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C-Reactive protein as a biomarker affecting neurorehabilitation outcomes in post-stroke patients: state of knowledge and global trends in research

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Abstract

Background: Stroke-related cerebrovascular diseases affect millions of people worldwide and the annual incidence rate is steadily increasing. The role of biomarkers is inevitably reflected in technological advances but also in the development of molecular methods in the field of laboratory diagnostics. C-reactive protein (CRP) is a commonly determined biomarker of inflammation and may reflect the progression of a vascular disease. CRP values within 12 to 24 hours of stroke symptom onset are an independent predictor of adverse functional outcome in terms of the level of motor recovery in the first year of follow-up.

Objective: This study aims to provide a complementary analysis of the scientific literature and critically review studies on the use of CRP as a potential biomarker associated with stroke and affecting the achievement of neurorehabilitation progress in post-stroke patients.

Methods: This critical review of the literature was prepared based on the international recommendations of the Scale for the Assessment of Narrative Review Articles (SANRA). Inclusion criteria included (1) original research-oriented publications, (2) studies indexed in PubMed, Scopus and PEDro databases, (3) full-text articles in English, (4) recent papers published in 2012 – 2022, (5) papers addressing the use of PCR assay as a biomarker of rehabilitation effectiveness, and (6) papers discussing the role in prognosis of post-stroke patients.

Results: Based on a review of PubMed, Scopus and PEDro databases, 47, 56 and 9 papers, respectively, were selected based on precisely selected keywords and included in full for further full text review. In this review, the most important scientific rationale was included in response to the aim of this paper.

Summary: Recognition of the role of inflammatory and immunological factors in the development of atherosclerosis and the occurrence of ischaemic stroke provides scope for the search for new methods of stroke risk assessment and the development of new methods to prevent stroke. Further empirical validation and unequivocal demonstration of the levels of CRP as a potential marker that affects the health status of a post-stroke patient are needed to ensure the greatest possible level of motor recovery and ability to function independently in terms of all activities of daily living.

Keywords: stroke, C-reactive protein, biomarker, neurorehabilitation, functional outcomes, state of knowledge, critical review

Introduction

Problematics of stroke

Stroke-related cerebrovascular diseases affect millions of people worldwide and the annual incidence rate is steadily increasing. In an ageing society with multiple risk factors, strokes and subsequent neurological deficits as a result of damage to central nervous system (CNS) structures will constitute an increasing challenge for the entire healthcare system [1,2]. Effective diagnostic and therapeutic management, but also prognostic management in terms of the prognosis of motor recovery after stroke remain an important interdisciplinary medical problem [3].

Stroke is characterised by a neurological deficit associated with acute focal CNS damage in vascular disorders, including cerebral infarction, intracerebral haemorrhage, and subarachnoid haemorrhage, excluding any other aetiology [4]. According to the American Heart Association (AHA) and the American Stroke Association (ASA), the definition of stroke needs consistent specification for the multidimensional needs of clinical practice, research and public health. The terminology should be based on advances in basic science, neuropathology and neuroimaging that enable a detailed observation and understanding of the complex mechanisms of stroke in ischaemia and cerebral haemorrhage [5].

Epidemiology of stroke

According to the World Health Organization (WHO), stroke is the second most fatal syndrome affecting people aged 60 years and older, with the incidence steadily increasing [6]. Approximately 15-17 million people worldwide suffer from strokes annually, with as many as 5 million cases resulting in death, while another 5 million are associated with permanent disability, indirectly involving the families of those affected as well as society as a whole [7,8].

According to data from a population-based study involving more than one million patients as part of the international EROS project [9], there is a slightly higher incidence of stroke among women (51.4%), the average age for peak incidence was found to be 73 years and the age range 75-84 years has the highest incidence, affecting almost 33% of individuals. It was revealed that the mean annual incidence of stroke in the European population is 101.2 per 100,000, with the highest incidence in Lithuania at 239.3 per 100,000 and the lowest in Italy at 101.2 per 100,000, and in Poland at 147.2 per 100,000 [9].

Consequences of stroke

It is worth drawing attention to the systemic European Stroke Action Plan (ESAP) 2018-2030 being implemented by the European Stroke Organisation (ESO) in collaboration with the Stroke Alliance for Europe (SAFE). The plan has 4 overarching goals for 2030: (1) to reduce the absolute number of strokes in Europe by 10%, (2) to treat 90% or more of all stroke patients in Europe in a dedicated stroke unit as the first level of care, (3) to have national stroke plans covering the whole chain of care, and (4) to fully implement national strategies for multi-sectoral public health interventions [10].

A cohort study conducted as part of the ARIC project involving nearly 500 post-stroke patients described the specific symptoms of cerebrovascular incidents according to prevalence, which included hemiparesis, facial muscle paralysis, limb muscle paralysis, unilateral and contralateral sensory abnormalities, speech impairment, non-specific headache, gait and balance impairment, loss of half of the visual field, dizziness and seizures [11].

In stroke, there is a reduction in conscious, coordinated and fine motor skills [12,13], as well as a significant deterioration in overall levels of activities of daily living (ADLs) and social participation, resulting in a negative impact on patients' health-related quality of life (HRQOL) [14,15].

The role of biomarkers in medicine

According to the Biomarkers Definitions Working Group (BDWG) [16], the role of biomarkers in the assessment and prediction of many conditions, including stroke, is inevitably reflected in technological advances related to the collection and processing of medical data, but also in the development of molecular methods in the field of laboratory diagnostics. This opens up great opportunities and creates hitherto unattainable potential for the search for specific substances linked to the risk of various conditions for preventive or predictive purposes. One approach to achieving faster and more informative therapeutic trials is to use precise clinical measurement tools to determine disease progression and the effects of therapeutic interventions. Another approach is to use a wide range of analytical tools to assess biological parameters, which are referred to as biomarkers. A biomarker is thus defined as a biological factor that is objectively measured and assessed as an indicator of normal biological processes, pathological processes or pharmacological responses to a therapeutic intervention [16].

