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Systematic Review

hsCRP level and cognitive function in ischemic stroke patients: systematic review

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ABSTRACT

Increased level of High sensitivity C-reactive protein (hsCRP) is associated with poor ischemic stroke functional outcomes according to several previous studies. However, there are no studies that specifically evaluate cognitive function. This systematic study aims to perform a narrative analysis of hsCRP levels with cognitive function in ischemic stroke patients. A systematic search of research articles was carried out on electronic databases using the PRISMA guidelines and on the bibliography on the references of the relevant articles. The electronic databases used are PubMed/Medline, Cochrane, Wiley Online Library, Scopus, Science Direct, and Google Scholar. The included study designs were cross-sectional, case-control, and prospective cohort studies. The risk of bias was analyzed by using ROBINS-1 and the quality of research by using GRADE. From eight studies, there were four studies that in addition to examining hsCRP also examined other inflammatory markers i.e.; fibrinogen (1 study) and homocysteine (3 studies). The risk of bias assessment tool for ROBINS-I indicated a high risk of outcome assessment blinding for eight studies. The quality of studies was assessed by GRADE showed low quality. Results indicated an association between elevated hsCRP and poor cognitive outcome in ischemic stroke patients. The hsCRP examination can be considered in ischemic stroke patients to predict cognitive function. However, as a routine examination, further studies are still needed.

Keywords: Cognitive function, hsCRP, Ischemic stroke

INTRODUCTION

Acute and chronic inflammation are both linked to ischemic stroke. Approximately 15-30% of post-stroke patients have permanent disabilities, and 25-30% of ischemic stroke patients have immediate or delayed cognitive impairment.[1,2] In population-based studies, elevated C-reactive protein (CRP), a plasma protein synthesized in the liver that has been widely used as a non-specific inflammatory marker, has been linked to cognitive impairment and dementia. High sensitivity C-reactive protein is a test that detects CRP with a sensitivity range of 0.01 to 10 mg/l using high sensitivity methods such as immunonephelometry, immunoturbidimetry, high-sensitivity Enzyme-linked immunosorbent assay (ELISA), and Resonant acoustic profiling (RAP). Increased High sensitivity C-reactive protein (hsCRP) levels during the acute phase of stroke have been linked to poor outcomes.[3,4] An early study by Alexandrova et al showed hsCRP may be a predictor of cognitive impairment in ischemic stroke after one year.[5] Rothenburg et al showed that CRP was demonstrated to be more significant than Interleukin (IL)-6 in predicting cognitive impairment in ischemic stroke patients.[6] Meanwhile, a study conducted by Kliper et al which aimed to correlate Erythrocyte sedimentation rate (ESR) and CRP levels with hippocampal volume in stroke patients found a correlation between ESR levels with hippocampal volume but not with CRP.[7] Narasimhalu et al compared the incidence of post-stroke cognitive impairment to several inflammatory markers (IL-6, IL-8, IL-12, and CRP). The finding revealed an independent relationship between IL-8 and the presence of cognitive impairment, followed by IL-12, while CRP and IL-6 seemed to have no direct relationship with the incidence of cognitive impairment.[8] The findings of these various

studies have attracted the interest of the authors in investigating the role of hsCRP and cognitive function in ischemic stroke. Several studies have found an increase in hsCRP levels in patients with cognitive decline, but the results are still inconclusive. The aim of the study was an attempt to qualitatively extrapolate data from earlier studies that evaluated hsCRP and cognitive function in ischemic stroke patients to general population.

METHODS

his systematic review evaluated with the guidelines of Preferred reporting items for systematic reviews and meta-analysis (PRISMA).[9] Study articles in Indonesia and English were collected by searching through databases PubMed/Medline, Cochrane, Wiley Online Library, Scopus, Science Direct, and Google Scholar from 01 January 2010 until 30 April 2020. The search strategy included combination key terms: 'C-reactive protein' or 'high-sensitivity CRP' or highly sensitive CRP or 'hsCRP' or 'protein reaktif C' or 'protein reaktif C sensitivitas tinggi'and 'stroke' or 'ischaemic stroke' or 'cerebrovascular disease' or 'penyakit serebrovaskular' or 'stroke iskemik' and 'prospective', 'observational' or 'follow-up'.Studies were considered eligible for inclusion if they fulfilled the following criteria: (1) cross sectional, case-control, and cohort prospective design studies that evaluated hsCRP level in stroke ischemic patients; (2) participants not younger than 18 years old with no history cognitive impairment and acute infection such as urinary tract infection and pneumonia; (3) high-sensitivity CRP measurement, if other inflammatory markers are present, they are compared; (4) cognitive outcome measured by validated tools. We excluded grey literatures to avoid non-peer-reviewed articles. Participants who enrolled in two studies were also excluded. Each study's effect on cognitive impairment as an outcome was examined using subgroup analysis. The potential bias was evaluated by referring to the Risk of Bias in Non-Randomized Studies of Interventions (ROBINS-1). The GRADEpro application is used to assess the quality of each study using the Grading recommendation assesement, development and evaluation (GRADE) criteria.

