THE ASSOCIATION BETWEEN PRO-INFLAMMATORY CYTOKINES AND C-REACTIVE-PROTEIN AND THE COGNITIVE AND NEUROLOGICAL OUTCOME IN STROKE SURVIVORS: A SYSTEMATIC REVIEW

LEILA KAHNAMI

A THESIS SUBMITTED TO THE FACULTY OF GRADUATE STUDIES IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF ARTS

GRADUATE PROGRAM IN CLINICAL DEVELOPMENTAL PSYCHOLOGY

YORK UNIVERSITY

TORONTO, ONTARIO

July 2021

ABSTRACT

The role of inflammation in neurological prognosis of stroke has been studied previously. However, very little research has thoroughly examined the association between inflammatory markers and neurocognitive outcome post-stroke. Our main goal was to examine the existing literature and this association between inflammatory markers and post-stroke functioning, primarily by examining the tools and methods chosen by researchers to assess neurocognitive outcomes. A systematic literature search retrieved 954 articles to review against inclusion criteria. A total of 21 articles were included in this review. Across the studies, we identified two common themes: 1) lack of research into the diverse stroke populations; and 2) lack of comprehensive neurocognitive measures. Our findings show that research on the area of inflammation and neurocognitive outcome post-stroke has been inconsistent in terms of the methods used, and our conclusions will direct future research exploring the role of inflammatory markers in prediction of cognitive functioning post-stroke.

ACKNOWLEDGEMENTS

First and foremost, I would like to thank my supervisor, Dr. Mary Desrocher. Your passion towards pediatric neuropsychology amplified my interest in this project and with your patience, I matured. Your never-ending support, encouragement and guidance throughout the past two years have been immensely invaluable and the reason for successful completion of this project.

I am deeply appreciative of Dr. Robyn Westmacott, who served on my thesis committee. Your valuable feedback, support and thorough editing were much appreciated.

Further, I am grateful for Justine Ledochowski and Dr. Nomazulu Dlamini who played an instrumental role in introducing and motivating me to pursue this field of research.

A special thank you to Samantha Feldman and Maria Orlando, who searched through over 900 articles with me. Without you two, this project could not have happened.

This project would not be possible without a number of supports. I am extremely thankful for the generous funding contributions made by Ontario Graduate Scholarships, and the Canadian Graduate Scholarships- Masters of the Social Sciences and Humanities Research Council. Last but not least, I would like to express my love and gratitude to my mother, my sister, and my partner for their persistence by my side. I will be forever grateful for their patience and support.

DEDICATION

This thesis is dedicated to the memory of my late father, who encouraged me to embrace hardship and learn from failures. I also dedicate this to the memory of my late grandfather, who inspired many of my career and life choices. They both were an inspiration to pursue my passion, and I know they will be by my side throughout all my hurdles and accomplishments.

TABLE OF CONTENTS

LIST OF TABLES & FIGURES

1. Introduction

It has been shown, both experimentally and clinically, that inflammation plays a prominent role in the pathogenesis of stroke. The brain responds to cerebrovascular injury with an acute and prolonged inflammatory process characterized by activation of resident immune cells and peripheral immune cells (Jin, Yang, & Li, 2010). At the instance of brain injury, the resting microglia become activated taking amoeboid morphology, secreting myriad neurotropic factors, and pro-inflammatory cytokines to fight pathogens (Napoli, & Neumann, 2009). This process is meant to protect neurons and ends at a predetermined time. However, unregulated microglial activation may be harmful to neurons, by releasing reactive oxygen species and proinflammatory cytokines (Phani, Loike, & Przedborski, 2012). Moreover, pro-inflammatory cytokines can contribute to the damage by promoting the trafficking of immunological cells from the periphery into the CNS by an increase in the permeability of blood-brain barrier or by increase in the expression of adhesion molecules (Argaw et al., 2006; Förster et al., 2008). Research in adults has indicated the importance of inflammatory markers in the prognosis of stroke (Amantea, Nappi, Bernardi, Bagetta, & Corasaniti, 2009). This systematic review aims to review the research conducted on the association between stroke, inflammatory markers, and the neurological and cognitive outcome in patients after the onset of stroke. The definitions of key terms can be found in the appendix A.

1.2. Stroke Background

Stroke is characterized as a neurological deficit persisting for at least 24 hours, producing focal symptoms and signs that correlate with the brain area affected (Sacco et al., 2013). It is a cerebrovascular event of acute onset, which results from a clot or ruptured vessel that disrupts the normal blood flow in one's brain (Festa, Lazar, & Marshall, 2008). In ischemic stroke, the interruption of blood flow deprives the affected brain regions of oxygen and nutrients which ultimately leads to permanent damage of brain tissue, called infarction (Festa, Lazar, & Marshall, 2008). Hemorrhagic stroke is caused by ruptured blood vessels, the most common underlying mechanism of hemorrhagic stroke is hypertensive small vessel disease (Sierra, Coca, & Schiffrin, 2011). Approximately 800,000 strokes occur each year in the U.S.; of these strokes, approximately 87% are ischemic infarctions (Ovbiagele, & Nguyen-Huynh, 2011). In 2013, it was estimated that 405,000 individuals in Canada suffer from stroke, with a rate of 1.53 per 100 000 children in Canada (Krueger, Koot, Hall, O'Callaghan, Bayley, & Corbett, 2015). Cerebral hemorrhage and ischemic stroke can both lead to neurological deficits such as hemiparesis, hemisensory loss, aphasia, ophthalmoplegia, and visual field cuts. In addition, cerebral hemorrhage causes blood leakage into the brain, resulting in compressing adjacent tissues and increasing intracranial pressure. This may further cause consequences beyond neurological deficits, such as progressive deterioration, neck stiffness, and coma (Runchey, & McGee, 2010). Stroke can be fatal, with mortality rates of 40%, causing permanent neurological and neuropsychological problems in 50% to 80% of survivors (Cárdenas, Rho, & Kirton, 2011; Roach et al., 2008). Problems such as intellectual disability, neurocognitive deficits, socioemotional difficulties, mental health issues, seizure disorders, motor impairments, and cortical sensory problems are very common after the onset of stroke (Greenham et al., 2015; Max et al., 2002). Childhood stroke can be associated with severe deficits in neurological and cognitive functioning. White matter-based skills such as working memory, processing speed, and parent reports of executive functioning are significantly lower in children with cortical stroke (Peterson, Williams, McDonald, Dlamini, & Westmacott, 2019). A similar pattern has been observed in children with subcortical stroke (Westmacott et al., 2018a), particularly pronounced in children with basal ganglia compared to thalamic stroke.