The search for increasingly specific, sensitive and specific biomarkers to improve the assessment of patients' prognosis of survival and their motor recovery and thus their return to work and active social life is of no little importance [17]. Biomarkers are crucial to ensure the sustainability of medical therapies; however, there is still considerable variation in the underlying concepts and terms associated with their use in research and clinical practice, particularly in the fields of chronic disease and nutrition [18]. CRP becomes one such factor in respect of stroke. The detailed mechanism of reduced functional outcome after ischaemic stroke is not yet fully elucidated and is related to a complex cycle of interconnected molecular and cellular mechanisms. Some studies point out that inflammation in the persistent phase after stroke may promote tissue repair and functional regeneration [19].

Potential of CRP in stroke

CRP is a commonly measured biomarker of inflammation and may reflect the progression of vascular disease. CRP was first discovered by Tiller and Francis in 1930 [20]. It plays an important role in the pathogenesis of atherosclerosis; high-sensitivity CRP (hs-CRP) correlates with the extent of atherosclerosis, and high triglyceride levels and BMI are closely associated with high hs-CRP levels in dyslipidemic patients [21]. CRP is a glycoprotein whose synthesis occurs mainly in hepatocytes of the liver and smooth muscles. The gene for CRP is located within chromosome 1 in a single copy. Normal CRP levels in healthy individuals should not exceed 5 mg/l. In inflammatory conditions, CRP levels are usually reached after 24-48 hours and may increase even 1000-fold. In contrast, CRP levels return to baseline values within 7 to 12 days [22].

The recognition of the role of inflammatory and immunological factors associated with the occurrence of ischaemic stroke provides room to explore new methods of assessing stroke risk and developing new methods to prevent stroke. In studies on predicting long-term functional outcomes of post-stroke patients, it was revealed that CRP levels within 12 to 24 hours of stroke symptom onset were independently predictive of adverse functional outcome after 1 year of follow-up. CRP levels measured 24 to 48 hours after symptom onset were even stronger predictors, but the time frame did not meet the inclusion criteria as it falls outside the time window for assessing acute inflammation [23].

Elevated CRP levels showed positively significant associations with long-term, >30 days, adverse functional outcome. Researchers in previous reports found that CRP levels were significantly and positively correlated with functional outcomes assessed by the Modified Rankin Scale (mRS) at 1, 3, 6 and 12 months of follow-up, with increasingly stronger observational associations as the time increased. An important highlight was that CRP levels measured 7 days after admission revealed a stronger statistical correlation with mRS scores at 12 months than CRP levels measured within 24 hours of admission [24].

Other studies also confirmed the association between ischaemic stroke and elevated CRP levels. Researchers found that high plasma CRP levels obtained in their study, independent of other risk factors for cardiovascular diseases, can be used as a predictor of transient ischaemic attack (TIA) and ischaemic stroke risk for the elderly group, i.e. those over 65 years of age [25]. As highlighted by Sproston and Ashworth [26], although elevations in inflammatory markers are usually observed in infections, increases in CRP levels in ischaemic stroke may reflect

non-infectious inflammation induced by ischaemia, contributing to a hypercoagulable state and extensive tissue damage.

Objectives

This study aims to provide a complementary analysis of scientific literature and a critical review of studies on the use of CRP as a potential biomarker associated with stroke and affecting the achievement of neurorehabilitation progress in post-stroke patients. The objective will also be to analyse the global trend in the publication of papers on the subject during the period under study, i.e., the last decade (2012–2022).

Methods

Methodological quality

This critical review of the literature was prepared based on the SANRA (Scale for the Assessment of Narrative Review Articles) international recommendations for assessing the methodological quality of such papers [27]. The PICO strategy [28] was used for the formulation of a guiding question and review of the literature for the following components: Patient (ischaemic stroke), Intervention (diagnosis, prognosis, rehabilitation), Control (not applicable), and Outcomes (CRP biomarker). The Narrative Review Checklist (NRC) was also used in the development of the publication in terms of the appropriate standard of content, form and structure of the paper [29]. Descriptors were selected according to the current MeSH terminology [30] and a combination of the following keywords was used: stroke, post-stroke patients, PCR biomarker, motor recovery, rehabilitation, neurorehabilitation.

Qualification procedure

Inclusion criteria included (1) original publications with a research and clinical focus, (2) studies indexed in PubMed, Scopus and PEDro databases, (3) full-text articles in English, (4) recent papers published in the last decade, i.e., 2012– 2022, (5) papers addressing the use of the PCR assay as a biomarker of rehabilitation effectiveness, and (6) papers discussing the role in post-stroke patient's prognosis.

Exclusion criteria included (1) review publications in the nature of systematic reviews, meta-analyses, as well as narrative reviews and range of literature, (2) studies indexed in medical databases other than those indicated above, (3) articles available only as abstracts or post-conference reports, (4) papers published before 2012, (5) publications significantly deviating from the target topic of this article and in languages other than English.

Results

Database search

In the PubMed database, 3,855 records were retrieved after using the initial keyword combination "stroke AND C-reactive protein". After changing the keywords to "ischemic stroke AND C-reactive protein", 1,239 records were retrieved. In the next step, the final keyword combination "ischemic stroke AND C-reactive protein AND rehabilitation" was used, where 58 records were found. Subsequently, after narrowing the scope of the search to the years 2012-2022, 47 papers were retrieved, of which 41 papers in English were available in the full-text version and were included in this review (Fig.1a and 1b).