RESULTS

The initial search yielded a total of 10.590 publications. The final included studies for narrative synthesis, after screening and evaluating, were eight articles. The PRISMA diagram was used to guide the article selection process (Figure 1).

The hsCRP studies without other inflammatory marker

There were four studies that examined hsCRP without other inflammatory markers, with a total of 195 participants. Two studies were undertaken in Indonesia, one study in China, and one study in Bulgaria. The average sample size was 48,75 (18-110). The distribution of sample sizes was varied, as outlined in Table 1. The mean age of the study samples in Alexandrova and Danovska et al was 63 years, 59.94 years in Syafrita's et al study, and 60.7 years in Sumanti et al study.[5,10,11] Meanwhile, Li et al study did not mention the mean, although both the case and control samples were between the ages of 40 and 80.[12] One study used a prospective cohort design, two studies used cross-sectional designs, and one study used a case control design. Cognitive function was the outcome. These parameters were measured after one year (one study), three months (two studies), and seven days (one study) of onset. The Mini mental state examination (MMSE) (one study) and the Montreal cognitive assessment (MoCA) (three studies) were used to assess cognitive function.

The hsCRP studies with other inflammatory marker

We discovered four additional research articles that looked at inflammatory markers besides hsCRP. Four studies with 1,341 participants were identified. All the research was conducted in China. The average number of samples from the four studies was 335 (104-725) per study, although the distribution of the number of samples was not evenly distributed. The characteristic of the included studies are shown in Table 2. In the study by Liu et al the mean age of the stroke patient group with cognitive impairment was 64.6±9.9 years, the mean age of the stroke patient group without cognitive impairment was 58.7±10.1 years, and the mean age of the control group was 61.5±3.9 years.[13] The mean age of patients with cognitive impairment in An et al study was 66.1±6.2 years, while those without cognitive impairment were 57.1±8.8 years.[14] Yan et al study reported lower mean ages in both their study groups. The therapy group was 52.0±4.5 years and the control group was 53.0±5.2 years.[15] Participants in the study of Lu et al had a mean age of 63.1±11.9 years in the acute ischemic stroke group with normal non-HDL X levels and 62.2±10.8 years in the acute ischemic stroke group with high non-HDL C levels.[16] Of these four studies, three were prospective cohorts and one was a case control. MMSE (one study), MoCA (one study), and both MMSE and MoCA (two studies) were employed to assess cognitive function. Other inflammatory markers examined apart from hsCRP included homocysteine (three studies) and fibrinogen (one study). One study evaluated homocysteine and hsCRP levels in addition to an assessment of cognitive function after DI-3-n-butylphthalide administration. A compound extracted from celery seeds.[15]

Risk assessment of bias in the hsCRP study without other inflammatory markers

Overall, there is one study with unclear risk of bias, i.e.; Alexandrova et al.[5] Because of the high-risk blinding of outcome assessment bias (Figure 2), none of the studies showed a low risk of bias. For the selection of participants' bias, there are two that we value as moderate because the number of samples is small.[10] Because there was no data on the results of earlier cognitive function tests, three publications had moderate cofounding variables.[5] It was only listed whether there was a history of previous

cognitive impairment. Because there was no baseline data on cognitive function, one study was assessed to have high confounding variables.[12] The hsCRP measurement method used in four studies had high sensitivity, which resulted in low bias in the measurement of exposure. Most studies had complete output data except for Syafrita's et al study, which had dropouts.[10]

Table 1: Characteristics of hsCRP studies without other inflammatory markers.