In addition to neurological deficits, stroke survivors may suffer from varying degrees of cognitive deficits in areas of episodic memory, visual perception, executive functions, attention, and language. Cognitive deficits are among the most common consequences of stroke. However, these deficits vary in severity and type. The degree of these deficits can further impact patients' ability to accomplish activities of daily living and can further cause mental health problems (Viscogliosi et al., 2011). Stroke survivors suffer from a wide range of sequelae; even patients with "good outcome" suffer from many cognitive impairments. A study conducted by Planton and colleagues (2012) measured neuropsychological outcome in patients after first ischemic stroke without any previous cognitive decline, with good motor, linguistic, and functional recovery. The results suggested that these patients demonstrated lower performance in every cognitive domain compared to controls. They exhibited problems in the realm of executive functioning, attention, and memory.

Childhood stroke has been associated with impairments in response inhibition (O'Keeffe, Liégeois, Eve, Ganesan, King, & Murphy, 2014). Childhood arterial ischemic stroke (AIS) is also associated with decline in verbal learning and memory, with early stroke being associated with more problems with recall and recognition (Lansing et al., 2004). Academic deficits have also been observed in children with ischemic stroke with particular weaknesses in math calculation and reading comprehension; more pronounced deficits have been observed in children with subcortical stroke (Peterson, Williams, McDonald, Dlamini, & Westmacott, 2019; Westmacott et al., 2018a). Further, children appear to be at risk of developing learning disability and ADHD (Peterson, Williams, McDonald, Dlamini, & Westmacott, 2019; Westmacott et al., 2018a).

Cognition is not a unitary concept, it includes areas such as attention, executive functioning, visuospatial abilities, memory, and language. These areas are often interrelated and incorporated with neglect, agnosia, apraxia, abstract thinking, and arithmetic abilities (Cumming, Marshall, & Lazar, 2013). Researchers have strived to find a distinct profile of cognitive impairments resulting from stroke. A study conducted by Srikanth and colleagues (2003), explored the cognitive profile of adult patients after stroke. The results suggested more pronounced deficits in areas of spatial ability, executive function, attention and language and less pronounced deficits in areas of memory and orientation. Other studies have also confirmed that the cognitive deficits associated with stroke are more weighted towards executive function and attentional problems (Sachdev et al., 2004). However, more recent studies illustrate the presence of memory problems in patients, with stroke being a strong independent risk factor for dementia (Tang, Price, Stephan, Robinson, & Exley, 2020). Stroke characteristics have been linked to the profile of cognitive decline observed in patients. Left anterior and posterior cerebral artery infarcts have been associated with greater cognitive impairment (Tatemichi, Desmond, Stern, Paik, Sano, & Bagiella, 1994). Similarly, middle cerebral artery infarcts have been associated with developing cognitive impairments (Jaillard, Grand, Le Bas, & Hommel, 2010). Stroke in cortical regions and hemorrhagic strokes have also been associated with cognitive impairments in multiple areas of cognition (Nys, et al., 2007). Although, there is substantial evidence of domain specific cognitive deficits after stroke, we observe lack of specific frameworks to define distinct profiles of cognitive impairments seen in stroke survivors.

1.3. Inflammation Background

Neuroinflammation is a compound response on a cellular and molecular level to stress. Neuroinflammation clears pathogens, damaged or dead cells, in an attempt to contain the injury or the infection. Nevertheless, previous research shows that neuroinflammation can have detrimental effects in many diseases such as stroke, multiple sclerosis, Alzheimer's disease (AD), Parkinson's disease, and spinal cord injury (Wang & Jin, 2015).

It has been clinically and experimentally shown that stroke induces inflammatory response in the central nervous system (CNS) and the periphery (Beamer, Coull, Clark, Hazel, & Silberger, 1995; Fassbender et al., 1994). In the intact brain, the blood-brain barrier (BBB) is responsible for trafficking cellular and molecular components from the periphery to the CNS. After brain injury, however, the BBB becomes permeable, allowing the peripheral immune cells to enter the brain parenchyma. The peripheral immune cells, along with the proinflammatory cytokines and chemokines, contribute to the inflammatory response following a brain injury. Acute inflammation is a result of the activation of resident immune cells, microglia, and the infiltrating immune cells of the periphery (Aktas, Ullrich, Infante-Duarte, Nitsch, & Zipp, 2007). It is characterized by production of proinflammatory cytokines, leukocytes, monocytes and the activation of resident glial cells (Amantea et al., 2009; Kriz, 2006). High levels of inflammatory markers, such as Interleukin-6 (IL-6), Interleukin-1b (IL-1b), and Tumour Necrosis Factor alpha (TNF- a) were detected, in the cerebrospinal fluid and the blood plasma of adult patients, within the first few days after the onset of ischemic stroke (Beamer, Coull, Clark, Hazel, & Silberger, 1995; Clark, 1997; Fassbender et al., 1994; Tarkowski, et al., 1995). One major assumption of this study is that the levels of inflammatory markers in patients' blood serum and plasma are representative of inflammation in the periphery and in the brain (Wardlaw et al., 2009).

Research with adults has stressed the importance of inflammation in the prognosis of ischemic stroke (Vila, Castillo, Dávalos, & Chamorro, 2000). Higher levels of IL-6, TNF- a, and C-reactive-proteins (CRP) have been associated with early neurological worsening as measured by the Canadian Stroke Scale (CSS) (Vila, Castillo, Dávalos, & Chamorro, 2000). High levels of inflammatory markers in the plasma within a week after the onset of ischemic stroke have been associated with poor functional outcomes, measured by neurological measures of disability and dependence, such as the modified Rankin Score (mRS) and Barthel Index (BI) (Smith et al., 2004). Moreover, recent evidence suggests that higher concentrations of inflammatory markers in the plasma are associated with lower post-stroke global cognition, measured using the Mini Mental State Examination (MMSE; Rothenburg et al., 2014).