In the Scopus database, after using the initial keyword combination "stroke AND C-reactive protein", 8,896 records were retrieved. After changing the keywords to "ischemic stroke AND C-reactive protein", 3,566 records were retrieved. In the next step, the final keyword combination "ischemic stroke AND C-reactive protein AND rehabilitation" was used, where 66 records were found. Subsequently, after narrowing the temporal scope of the search to 2012-2022, 56 papers were retrieved, of which 53 papers in English were available in the full-text version and were included in this review (Fig. 2a and 2b). In contrast, in the PEDro database, after using the initial keyword combination "stroke AND C-reactive protein", only 9 records were retrieved, all of which were included for further full-text review (Fig. 3).

Literature review

It should be emphasised that from the biological point of view, on the one hand, the post-stroke CRP biomarker will cause cell death, brain damage and disruption of the blood-brain barrier (BBD), which directly contributes to damage and worse functional outcome, but on the other hand, it can exacerbate atherosclerosis via atherosclerotic plaque rupture, platelet aggregation and intravascular thrombosis [31,32]. Various biological mechanisms underlying stroke disorders are presented, the understanding and elucidation of which may contribute to a faster and more complete diagnosis. This can also guide both pharmacological and rehabilitation therapy as a whole treatment process led by an interdisciplinary team. All of these coordinated actions aim to increase the effectiveness of patients' functional recovery and thus reduce the marginalisation of this patient group. The following review considers the most important scientific rationale in response to the objective set out in this paper.

In their study, Wnuk et al. [33] observed that non-infectious CRP levels are an independent risk factor for poor short- and long-term functional outcomes with ischaemic stroke undergoing thrombolytic treatment. In their study, conducted as a retrospective analysis of prospective data, they included a group of 158 patients with a mean age of 72 years (63-82). They used mRS to assess functional outcome. They considered a functional outcome to be poor when the value obtained in the score assessment 90 days after the ischaemic incident was greater than three points. They found that a poor functional outcome assessed using mRS 3 was obtained by patients with CRP levels > 8.65 mg/l compared to patients with CRP levels below 5 mg/l.

Geng et al. [34] prospectively investigated 301 patients with acute ischaemic stroke and assessed CRP levels as an inflammatory marker associated with stroke severity and long-term outcome. Patient demographic and clinical data were collected and assessed on admission. Adverse patient outcomes at hospital discharge were assessed using mRS > 2. The researchers conclude that the CRP levels measured at admission proved to be an independent predictor of adverse outcome at hospital discharge.

Tu et al. [35] investigated 189 patients with acute ischaemic stroke who were admitted to hospital within 24 hours of symptom onset. They observed that serum hs-CRP levels were significantly higher in stroke patients compared with controls ($p < 0.0001$). The conclusion was that hs-CRP may be one of the independent predictors of short-term outcome and mortality in acute ischaemic stroke.

Nozoe et al. [36] investigated the link between changes in quadriceps muscle thickness as a component of lower limb motor function and the severity of the condition, nutritional status as well as CRP levels among patients with acute intracerebral haemorrhage or ischaemic stroke. It was revealed that quadriceps muscle thickness was more reduced in CRP-positive patients (≥ 0.3 mg/dL) than in CRP-negative patients (< 0.3 mg/dL) in the limb not affected by paresis. The results indicate that positive CRP on admission was significantly correlated with reduced quadriceps muscle thickness after acute stroke which may be indicative of a lower level of lower limb motor function.

In October 2003 – December 2011, Karlinski et al. [37] investigated the link between routine CRP measurement within 24 hours of admission and outcome in ischaemic stroke patients treated with intravenous thrombolysis, taking into account a history of recent infection. It was observed that patients with elevated CRP levels (135/341, 42.5%) were significantly older compared to patients with normal CRP levels and more likely to present with pre-existing disability, comorbidities and they suffered more severe strokes. That group of patients also had a higher rate of symptomatic intracranial bleeding according to the European Cooperative Acute Stroke Study (ECASS) II classification (7.2% vs. 1.6%, $p = 0.010$), higher 3-month mortality (25.6% vs 11.3%, $p = 0.001$) and was significantly less independent at 3 months (45.9% vs 63.7%, $p = 0.002$).

In contrast, Jiménez et al. [38] observed that the risk of higher CRP levels and worse functional outcome were associated with hypertension in men who had ischaemic stroke in the past compared to men without hypertension as a comorbidity. Moreover, they emphasise that carotid atherosclerosis may be associated with elevated serum CRP levels in patients with internal carotid artery stenosis, resulting in carotid artery obstruction and subsequent large-artery atherosclerotic (LAA) stroke [39].

Matsuo et al. [40] assessed the link between CRP levels and functional outcomes in their prospective studies conducted from June 2007 to May 2014. They used mRS to assess the functional outcome (as in this study). Poor functional outcome of 3> mRS was defined as a disability at 3 months after stroke, and was tested using the logistic regression analysis. The mean age of the participants was 70.8 ± 12.2 years. Matsuo et al. found that CRP levels were independently associated with adverse functional outcomes. Those Japanese researchers proved

that elevated CRP levels increased with age and that functional outcome after stroke was generally poorer in the elderly.

Also, Peña Sánchez et al. [41] emphasised that the age of patients should be taken into account when assessing the usefulness of CRP and other blood biomarkers as clinical tools for predicting long-term or short-term neurological outcomes and, consequently, functional performance outcomes in ischaemic stroke patients. According to the authors of the above-mentioned report, CRP levels only increase in patients older than 55 years. The authors concluded that CRP levels and age were directly correlated in stroke patients, and older age correlates with more severe neurological impairment.