S. no.	Authors	Country	Sample size	Location and timing hsCRP sampling	Design	Measurement of hsCRP	Cognitive assessment method	Cognitive assessment measure time
1	Alexandorova et al[5]	Bulgaria	47	1 hospital, within 48 hours of the onset of ischemic stroke	Prospective cohort	Turbidimetric	MMSE	12 months after stroke onset
2	Syafrita et al[10]	Indonesia	20	1 hospital, within 72 hours of the onset of ischemic stroke	Cross sectional	High-sensitive (hs) 8C-Reactive Protein COBAS (Latex)	MoCA INA	3 months after stroke onset
3	Sumanti et al[11]	Indonesia	18	1 hospital, within 72 hours of the onset of ischemic stroke	Cross sectional	hsCRP (not specific)	MoCA INA	7 days after stroke onset
4.	Li et al[12]	China	110	1 hospital, within 3 months of the onset of ischemic stroke	Case-control	Immuno-scatter turbidometry	MoCA	3 months after stroke onset

Note: hsCRP: High sensitivity C-reactive protein, MMSE: Mini-mental state examination, MoCA INA: Montreal cognitive assement indonesian version, MoCA: Montreal cognitive assement.

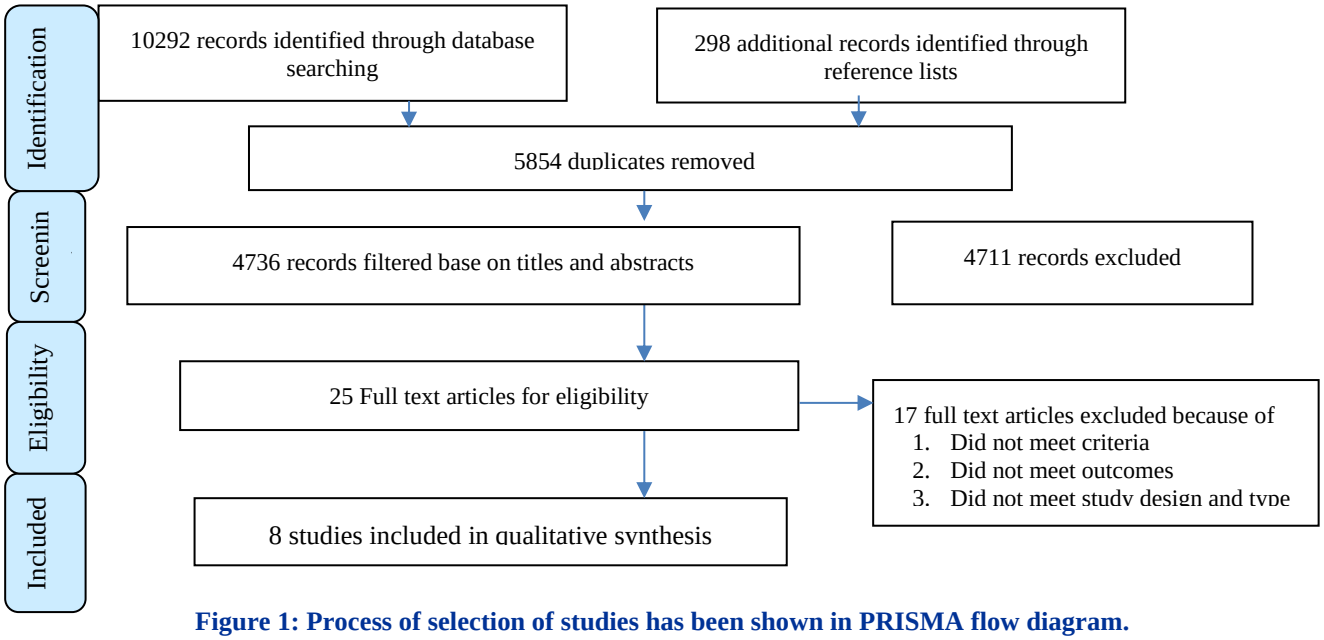

Figure 1: Process of selection of studies has been shown in PRISMA flow diagram.

Table 2: Characteristics of hsCRP studies with other inflammatory markers.