1.4.Summary

Despite the knowledge that inflammatory markers play a role in the prognosis of stroke, research on the association between the inflammatory markers and cognitive and neurological outcome in both adults and children with ischemic and hemorrhagic stroke is lacking. In addition, preliminary evaluation of select studies revealed discrepancies in the methodologies when assessing cognitive and neurological outcomes. The results summarize the extant methodology, the variability in quality and type of cognitive and neurological outcome measured, and how researchers have defined cognitive and neurological outcome. Effectiveness and limitations of the current methods will help inform future research, which can address the gaps in our knowledge of how inflammatory markers can aid in the prediction of neurocognitive outcomes.

1.5.Research Objectives

The overall objective of this systematic review was to explore previous research on the association between pro-inflammatory cytokines, CRP, and neurocognitive outcome in stroke survivors. The primary aim of this study was to assess tools and methods chosen by researchers to assess neurological and cognitive outcomes and to document the areas of cognition studied. Further, this study aimed to identify the most common inflammatory markers investigated and the characteristics of the patients investigated. In addition, inclusion of rodent studies was important in exploring the biological bases of inflammation, which informs studies with stroke patients. The majority of pharmacotherapy research is conducted in rodent models of stroke (Sharp, & Jickling, 2014), as such exploring post-stroke inflammatory response in rodents would summarize the extent of the generalizability of those findings to human populations. This review is the first step in determining the extant of knowledge on the association between inflammation and cognitive outcome across various patient populations with stroke.

2. Methods

This study was submitted to PROSPERO and follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses' (PRISMA) statement guidelines (Moher, Liberati, Tetzlaff, Altman, & The PRISMA Group, 2009).

2.2.Search Strategy

The following databases were searched in October 2020: PsycINFO (via ProQuest), PubMed (via Medline), Web of Science, and Ovid (via Medline). To identify articles on the association between inflammatory markers and outcome after stroke onset, the following search criteria were used: [(p*ediatric OR child* OR youth OR adults OR patients OR rodent*) AND (stroke OR "cerebrovascular accident" OR ischemi* OR hemorragi*) AND ("proinflammatory cytokines" OR inflammation* OR "inflammatory markers") AND ("neurological outcome" OR cognitive*)]. Articles were restricted to English-language literature and searches were not restricted to human studies. No distinction was made regarding the sampling setting, the number of strokes, the mechanism of stroke, the timing of blood collection and outcome assessment. Review articles and theses were excluded from this review.

2.3. Title and Abstract Screening

The initial literature search yielded 1238 articles. All 1238 article were imported into Covidence, a systematic review software. Upon importing, duplicates were automatically removed by Covidence, and 898 articles remained for screening. Additionally, 56 articles were identified and imported to Covidence, by searching the references of selected manuscripts (N= 954).

The title and abstract screening process took place in two steps. Initially, two reviewers (L.K. and M.O.), independently reviewed titles and abstracts, sorting them as “keep”, “reject”, and “maybe” to determine if they meet the following inclusion criteria:

1. The article focused on patients with stroke primarily/rodent models of stroke, rather than stroke being a result of genetic conditions (e.g., a study examining Sickle Cell Disease or Moya Moya, wherein participants had a stroke);
2. The patients suffered a stroke between the ages of 0-95 years (i.e., a life-span approach is taken). As such, patients who suffered from perinatal stroke were excluded, due to the different effects of inflammatory markers in the neonatal brain (Fernández-López, Natarajan, Ashwal, & Vexler, 2014);
3. The article focused mainly on neurological and cognitive outcome measures (i.e., it included findings on any aspect of cognition such as memory, information processing, or attention);
4. The article primarily focused on pro-inflammatory cytokines and c-reactive proteins as measures of inflammation (i.e., studies that focused on microglia as the main measure of inflammation were excluded). We only looked at the pro-inflammatory cytokines and creactive proteins, as they play a more direct role in neurodegeneration and neuroprotection.

5. The inflammatory markers were collected from blood plasma or serum, studies that obtain the inflammatory markers by other means were excluded.

If the title and abstract did not provide sufficient information, the full text was reviewed. Articles labelled as “reject” by both reviewers were automatically excluded from the review. Articles which were rated differently by the reviewers were characterized as “conflict”. The reviewers both read the full text of the articles labeled as “maybe” and “conflict”, they discussed their final decision, arriving to a consensus. Finally, the full text of those labeled as “keep” were retrieved. The title and abstract screening resulted in the exclusion of 922 articles.

2.4.Data Extraction

The 32 remaining were evaluated for quality and risk assessment using STROBE guidelines (Von Elm et al., 2007) by two reviewers (L.K. and M.O.). At this stage one article was excluded as the full text was not available. The 31 remaining articles were evaluated for eligibility using a team-based approach. Two raters (L.K. and S.F.) assessed the articles, reading and discussing the full texts to reach consensus. Discrepancies were resolved by a third rater (M.D). Data extracted included; study type, stroke type, sample size, demographic characteristics, number of the inflammatory markers measured, time of blood collection, type and number of outcome measures (neurological measure, cognitive testing, and mental health questionnaires in human studies and neurological measure, cognitive testing, and behavioural measure in rodent studies), time when outcome was measured, and the domain of cognition assessed (e.g., language, memory, executive functioning). The heterogeneity between studies’ design (i.e., type and time of inflammatory markers measured, and type and time of outcome measured) lowered the power of this review; hence conducting a meta-analysis was not plausible. At the final extraction stage, 10 articles were excluded, leaving a total of 21 articles for inclusion in this systematic review (Figure 1).