Peng et al. [42] evaluated links between CRP levels and the occurrence of stroke in their cross-sectional studies involving U.S. resident population. They enrolled 32,408 participants, including 15,495 men and 16,913 women. Multivariate analyses stratified by sex revealed a non-significant link between higher CRP levels and stroke in men. In the overall population, 13% of stroke cases could be attributed to higher CRP levels (> 5 mg/l). The authors found that higher CRP levels tended to be a more significant risk factor for stroke among women than men, as they confirmed by the multivariate logistic analysis.

Those findings were consistent with an earlier Framingham study [43], which revealed that the highest quartile CRP levels were associated with a significant increase in ischaemic stroke or TIA in women (risk ratio = 2.1; 95% CI: 1.19-3.83), while the association disappeared in men (risk ratio = 1.6; 95% CI: 0.87-3.13). Different results were obtained by Chinese researchers, who observed that elevated CRP levels had a significant effect in male patients, but not in female patients [44]. Those inconsistent findings regarding sex differences may have been partly due to genetic and hormonal differences between men and women; the above-mentioned processes need to be clarified and thus further studies to dissect this phenomenon need to be performed.

Rajeshwar et al. [45] by using the multiple logistic regression showed that higher levels of hs-CRP were significantly associated with poor outcomes in their sample of 581 patients after taking into account several confounding variables. They examined the link between CRP levels and poor outcome (>2 mRS and <5 on the Glasgow Coma Scale Extended, GCS-E). There was a significant link between elevated hs-CRP levels and nitric oxide (NO) levels with stroke occurrence. The regression analysis confirmed those results after adjusting for potential confounders for hs-CRP (adjusted OR = 2.890; 95% CI = 1.603-5.011; $p < 0.01$) and NO (adjusted OR = 2.364; 95% CI = 1.312-3.998; $p < 0.01$). After adjusting for potential confounders, patients with high CRP levels had a significantly increased risk of poor clinical outcome (adjusted OR = 3.50; 95% CI = 1.312-6.365; $p < 0.001$). The researchers conclude that hs-CRP and NO biomarker levels predict the occurrence of ischaemic stroke and, additionally, hs-CRP is an independent predictor of poor outcome at 3 months after stroke onset.

Imaging studies have revealed that the progression of infarct evolution is not further altered after approximately 30 days, which correlates with the patient's overall disability originating from ischaemic stroke. The most current evidence questions and emphasises that blood biomarkers may be as effective in predicting functional outcome as imaging biomarkers; however, this needs to be confirmed by further studies on the effectiveness of blood biomarkers in predicting recovery while monitoring imaging results. As highlighted by Van Gilder et al. [46], long-term functional outcome scales such as the Barthel Index (BI) and mRS are commonly used to measure dependence in activities of daily living and assessing disability and have high inter-rater reliability compared to other scales.

In their studies, Ye et al. [47] evaluated whether CRP levels in acute ischaemic stroke could act as a prognostic marker of long-term functional disability. In their project, they prospectively studied patients with first ischaemic stroke registered in the Nanijing Stroke Registry in the period from January 2012 and June 2014. For analyses, venous blood was collected from 625 patients within 14 days of stroke onset. Patients were followed up for one year. There were 458 men and 167 women in the study group. Elevated CRP as an independent predictor of functional disability was found in both sexes after one year, in men ($p=0.017$) and in women ($p=0.042$). The authors emphasise that elevated CRP levels are associated with greater motor disability.

In contrast, Ahmadi Ahangar et al. [48] conducted a cross-sectional analytical study among 214 patients after neuroimaging-confirmed ischaemic stroke (CT or MRI). Stroke severity was determined by NIHSS (National Institutes of Health Stroke Scale) criteria: score ≤ 8 mild stroke; 9-15 moderate stroke, ≥ 16 severe stroke. Serum CRP levels were measured using the Latex Agglutination Test. In this method, anti-CRP sensitised latex particles adjacent to CRP that is present in the serum sample causes agglutination. In that study, CRP levels greater than 5 mg/dl of serum were considered positive and lower values were considered normal. The authors found that serum CRP levels were positive in 122 cases (57%). Out of 122 cases of positive CRP, 64 cases (52%)

included women and the remaining 58 cases (48%) included men (p=0.21). The results of this study revealed that positive serum CRP levels were associated with ischaemic stroke severity and poor prognosis.

Totan et al. [49] also conducted a retrospective study in which they enrolled 81 patients diagnosed with ischaemic stroke. The mean age of the patients included in the study was 73.49 years (45-95). Seventy-nine per cent of the patients had elevated CRP levels, 56% of the patients had CRP levels between 5 and 50 mg/dl and 23% of the patients had CRP levels above 50 mg/dl. The authors examined the correlation between CRP levels and the degree of motor deficit. The degree of motor impairment was measured using mRS and was assessed in all patients included in the study. Motor deficits predominated in the study group, with CRP levels in the range of 5-50 mg/dl. There were no significant differences in terms of the cases studied between patients with severe motor impairment and those with moderate motor impairment. Since the most important risk factors present in the patients included in the above-mentioned study were hypertension and atherosclerosis, the authors also investigated the correlations between these risk factors and CRP levels. The majority of patients with those two risk factors had average CRP levels (5-50 mg/l).