S. No.	Authors	Country	Sample size	Location and timing hsCRP sampling	Design	Measurement of hsCRP	Cognitive assessment method	Cognitive assessent measure time	Other inflammatory markers
1	Liu et al[13]	China	212	1 hospital, after 7 days of the onset of ischemic stroke	Prospective cohort	Not specified	MMSE	3 months after onset	Fibrinogen
2	An et al[14]	China	300	Neurology clinic, <48 hours after the onset of ischemic stroke	Prospective cohort	Not specified	MoCA	Day-2 and day-60 after onset	Homocysteine
3	Yan et al[15]	China	104	1 hospital, <24 hours after the onset of ischemic stroke	Prospective cohort	Immunoturbidimetry	MoCA-B and MMSE	At admission and 1 month after onset	Homocysteine
4.	Lu et al[16]	China	725	1 hospital, <1 week after the onset of ischemic stroke	Case control	BNP II protein analyzer	MMSE and MoCA,	3 days after onset	Homocysteine

Note: hsCRP: High sensitivity C-reactive protein, MMSE: Mini-mental state examination, MoCA INA: Montreal cognitive assement indonesian version, MoCA: Montreal cognitive assement.

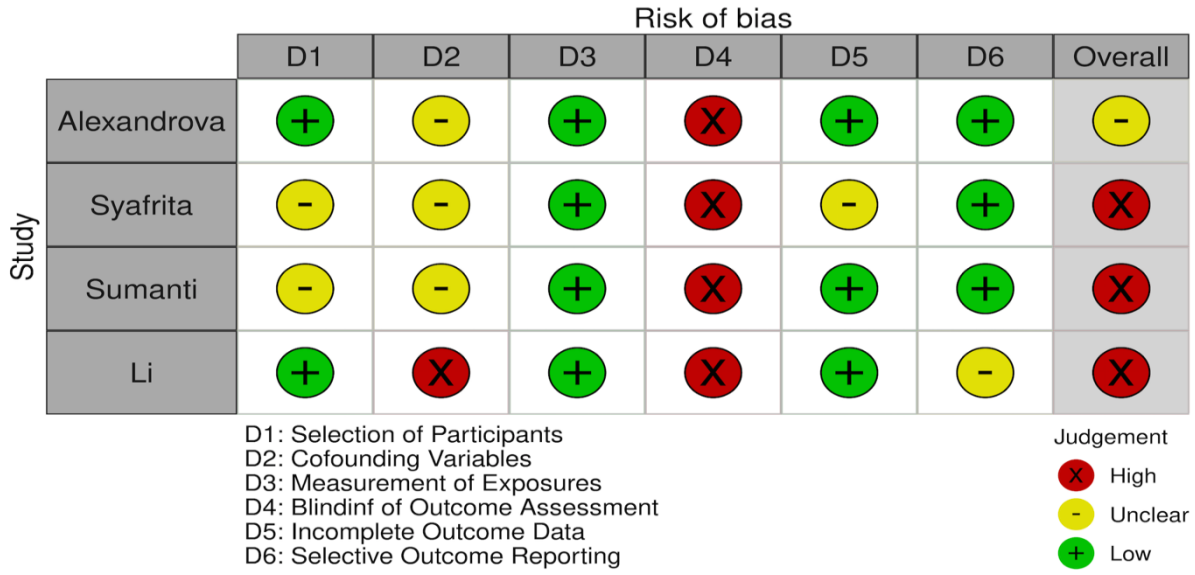

Figure 2: Risk of bias summary in the hsCRP studies without other inflammatory markers.