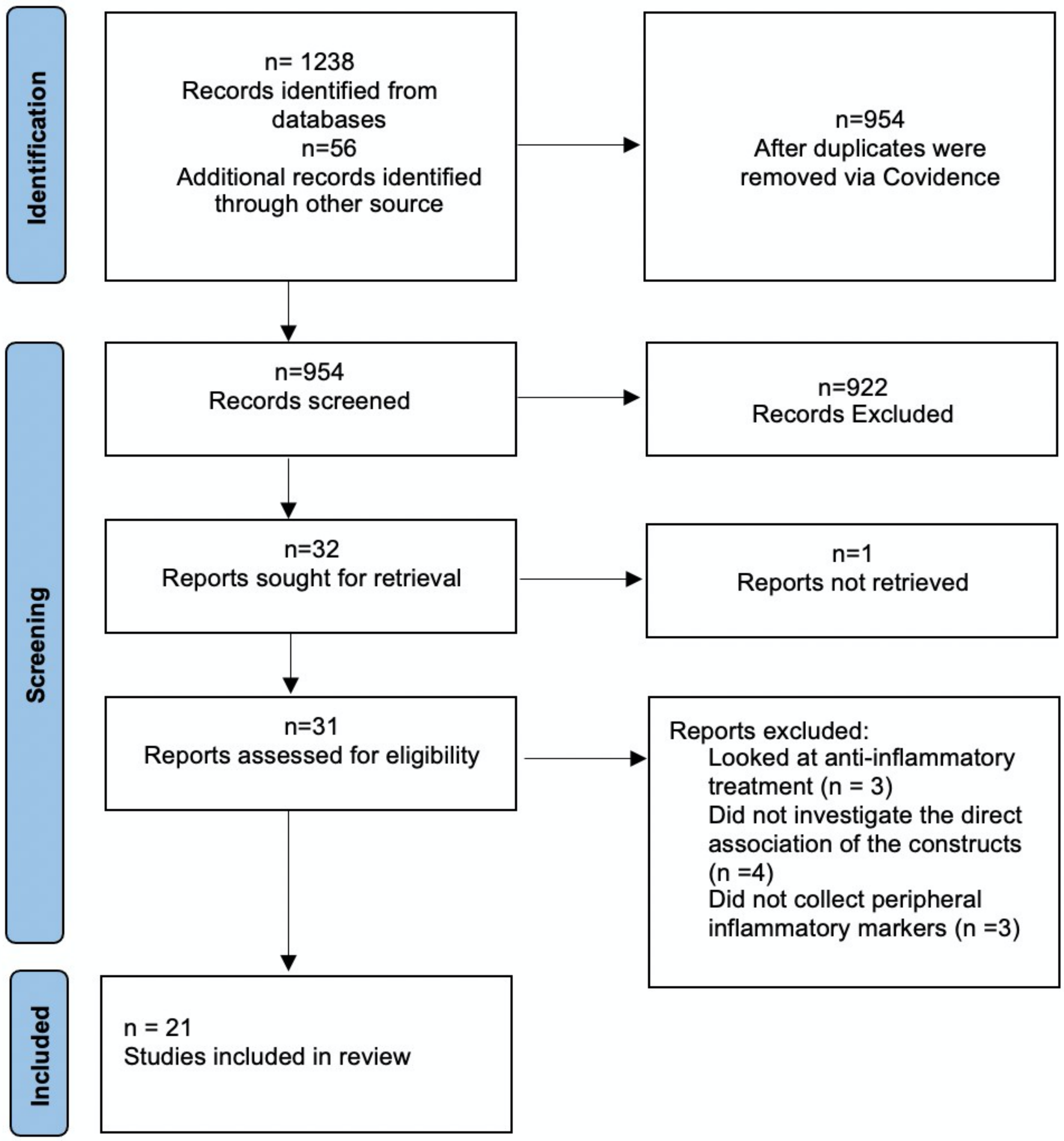

Figure 1. PRISMA (2020) flow chart of studies assessed and included.

2.5.Analysis

All analyses were performed using IBM SPSS 27.0 Statistics Software. Descriptive statistics, specifically frequencies, were conducted to explore the number of studies that reported each of the constructs.

3. Results

Of the 31 articles that met inclusion criteria, 10 were excluded; 3 studied the effect of anti-inflammatory treatment, 4 did not directly study the association between inflammation and neurological or cognitive outcome, and 3 did not collect peripheral inflammatory markers. Studies were published between 1994 and 2020. Of the 21 studies, 18 were human studies and 3 were rodent studies. Due to the heterogeneity between the types of studies, the results will be presented separately. The characteristics of the 18 human studies and 3 rodent studies included in this review are shown in Table 1.

Table 1. Study characteristics.

Study	Study Type	Stroke Type	N	F%	Age range (age mean)	Country
Alexandrova (2016)	Human	Ischemic	47	45	56-76 (63)	Bulgaria
Bunecicius (2014)	Human	Ischemic	88	35	66-80 (72)	Lithuania
deLima (2017)	Mouse	Ischemic	25	0	Not indicated	Brazil
Fassbender (1994)	Human	Ischemic	19	58	39-89 (73)	Germany
Garcia-Berrocoso (2014)	Human	Ischemic	36	Not indicated	Not indicated	Spain
Gelderblom (2018)	Mouse	Ischemic	24	0	12 week old mice	Germany
Johansson (2000)	Human	Ischemic	22	33	56-89 (73.7)	Sweden
Kliper (2013)	Human	Ischemic	368	44	Range not indicated (67.3)	Israel
Kulesh	Human	Ischemic	57	35	Range not	Russia

(2018)					indicated (64.6)	
Lee (2020)	Human	Hemorrhagic	146	67	Range not indicated (59.6)	South Korea
Liu (2020)	Human	Ischemic	212	26	26-92 (59.6)	China
Molad (2018)	Human	Ischemic and TIA	239	Not indicated	Range not indicated (67.9)	Israel
Narasimhalu (2015)	Human	Ischemic	243	35	Range not indicated (61)	Singapore
Oto (2008)	Human	Ischemic and Hemorrhagic	37	40	Range and mean age not indicated	Japan
Protti (2013)	Human	Ischemic	26	54	31-86 (65.5)	Brazil
Rothenburg (2010)	Human	Ischemic	48	46	33-95 (71.6)	Canada
Shaheen (2019)	Human	Ischemic	88	39	21-71 (53)	Egypt
Smith (2004)	Human	Ischemic	37	35	Range not indicated (69)	UK
Swardfager 2014	Human	Ischemic	47	36	Range not indicated (71.8)	Canada
Vila, 2000	Human	Ischemic	231	43	Range not indicated (68.3)	Spain
Zhang 2017	Rat	Ischemic	15	0	Not indicated	China

3.2.Human Studies

3.2.1. Study and demographic characteristics

The number of stroke participants included at baseline ranged from 19 to 368 across the studies, with 55% (n=10) of studies having a sample size smaller than 50. The population age ranged from 21 to 95, and the mean age of the participants, when reported (n=17), was 66.31. The majority of the studies were conducted in Canada (n=2), Israel (n=2), and Spain (n=2), followed by Brazil (n=1), Germany (n=1), Lithuania (n=1), Japan (n=1), Russia (n=1), Bulgaria (n=1), Singapore (n=1), Egypt (n=1), South Korea (n=1), Sweden (n=1), UK (n=1), and China (n=1). Among stroke patient populations, ischemic stroke patients were studied the most (n=15), one study looked at both ischemic and hemorrhagic stroke patients, one study looked at only hemorrhagic patients, and one study looked at ischemic and transient ischemic attack patients. The percentage of females in the 18 studies ranged from 26% to 67%, with a mean of 42%.