Chinese researchers Hong-Qiu et al. [50] conducted a randomised, observational study. They assessed the link between CRP levels in patients after first ischaemic stroke and recurrent stroke plus functional disability, which they defined as a score assessed by mRS >2 (as in this project) at a follow-up of 90 days after the incident. The mean age of the participants was 62.3±11.3 years. Factors known to be associated with stroke recurrence and functional outcomes were included as confounders in analyses and included demographic data (age, sex, BMI), smoking, hypertension, diabetes. The analysis of the results revealed that less than 20% of the poor functional outcome could be explained by recurrent stroke, meaning that more than 80% of the functional damage was due to disability. Therefore, typical secondary prevention strategies, e.g., rehabilitation, are very important for preventing stroke recurrence.

Among all the studies cited, three reports questioned the use of CRP as a marker for predicting the level of motor function after stroke. Therefore, Taheraghdam et al. [51], in their prospective study involving 102 patients hospitalised for their first ischaemic stroke, report critical results and conclude that CRP is not an appropriate marker for predicting the severity of short-term functional disability as measured by mRS and may not be useful as a clinical factor for predicting treatment outcome.

In contrast, Ozkan et al. [52] assessed the predictive value of hs-CRP and ferritin levels for functional disability in patients with acute ischaemic stroke at 3-month follow-up. Plasma hs-CRP and ferritin measurements were obtained from patients within 48 hours after stroke onset and at 3-month follow-up in two groups of patients: elevated serum hs-CRP ≥0.5 mg/dl and normal serum hs-CRP<0.5 mg/dl. Treatment outcomes were assessed using the NIHSS and Functional Independence Measure (FIM) scales. According to the researchers, hs-CRP levels could not predict functional disability 3 months after stroke onset.

Åberg et al. [53] assessed the value of serum biomarkers such as CRP, D-dimers, fibrinogen and S100β protein in predicting the 3-month functional performance outcome on the mRS in 131 acute ischaemic stroke patients. Peripheral blood levels of the biomarkers studied were determined on admission (CRP, D-dimers and fibrinogen) or 48 hours after stroke (S100β). It was proven that although S100β protein levels were significantly associated with mRS scores at 3-month follow-up (p <.001), this association was not apparent for the other biomarkers assessed, including CRP.

Zhao et al. [54] conducted an interesting randomised trial to evaluate the effect of different doses of clopidogrel in combination with early rehabilitation on motor function and inflammatory markers in patients with ischaemic stroke. Patients' motor function-related outcomes were collected, including scores of scales such as BI, NIHSS, Fugl-Meyer Scale (FMS), scores of inflammatory markers such as hs-CRP, interleukin-6 (IL-6), tumour necrosis factor-α (TNF-α), and the rate of adverse events. It was revealed that high-dose clopidogrel and early rehabilitation were superior to low-dose treatment to effectively attenuate the inflammatory response by promoting restoration of neurological function, improving the level of motor function in patients with ischaemic stroke.

It should be mentioned that there is a link between CRP levels and the occurrence of post-stroke depression. Cheng et al. [55] investigated changes in hs-CRP and homocysteine levels in acute ischaemic stroke and assessed the link of those two risk factors with long-term post-stroke depression (PSD). They examined 259 patients, who were classified based on depressive symptoms according to the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) criteria for depression at 1 year after stroke. It was found that 94 patients (36.3%) were diagnosed with PSD. On the other hand, the multivariate logistic regression analysis revealed that the third and fourth quartiles of hs-CRP or homocysteine levels were significantly associated with PSD (p <

0.05), confirming the hypothesis that elevated serum levels of hs-CRP were related to a higher risk of developing PSD one year after stroke.

Summary

The recognition of the role of inflammatory and immunological factors in the development of atherosclerosis and the occurrence of ischaemic stroke provides room for the search for new methods to assess stroke risk and develop new methods to prevent stroke. The studies revealed the important role of inflammatory mechanisms in the dynamics of the development of stroke focus. In response to necrotic tissues (antigens released from them), an acute inflammatory response develops, which contributes to the enlargement of the infarct area and is reflected in neurological deterioration. This also significantly affects the subsequent prognosis of the stroke patient and has a direct bearing on the effectiveness of therapeutic rehabilitation and the progress the patient makes in the recovery of motor functions lost due to stroke. Further empirical verification and unequivocal demonstration of CRP levels as a potential marker that affects the health status of a post-stroke patient is needed to ensure the greatest possible level of motor recovery and ability to function independently in terms of all activities of daily living.

Abbreviations

ADL	activities of daily living
AHA	American Heart Association
ASA	American Stroke Association
BDWG	Biomarkers Definitions Working Group
BI	Barthel Index
CNS	central nervous system
CRP	C-reactive protein
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders-IV
ECASS II	European Cooperative Acute Stroke Study II
ESAP	European Stroke Action Plan
ESO	European Stroke Organization
FIM	Functional Independence Measure
FMS	Fugl-Meyer scale
GCS	Glasgow Coma Scale
HRQOL	health-related quality of life
IL-6	interleukin-6
LLA	large-artery atherosclerosis
mRS	Modified Rankin Scale
NIHSS	National Institutes of Health Stroke Scale
NO	nitric oxide
NRC	Narrative Review Checklist
PSD	post-stroke depression
SAFE	Stroke Alliance for Europe
SANRA	Scale for the Assessment of Narrative Review Articles
TNF-α	tumor necrosis factor-α
WHO	World Health Organization

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Figure 1a. Search stages and results from PubMed database (part 1).