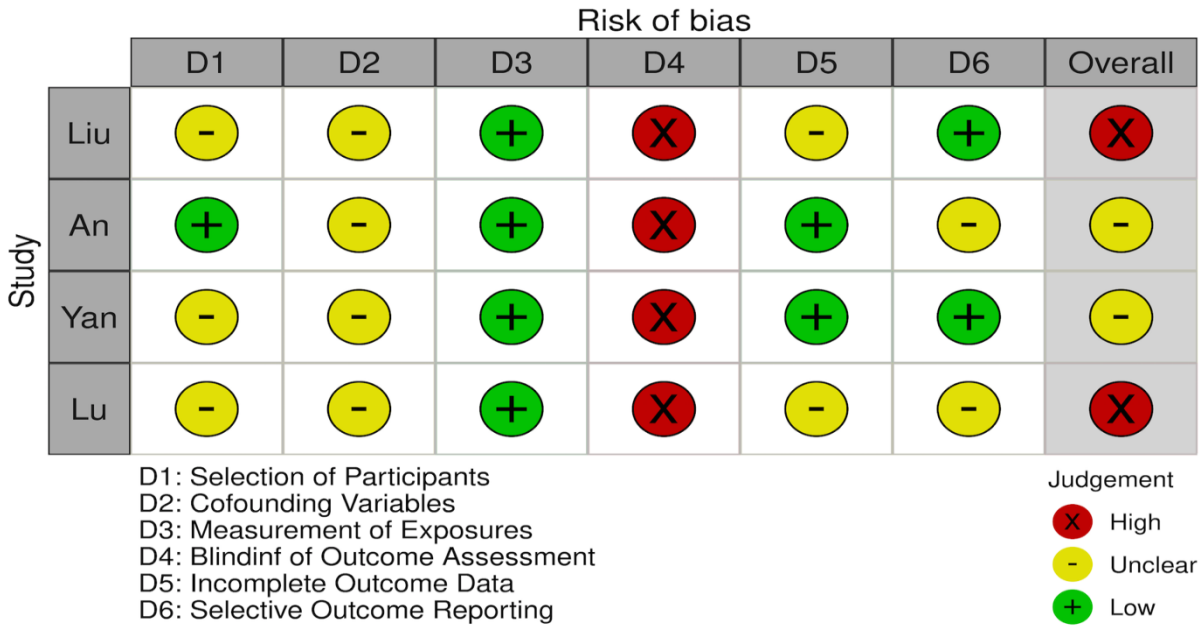

Figure 3: Risk of bias summary in the hsCRP studies with other inflammatory markers.

Risk assessment of bias in the hsCRP study with other inflammatory markers

There were two studies showing an unclear risk of bias and two studies with a high risk of bias in all six domains (Figure 3).[13,14,16] These four studies had a high blinding bias in the measurement of the outcome value because there was moderate blinding process.

The selection of the participants' bias domain in our three studies was moderate due to the unequal number of case and control samples, differences in baseline between cases and controls and possible recall bias due to retrospective studies.[13,15,16] Confounding variable bias was, assessed as moderate in all four studies because they did not have initial data on cognitive function. However, the exclusion criteria questioned a history of dementia or cognitive impairment prior to the stroke. Some studies had incomplete outcome data because patients dropped out during the study and the comparison of exposure values with the outcomes was not completed.[13,16] Because of possible reporting selection, two studies, have a moderate risk of bias in domain-selective outcome reporting.[13,14,16] We then conducted a narrative quality assessment of the studies with GRADEPro. The overall analysis of the hsCRP studies, with and without an inflammatory comparator, yielded low-quality results.

DISCUSSION

The focus of previous hsCRP meta-analyses and systematic reviews has mostly been on the risk of stroke and functional outcome. Unlike the other studies, ours aims to systematically examine the impact of cognitive function on the results of existing observational studies. Furthermore, this study performed a narrative analysis of several data points that were inconsistent with previous studies.

Our systematic review of eight observational studies, involving 1536 participants, found an association between hsCRP and cognitive function in ischemic stroke patients. Most of the included studies showed an association between hsCRP levels and cognitive function in ischemic stroke patients, especially when compared to controls. Post-stroke cognitive impairment itself is a major post-stroke complication. This condition encompasses a wide variety of conditions, ranging from mild cognitive impairment to stroke-related dementia.[17]

The relationship between inflammation, stroke, and cognitive function has recently received a lot of attention. The activation of resident microglia, as well as the uptake and infiltration of systemic inflammatory cells, is a distinguishing hallmark of the inflammatory response in the brain. This systemic inflammatory cell activation stimulates the production of proinflammatory factors, which further stimulates CRP synthesis in the liver.[18] This supports the association between serum hsCRP at initial admission and cognitive impairment in ischemic stroke in the five research articles that we included.

Three other studies, however, found statistically insignificant results for the association of cognitive impairment in ischemic stroke with other inflammatory markers, specifically homocysteine and fibrinogen ($p>0.05$). This may be because the studies of Lu et al and Liu et al included ischemic stroke patients until after seven

days after onset, while the study of Yan et al was conducted in the first 24 hours.[13,15,16] hsCRP measurements were taken between 24 and 72 hours after onset in four other studies.

The research of Winbeck et al and Song et al investigated the relationship between CRP levels and functional outcomes.[19] Increased hsCRP levels 24 to 48 hours and 7 days after the onset of stroke were related to a poor outcome.[19,20] In the Winbeck et al study, measuring CRP levels in the first twelve hours was not associated with stroke prognosis.[19] This could explain why Yan et al was not statistically significant.[15]

According to the findings of the studies by Lu et al and Liu et al inflammation is not the only pathway that causes cognitive impairment in stroke patients.[13,16] Differences in the findings of these studies can also be attributed to a variety of factors that influence CRP levels, including ethnicity, metabolism, and medical conditions. Furthermore, CRP levels can fluctuate significantly after a stroke.[3]

We conducted a systematic review of the use of hsCRP. This test measures CRP more precisely than conventional tests. The hsCRP assay can detect CRP levels as low as 0.1 mg/l, enabling the analysis of particular changes that may be clinically significant. In contrast to conventional CRP, the ability to detect CRP levels is around 3-6 mg/l.[21,22] Although there were five studies showing a significant correlation between elevated acute hsCRP levels and cognitive function, no hsCRP cut-off value predicted cognitive impairment.