3.2.2. Inflammatory Markers

The majority of the studies only measured the pro-inflammatory cytokines (n=9), followed by CRP (n=6), while 3 studies investigated both CRP and pro-inflammatory cytokines. The number of biomarkers measured ranged from 1 to 7, with a mean of 2.5. The most widely investigated biomarkers were CRP (n=9), IL-6 (n=8), TNF- a (n=7), IL-1 b (n=5), and IL-10 (n=5). Other biomarkers measured were INF-Y (n=2), IL-2 (n=1), IL-4 (n=1), IL-8 (n=1), IL-12 (n=1), IL-17 (n=1), IL-20 (n=1), and IL-23 (n=1).

The time of initial blood collection ranged from on admission to within 3 months poststroke. Of the 18 studies, only 7 conducted recurrent blood collection (38.9%), which ranged from 6 hours after admission to 12 months post-stroke. Further, the number of times blood was collected ranged from 1 to 20, with a mean of 3.34.

3.2.3. Assessment of Outcome

The measures of functional outcome were divided into the following classifications: neurological measures, cognitive testing, and mental health questionnaires. Equal number of studies used both neurological and cognitive tests (n=7), or only neurological (n=7), and 2 studies only used cognitive tests. Only one study used all three types of measures (Rothenburg et al., 2010), and the study by Liu and colleagues (2020), used neurological and mental health questionnaires.

The most commonly used neurological measure was the National Institutes of Health Stroke Scale (NIHSS) (n=8). The NIHSS is a systematic assessment tool used by neurologists to measure the level of consciousness, gaze, visual fields, facial weakness, motor performance, sensory deficits, coordination, language, speech, and hemi-inattention (Ortiz & Sacco, 2014). Further, the modified Rankin Scale (mRS) was used in 5 of the studies. The mRS assesses global outcome and disability, by measuring limitations in activity and participation after stroke (Wilson et al., 2005). The Scandinavian Stroke Scale (SSS) was used in some of the studies (n=3). The SSS is a similar measure to NIHSS, and it measures consciousness, eye movement, motor movement, orientation, speech, facial palsy, and gait (Lindenstrøm, Boysen, Christiansen, & Nielsen, 1991).

The most commonly cognitive test used was the Mini Mental State Examination, MMSE (n=7). MMSE is used as a brief cognitive instrument, an 11-question questionnaire which measures cognitive impairment in domains of orientation, registration, attention, calculation, recall, and language (Folstein, Folstein, & McHugh, 1975). The next commonly used cognitive test was the Montreal Cognitive Assessment (MoCA), (n=4). MoCA is also used as a brief cognitive instrument, which measures impairments in domains of short-term memory, visuospatial abilities, executive functions, verbal fluency, attention, concentration, working memory, language, and orientation (Nasreddine et al., 2005). Only two studies used a comprehensive neuropsychological battery. The study by Narasimhalu and colleagues (2015), used a customized neuropsychological battery which is normed for the population in Singapore; they assessed areas of attention, language, visuomotor speed, and memory (verbal and visual). The study by Kliper and colleagues (2013), used the Mindstreams computerized neuropsychological battery and assessed areas of attention, concentration, executive functions, memory, language, visuospatial skills, abstraction, calculation, and orientation.

The timing of the initial measurement of the outcome ranged from on admission to 6 months post-stroke. Of the 18 studies, 8 included recurrent testing of outcome (44.4%), which ranged from 48 hours after admission to 24 months post-stroke. Further, the number of times the measures were administered ranged from 1 to 6, with a mean of 2.1.

3.3.Rodent Studies

3.3.1. Study and demographic characteristics

Only 3 rodent studies met the inclusion criteria. The participants were mice (n=2) and rats (n=1). Only the study conducted by Gelderblom, and colleagues (2018) reported the age of the rodents (12-week-old mice). All the studies investigated ischemic stroke, by induction of middle cerebral artery occlusion. The studies were conducted in China (n=1), Brazil (n=1), and Germany (n=1).

3.3.2. Inflammatory Markers

The rodent studies included in this review only investigated the pro-inflammatory cytokines. The number of biomarkers measured ranged from 1 to 2. TNF- a was investigated in two of the studies, whereas IL-6, IL-17, and IL-23 were only investigated once. The time of initial blood collection ranged from 24 hour to 14 days after stroke induction. Recurrent blood collection was performed on different rodent groups.

3.3.3. Assessment of Outcome

The measures of outcome were divided into the following classifications: neurological, cognitive, and behavioural. One study included both cognitive and behavioural measures, one study included both neurological and behavioural measures, and one study only used neurological measures. The neurological measures used were Bederson Scale (n=1), which investigates the degree of gross neurological deficit; and a spontaneous motor and behaviour function test (n=1) described in deLima et al., (2017). The cognitive tests used were Morris Water Maze (n=2), which investigates cognitive function in the areas of learning and memory; Passive Avoidance Test (n=1), which measures aversive memory; and Object Recognition Test (n=1) which evaluates recognition memory. The behavioural tests used were the Open-Field test (n=2), a measure of behaviour and general activity (the quality and quantity of activity is measured) (Gould, & Kovacsics, 2009); and Elevated Plus Maze (n=1), a measure of behaviour and anxiety.

The timing of the initial measurement of outcomes ranged from 1 day after stroke induction to 7 days. The measures were re-administered in 2 of the studies, which ranged from 2 days to 14 days after stroke induction. Further, the number of times measures were administered ranged from 1 to 3. The main results of all human and rodent studies are summarized in Table 2.

Table 2. Description of main findings of the studies.