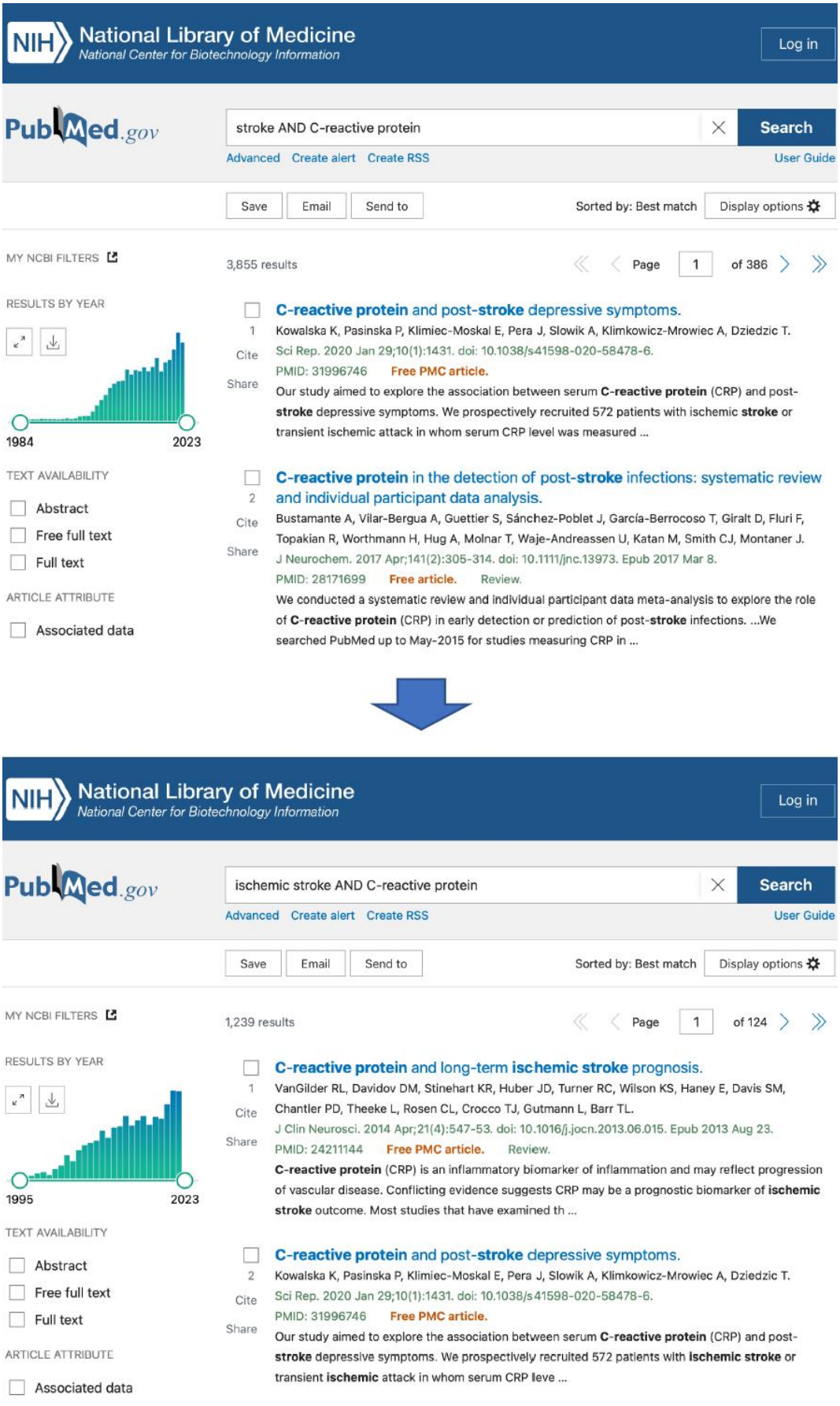


Figure 1b. Search stages and results from PubMed database (part 2).

