Supplemental Material

Biomarkers and Their Function.

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