Study	Main Results
Alexandrova (2016)	CRP was found to be an independent predictor of cognitive status at 12 months following stroke, as measured by MMSE.
Bunecicius (2014)	Stroke severity was found to be associated with elevated CRP concentration. Higher CRP concentration was found to be an independent predictor of worse functional outcomes.
deLima (2017)	Higher levels of TNF- a were found to be associated with deficits in spatial, object recognition, and working memory following induced ischemic stroke.
Fassbender (1994)	Higher levels of IL-6 post-stroke predicted poor functional and neurological outcome.
Garcia-Berrocoso (2014)	IL-4 was found to be an independent predictor of decline in functional outcome at 24 h post-stroke.
Gelderblom (2018)	IL-23 was found to be associated with worse functioning on neurological measures following ischemic stroke.
Johansson (2000)	Higher levels of IL-6 were correlated with severity of paresis. And on day 7, higher levels IL-6 were found to be associated with poor performance on MMSE.
Kliper (2013)	Higher levels of CRP were found to be associated with lower performance on cognitive tests, with significantly lower performance in memory.
Kulesh (2018)	Patients with dysexecutive cognitive impairment had a higher concentration of IL-1β, IL-10, IL-6 level in the periphery.

Lee Initial CRP (within first 12 hours) and maximal CRP levels were found to be (2020) significantly higher in group with poor neurological outcome.

Liu A positive correlation between plasma CRP and fatigue scale for motor and (2020) cognitive assessment at 6 months, was found. NIHSS admission scores positively correlated with higher CRP.

Molad (2018) Stroke patients were found to have significantly elevated CRP compared to TIA, even after adjustment of lesion volume. Cognitive scores were significantly better in TIA than Stroke.

Narasimhalu Interleukin-8 levels were found to be independently associated with (2015) cognitive outcome. And IL-12 were found to be an independent predictor of subsequent cognitive decline. No significant association was found between cognitive outcome and IL-6 levels at 3 months.

Oto IL-6 and IL-10 levels were higher in patients with poor outcome. Higher levels (2008) of IL-6 in the periphery were significantly associated with clinical outcome at 1 month, no significant difference between hemorrhagic and ischemic patients was found.

Protti IL-10 was found to be associated with neurological outcome following 72h of (2013) stroke onset

Rothenburg (2010) The levels of IL-6 and CRP protein were higher in stroke patients. Only higher concentrations of serum CRP predicted lower post-stroke global cognition.

Shaheen Higher levels of IL-8 were found to be correlated with poor cognitive (2019) functioning as measured by MMSE.

Smith (2004)	Peak plasma IL-6 concentration correlated significantly with lower performance on mRS at 3 months. Higher levels of IL-6 were associated with poor clinical outcome at 12 months and stroke severity. The higher concentration of CRP was found to be associated with poor outcome.
Swardfager 2014	IL-17 concentrations were associated with poorer cognitive status in patients with depressive symptoms as measured by NIHSS.
Vila, 2000	Levels of TNF-α and IL-6 in the periphery, were found to be higher in patients with lower performance on Canadian stroke scale.
Zhang 2017	A strongly negative correlation was observed between the levels of IL-6 and TNFα in the periphery and anxiety-like behavior and performance on Morris Water Maze.

4. Discussion

The purpose of the current review was to better understand the association between inflammation and neurocognitive outcome post-stroke. The evaluation of 21 studies on the association between inflammatory markers and neurological and cognitive outcome in stroke patients revealed some interesting findings on patient characteristics, inflammatory measures, and outcome measures used. The following paragraphs will discuss the key findings and trends and patterns observed in the results. Overall, this review unveiled two problematic issues pertaining to research on the association between inflammatory markers and neurological and cognitive outcome and revealed some strengths in parallel.

4.2. Characteristics of the stroke populations

The majority of these studies included a small sample size. As such, many were unable to undertake statistical analysis such as multiple regression to allow for prediction of outcomes through use of neuroinflammatory markers. The low sample sizes resulted in heterogeneity between the results and also affected our ability to statistically compare the main findings across the studies. Further, the results of this study suggest a lack of research into diverse stroke subgroups. For one, all the human studies focused on the adult stroke population, the youngest participants in the 18 human articles were 21 years old, and the mean age across studies was 66.31. The lack of research with pediatric and young adult stroke populations represents a notable gap that needs to be addressed. As previous literature suggests, due to brain plasticity in early developmental years, childhood stroke may be associated with severe neurological and cognitive deficits (Peterson, Williams, McDonald, Dlamini, & Westmacott, 2019). Inflammatory markers, which play an important role in the neurological prognosis of stroke in adults may also be implicated in children's stroke prognosis. This represents a significant gap in understanding predictors of neurological and cognitive outcome in pediatric stroke.

Further, the majority of the human and rodent studies (95.2%) investigated the association between inflammatory markers and neurological and cognitive outcome in ischemic stroke populations. This illustrates the lack of research into hemorrhagic stroke population. Given the higher prevalence of ischemic stroke (87%) in United states (Ovbiagele, & NguyenHuynh, 2011), the limited research into hemorrhagic stroke might seem logical. However, previous research suggests that hemorrhagic stroke may be associated with more severe neurological and cognitive deficits resulting in further complications (Runchey, & McGee, 2010). Further, a retrospective study by Shiber and colleagues (2010) found that the rate of hemorrhagic stroke in United States is greater than what is reported. As such, further research into the association between inflammatory markers and outcome after hemorrhagic stroke is warranted.

4.3. Inflammatory Markers

The findings of this review on the measures of inflammation suggest that CRP, IL-6, TNF- a, IL-1b, and IL-10 were the most investigated markers in humans and TNF- a was the most investigated marker in rodent models. This is consistent with neuroinflammation and cognitive decline research in patients with AD. Higher levels of IL-6, TNF- a, and IL-1b in periphery were found to be potential predictors for development of AD (Michaud et al., 2013).

Further, in majority of the human studies, blood was collected within 72 hours of admission. However, there were a few studies which measured the peripheral inflammatory markers between 1 month to 3 months post-stroke and remarkably found significant associations between inflammatory markers and cognitive outcomes. In the study by Narasimhalu and colleagues (2015), peripheral pro-inflammatory cytokines were collected at a median of 47 days after stroke. Their findings suggested that higher levels of IL-8 were independently associated with post-stroke cognitive impairment and higher levels of IL-12 were strong predictor of subsequent cognitive decline. Interestingly, this study did not find significant associations between IL-6, CRP and cognitive impairment. While, it has been suggested previously that delayed blood sampling may not provide accurate results (Chen, et al., 2020), the findings of this study may suggest that different pro-inflammatory markers may peak at distinct times, contributing to post-stroke cognitive decline. Previous research on the level of pro-inflammatory markers suggests that there are higher levels of IL-6 in the periphery of patients, within the first month post-stroke, with a peak at day 4 (Ferrarese et al., 1999). Contrary to IL-6, only a few studies have looked at the role of IL-8 in post-stroke outcome and a few have linked the levels of IL-8 to older age (Ormstad, Aass, Lund-Sørensen, Amthor, & Sandvik, 2011). This warrants further research into the role of IL-8 and, more importantly, the levels of various post-stroke proinflammatory markers at different time intervals.