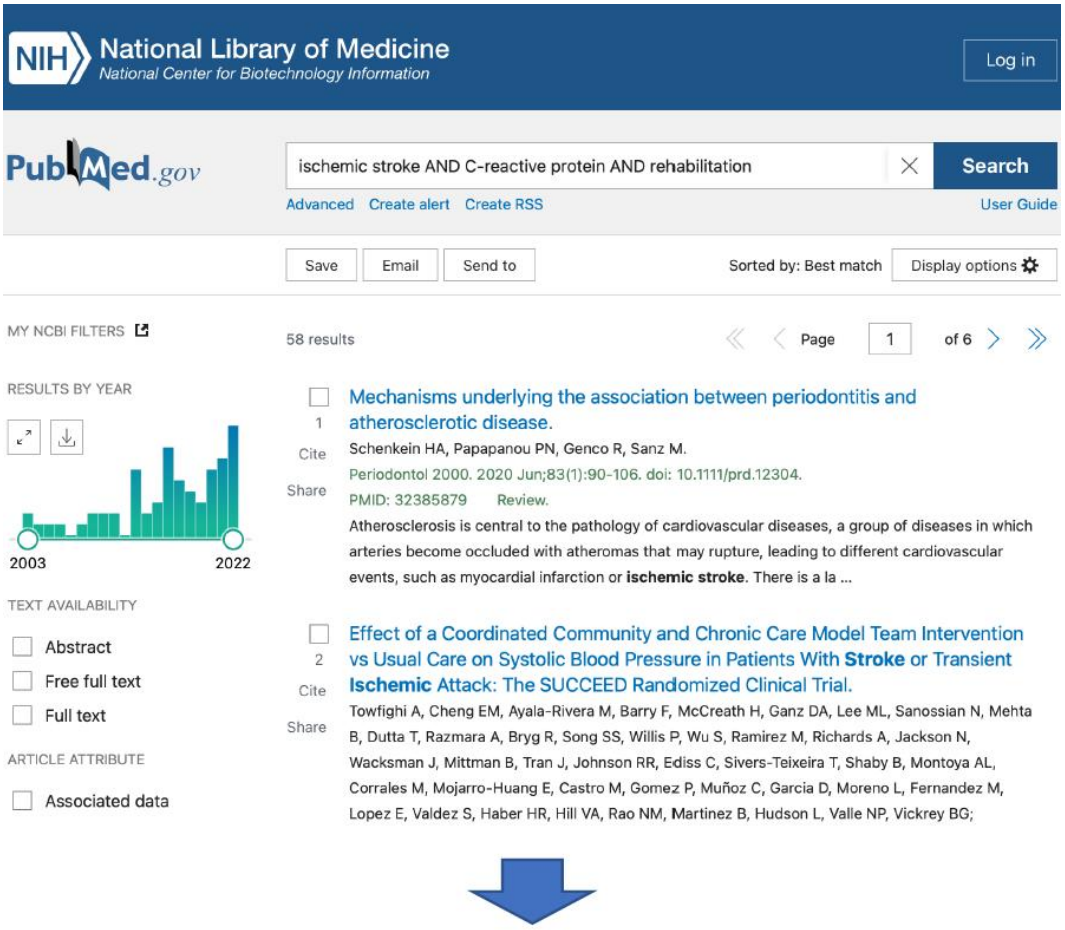
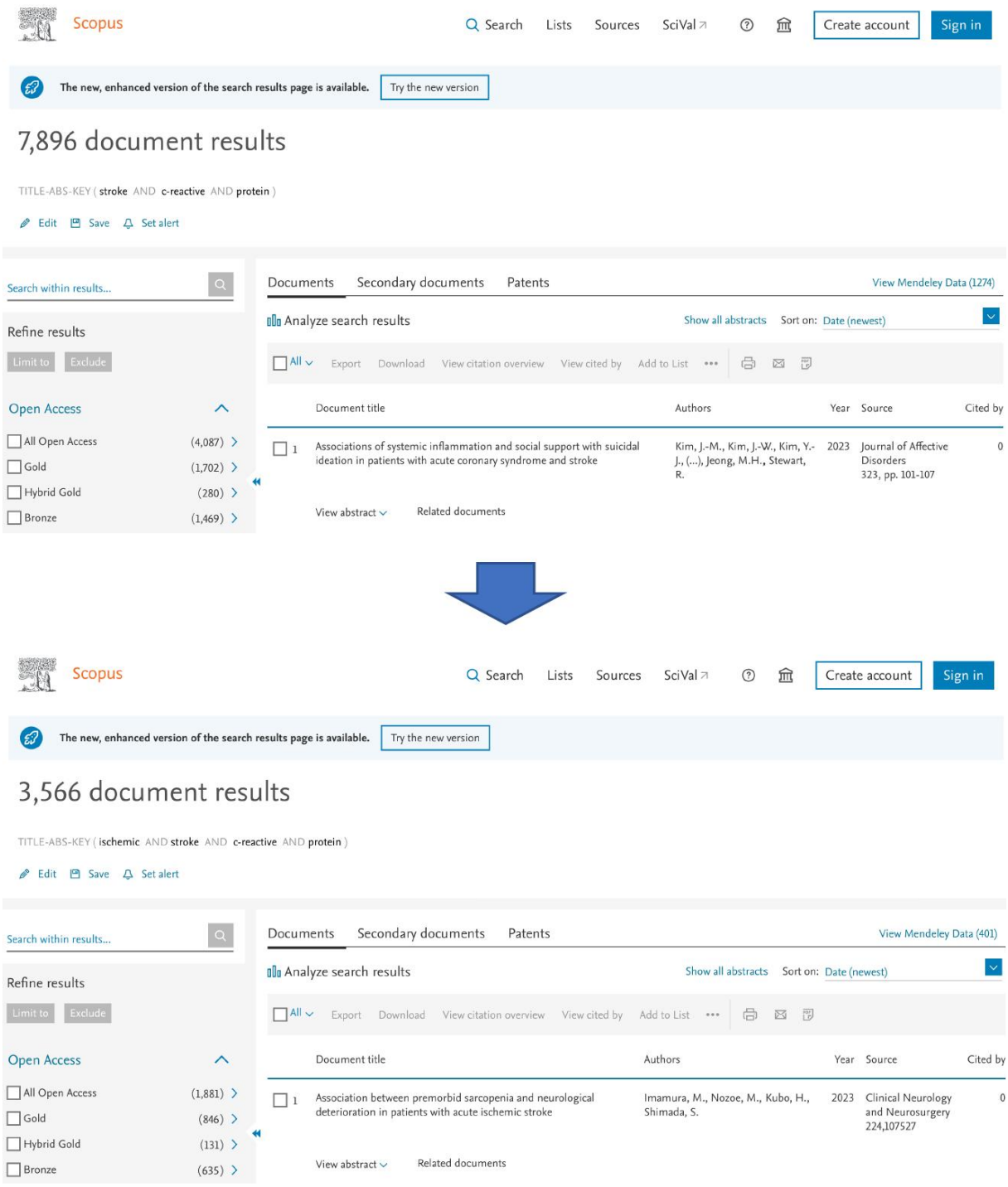


Figure 2a. Search stages and results from Scopus database (part 1).