The mechanism underlying the association between increased hsCRP levels and ischemic stroke is undetermined. Atherosclerosis is the most common cause of ischemic stroke, and inflammation is related to the degree of atherosclerosis and atheroma instability. Endothelial cell dysfunction and atherosclerosis progression are both linked to high levels of hsCRP. Moreover, key risk factors for stroke, such as smoking, diabetes, and hypertension, are linked to high hsCRP levels.[21] Previous studies have linked an increase in hsCRP to poor cognitive function outcomes in individuals with ischemic stroke, with an elevation in CRP per 1 mg/dl being correlated with poor functional outcomes.[21,23]

Homocysteine was another inflammatory marker studied with hsCRP in the studies of An et al, Yan et al, and Lu et al.[13-15] Ischemic stroke patients showed high homocysteine levels.[15] Homocysteine is also a predictor of cognitive impairment in Alzheimer's disease patients. Homocysteine levels are high, hastening the deterioration of cognitive function. High homocysteine levels can cause cognitive impairment by inducing atherosclerosis and increasing the formation of hydrogen peroxide and oxygen free radicals, which harm endothelial cells and neurons while also impairing the DNA repair capacity of cells.[15,24] Oxidative processes can both promote and result in an increase in homocysteine.[25] Homocysteine can also lead in endothelial dysfunction.[17] As a result, homocysteine can be used to predict cognitive impairment in ischemic stroke patients.[15]

Liu et al investigated fibrinogen in addition to hsCRP.[13] Fibrinogen enters the blood vessels and accumulates in the central nervous system when the blood-brain barrier is disrupted in an ischemic stroke.[13] Fibrinogen will bind to the protein amyloid beta 42 (Aβ42), activate microglia, and eventually cause central nervous system neurodegeneration. It is thought that the binding of Aβ42 to fibrinogen causes a more severe decline in cognitive function.[13,26,27]

The overall outcomes of the bias evaluation in the study that we evaluated in this systematic review were 'unclear' and 'high'. The bias is influenced by the small number of samples and the high drop-out rate. The outcomes of narrative research quality measurement with GRADEPro in hsCRP investigations, either without or with other inflammatory markers, are low. The lack of blinding in the reviewed studies, as well as the enormous number of confounding variables that affect hsCRP levels and cognitive function, are some of the explanations.

This systematic review conducted a literature search on six databases, namely PubMed/Medline, Cochrane, Wiley Online Library, Scopus, Science Direct, and Google Scholar. According to our findings, hsCRP levels have the potential to be used as a benchmark for risk stratification of cognitive impairment in patients with ischemic stroke. However, a number of limitations must be acknowledged. First, this systematic review may have publication bias because a literature search did not identify all relevant studies based on the inclusion and exclusion criteria. Access to unpublished literature remains difficult, which is a limitation of studies in general. Second, according to the GRADEPro results, several of the papers we chose were of low quality, and the sample size was modest. Third, the heterogeneity between studies was quite high. Sampling time, hsCRP measurement method, hsCRP cut-off, follow-up time period, and cognitive function testing methodologies were all put into consideration.

Based on the findings of our systematic review, we suggest that more clinical studies be undertaken to standardize the suitable timing of hsCRP evaluation before hsCRP testing is recommended for routine examination. Furthermore, it is necessary to investigate if CRP is simply a reflection of an activated inflammatory response or if it has a direct influence on brain damage that leads to reduced cognitive performance.

CONCLUSION

Elevated hsCRP is linked to the occurrence of cognitive impairment in ischemic stroke patients, so it can be used to predict cognitive impairment in ischemic stroke patients. In addition to hsCRP, other inflammatory

markers (homocysteine and fibrinogen) can be used to predict cognitive impairment in ischemic stroke patients. A better understanding of hsCRP's prognostic value in ischemic stroke patients with cognitive impairment can provide a new perspective on post-stroke cognitive impairment management.

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