4.4. Assessment of outcome

The findings on the outcome measures suggest that, to date, progress toward a comprehensive measure of cognition in this field has been limited. From the studies screened only 55% of human studies and 33% of rodent studies used cognitive testing. The most commonly cognitive test used is the Mini Mental State Examination, MMSE (n=7). MMSE is used as a brief cognitive instrument, an 11-question screener which measures cognitive impairment in domains of orientation, registration, attention, calculation, recall, and language (Folstein, Folstein, & McHugh, 1975). The next commonly used cognitive test is the Montreal Cognitive Assessment (MoCA), (n=4). MoCA is also used as a brief cognitive instrument, which measures impairments in domains of short-term memory, visuospatial abilities, executive functions, verbal fluency, attention, concentration, working memory, language, and orientation (Nasreddine et al., 2005). MMSE's usefulness for detecting deficits in the areas of executive functioning, visuospatial, and attentional deficits has been questioned, whereas MoCA has shown more sensitivity in detecting general cognitive disorders, especially in detecting deficits of executive functioning (Gluhm et al., 2013). Nevertheless, both measures are brief cognitive instruments and do not capture all aspects of cognition. A battery of neuropsychological tests assessing many domains of cognitive functioning is the accepted 'gold standard' for assessing cognitive impairments (Cumming, Marshall, & Lazar, 2013).

Only two studies used a comprehensive neuropsychological battery. The study by Narasimhalu and colleagues (2015), used a customized neuropsychological battery which is normed for the population in Singapore, they assessed areas of attention, language, visuomotor speed, and memory (verbal and visual). The study by Kliper and colleagues (2013), used the Mindstreams computerized neuropsychological battery and assessed areas of attention, concentration, executive functions, memory, language, visuospatial skills, abstraction, calculation, and orientation. In addition, of the two studies that investigated cognitive assessment through neuropsychological batteries, only the study by Kliper and colleagues (2013), captured various aspects of cognition. In short, few researchers aimed to gain a comprehensive, multifaceted understanding of cognitive functioning by examining several cognitive areas. This suggests a lack of research into the association between inflammatory markers and different cognitive domains.

Additionally, the result of this review suggests interesting findings regarding the association between inflammatory markers and outcome. A significant heterogeneity in the initial and recurrent outcome assessment time in the 18 human studies can be observed. However, all the studies found significant associations between the level of inflammatory markers in the plasma and serum of stroke patients and the neurological or cognitive impairments. This suggests that inflammatory markers may play a major role in the prognosis of stroke and warrants further research.

The initial measurement of the outcome ranged from on admission to 6 months poststroke. Of the 18 studies, 8 conducted recurrent test of functional outcome (44.4%), which ranged from 48 hours after admission to 24 months post-stroke. Further, the number of times measures were administered ranged from 1 to 6, with a mean of 2.1.

4.5. Limitations

The first limitation of this review is the small number of studies and the limited data available on the association between pro-inflammatory markers, CRP, and post-stroke cognitive and neurological outcome. The number of studies were too small to undertake statistical analyses and perform a metanalysis to determine the strength of the association between each of the inflammatory markers and the neurocognitive outcome. Thus, we were only able to provide descriptive statistics and were unable to undertake statistical analyses such as regression, which would allow us to examine contribution of different variables such as age, stroke onset, time of blood collection, and time of assessment. The small number of studies found was due to selecting only studies that measured pro-inflammatory cytokines and CRP in the periphery. Thus, future reviews could include studies looking at other inflammatory markers (e.g., microglia) and/or studies obtaining inflammatory markers by other means (i.e., obtaining CSF through lumbar puncture), this could result in a higher statistical power.

Second, high heterogeneity was found between the studies. The heterogeneity is due to the differences in methodologies between studies. Several different measures were used to measure neurocognitive outcome. In addition, studies had different timelines for blood collection and measurement of outcome. This also affected our ability to conduct statistical comparisons between the studies. Future research could focus on the latter and identify the association between the time of blood collection and the inflammatory response, post-stroke. Despite these limitations, the findings of this review have been consistent with the limited research that has been done thus far in understanding the role of pro-inflammatory cytokines and CRP protein in neurological and cognitive outcome post-stroke.

4.6. Future Directions

The findings of this review suggest that, to date, progress toward a comprehensive understanding of the link between inflammatory markers and the neurological and cognitive outcome post-stroke is very limited. First, future reviews could further look at other inflammatory markers such as microglia in both periphery and CSF of patients with stroke to further understand the gaps in this area. Additionally, research teams should aim to assess outcome with multiple measures that capture many aspects of cognition. Further, the results of this review suggest a lack of research into diverse groups. Future research should look at this association in various stroke populations; studying this link in pediatric and young adults could help depict a better picture of the role of inflammatory markers in prognosis of stroke in early years of development.

4.7. Review contributions to the literature

To our knowledge, this is the first systematic review investigating the link between inflammatory markers and neurocognitive outcomes post-stroke. In doing so, we were able to identify weaknesses in methodologies of previous research. The results of this review have begun the process of better understanding the role of inflammation in prognosis of stroke. The large gaps elucidated in this review can provide a framework for future research in the field. In particular, understanding the role of inflammation in paediatric and young adult stroke populations and hemorrhagic stroke populations remains largely unknown.

4.8. Clinical Implications

The findings of this review confirm a potential link between pro-inflammatory cytokines and neurocognitive outcome post-stroke. This review summarized the findings on the structural/functional biomarkers of outcome which can be used to predict prognosis post-stroke.

Clinicians should assess the level of inflammatory markers after the onset of stroke, which could potentially aid in prediction of neurocognitive outcomes. Additionally, research into this link could unveil the relative impact and contribution of inflammatory markers on important cognitive and neuropsychological functions. This could further assist clinicians in developing and tailoring interventions such as pharmacotherapy and cognitive rehabilitation, specific to patients' inflammatory response to stroke.