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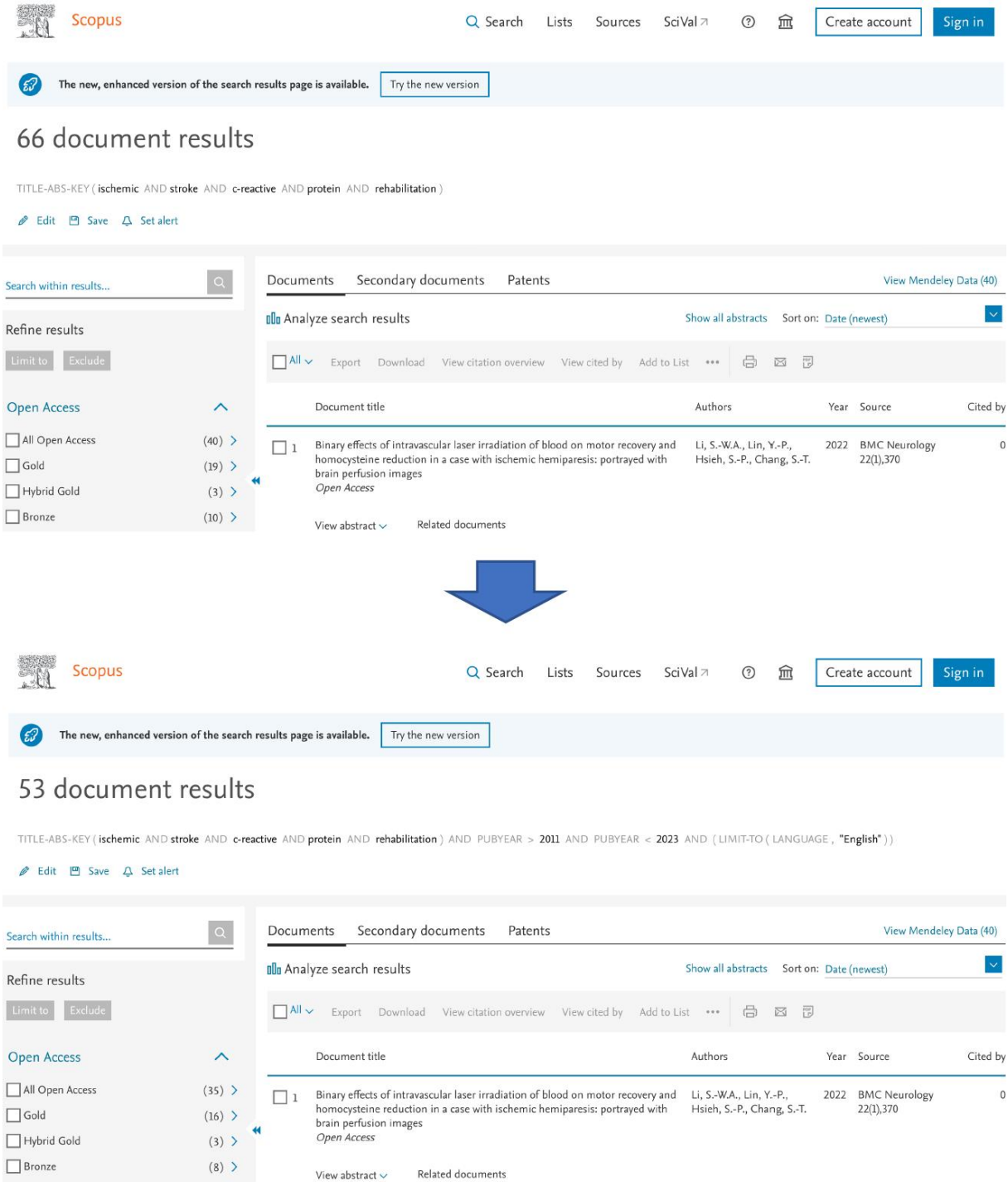

Figure 3. Search stages and results from PEDro database.

PEDro
Physiotherapy Evidence Database

PEDro is a free database of randomised controlled trials, systematic reviews and clinical practice guidelines in physiotherapy. You can search PEDro using this Advanced Search page. Those who are new to searching may like to begin with the Simple Search page. Patients and users of physiotherapy may prefer the Consumer Search page. For more information please visit the PEDro home page.

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Abstract & Title:	stroke AND C-reactive protein
Therapy:	
Problem:	
Body Part:	
Subdiscipline:	
Topic:	
Method:	
Author/Association:	
Title Only:	
Source:	
Published Since:	[YYYY]
New records added since:	[DD/MM/YYYY]
Score of at least:	[/10]
Return:	20 records at a time
When Searching:	Match all search terms (AND)

PEDro
Physiotherapy Evidence Database

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Search Results

Click on a title to view details of that record. If your search has returned many records you may need to move to the next page (at the top or bottom of the list of records). To display a list of records from one or a series of searches, click on *Select* and then *Display Selected Records*

Found 9 records

Title	Method	Score (/10)	Select Record
The cardiac model of rehabilitation for reducing cardiovascular risk factors post transient ischaemic attack and stroke: a randomized controlled trial [with consumer summary]	clinical trial	8/10	Select
Secondary prevention of new vascular events with lifestyle intervention in patients with noncardioembolic mild ischemic stroke: a single-center randomized controlled trial	clinical trial	8/10	Select
(Effect of acupuncture on neurological function and high-sensitivity creactive protein in patients with acute cerebral infarction) [Chinese - simplified characters]	clinical trial	7/10	Select
Task-oriented circuit training as an alternative to ergometer-type aerobic exercise training after stroke	clinical trial	6/10	Select
Effects of continuous positive airway pressure on early signs of atherosclerosis in obstructive sleep apnea [with consumer summary]	clinical trial	6/10	Select
(Effect of acupuncture combined with rehabilitation on immune and neural functions in elderly patients with stroke) [Chinese - simplified characters]	clinical trial	5/10	Select
Randomization to treadmill training improves physical and metabolic health in association with declines in oxidative stress in stroke	clinical trial	4/10	Select
The effects of CPET-guided cardiac rehabilitation on the cardiopulmonary function, the exercise endurance, and the NT-proBNP and hscTnT levels in CHF patients	clinical trial	4/10	Select
Comparison of the effects between isokinetic and isotonic strength training in subacute stroke patients	clinical trial	3/10	Select