4.9. Conclusion

The findings of this review confirm a potential link between pro-inflammatory cytokines, CRP, and neurocognitive outcome post-stroke. We aimed to include all studies investigating the link between pro-inflammatory cytokines, CRP, and neurocognitive outcome, as such we included studies with delayed blood sampling. This further uncovered the potential role of various pro-inflammatory cytokines at different timelines, post-stroke. However, due to the limited evidence and heterogeneity between the samples, more studies and epidemiological evidence is necessary to determine the strength of these associations.

The current review uncovered two problematic issues. The first problem pertains to the lack of research on diverse stroke populations. Most studies focused on ischemic stroke and investigated neurocognitive outcome in older adult populations. Further, while many of the studies aimed to measure cognitive outcome, their measurement tools were mostly neurological or brief cognitive screeners, overlooking patients' performance in different areas of cognition. In conclusion, current methods used are varied and provide valuable data, but lack ecological validity, exhaustiveness, and generalizability. This paper outlines the existing state of knowledge and provides future directions that will add to our clinical research on prediction of outcomes after stroke.

References

Aktas, O., Ullrich, O., Infante-Duarte, C., Nitsch, R., & Zipp, F. (2007). Neuronal damage in brain inflammation. *Archives of neurology*, *64*(2), 185-189. https://doi:10.1001/archneur.64.2.185

Alexandrova, M. L., & Danovska, M. P. (2016). Cognitive impairment one year after ischemic stroke: predictorsand dynamics of significant determinants. *Turkish journal of medical sciences*, *46*(5), 1366-1373. https://doi:10.3906/sag-1403-29

Amantea, D., Nappi, G., Bernardi, G., Bagetta, G., & Corasaniti, M. T. (2009). Post-ischemic brain damage: pathophysiology and role of inflammatory mediators. *The FEBS journal*, *276*(1), 13-26. https://doi:10.1111/j.1742-4658.2008.06766.x

Argaw, A. T., Zhang, Y., Snyder, B. J., Zhao, M. L., Kopp, N., Lee, S. C., ... & John, G. R. (2006). IL-1β regulates blood-brain barrier permeability via reactivation of the hypoxiaangiogenesis program. *The Journal of Immunology*, *177*(8), 5574-5584. https://doi: 10.4049/jimmunol.177.8.5574

Beamer, N. B., Coull, B. M., Clark, W. M., Hazel, J. S., & Silberger, J. R. (1995). Interleukin-6 and interleukin-1 receptor antagonist in acute stroke. *Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society*, *37*(6), 800-805. **https://doi.org/10.1002/ana.410370614**

Bunevicius, A., Kazlauskas, H., Raskauskiene, N., Janusonis, V., & Bunevicius, R. (2014). Ischemic stroke functional outcomes are independently associated with C-reactive protein concentrations and cognitive outcomes with triiodothyronine concentrations: a pilot study. *Endocrine*, *45*(2), 213-220. https://doi.org/10.1007/s12020-013-9958-2

Cárdenas, J. F., Rho, J. M., & Kirton, A. (2011). Pediatric stroke. *Child's Nervous System*, *27*(9), 1375–1390. https://doi:10.1007/s00381-010-1366-9

Chen, Y., Pu, J., Liu, Y., Tian, L., Chen, X., Gui, S., ... & Xie, P. (2020). Pro-inflammatory cytokines are associated with the development of post-stroke depression in the acute stage of stroke: A meta-analysis. *Topics in stroke rehabilitation*, *27*(8), 620-629. https://doi.org/10.1080/10749357.2020.1755813

Clark, W. M., Warach, S. J., Pettigrew, L. C., Gammans, R. E., Sabounjian, L. A., & Citicoline Stroke Study Group. (1997). A randomized dose-response trial of citicoline in acute ischemic stroke patients. *Neurology*, *49*(3), 671-678. https://doi.org/10.1212/WNL.49.3.671

Cumming, T. B., Marshall, R. S., & Lazar, R. M. (2013). Stroke, cognitive deficits, and rehabilitation: still an incomplete picture. *International Journal of stroke*, *8*(1), 38-45. https://doi.org/1010.1111/j.1747-4949.2012.00972.x

Dalva, M. B., McClelland, A. C., & Kayser, M. S. (2007). Cell adhesion molecules: signalling functions at the synapse. *Nature Reviews Neuroscience*, *8*(3), 206-220. https://doi.org/10.1038/nrn2075

de Lima, N. M. R., Ferreira, E. D. O., Fernandes, M. Y. S., Lima, F. A. V., Neves, K. R. T., do Carmo, M. R. S., & de Andrade, G. M. (2017). Neuroinflammatory response to experimental stroke is inhibited by boldine. *Behavioural pharmacology*, *28*(2), 223-237. https://doi.org/10.1097/FBP.0000000000000265

Dinarello, C. A. (2000). Proinflammatory cytokines. *Chest*, *118*(2), 503-508. https://doi.org/10.1378/chest.118.2.503

Fassbender, K., Rossol, S., Kammer, T., Daffertshofer, M., Wirth, S., Dollman, M., & Hennerici, M. (1994). Proinflammatory cytokines in serum of patients with acute cerebral ischemia: kinetics of secretion and relation to the extent of brain damage and outcome of disease. *Journal of the neurological sciences*, *122*(2), 135-139. https://doi.org/10.1016/0022-510X(94)90289-5

Fernández-López, D., Natarajan, N., Ashwal, S., & Vexler, Z. S. (2014). Mechanisms of perinatal arterial ischemic stroke. *Journal of Cerebral Blood Flow & Metabolism*, *34*(6), 921-932. https://doi.org/10.1038/jcbfm.2014.41

Ferrarese, C., Mascarucci, P., Zoia, C., Cavarretta, R., Frigo, M., Begni, B., ... & De Simoni, M. G. (1999). Increased cytokine release from peripheral blood cells after acute stroke. *Journal of Cerebral Blood Flow & Metabolism*, *19*(9), 1004-1009. https://doi.org/10.1097/00004647-199909000-00008

Festa, J. R., Lazar, R. M., & Marshall, R. S. (2008). Ischemic stroke and aphasic disorders. In J. E. Morgan & J. H. Ricker (Eds.), Textbook of clinical neuropsychology (pp. 363–383). New York, NY: Taylor & Francis Group.

Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. *Journal of psychiatric research*, *12*(3), 189-198.

Förster, R., Davalos-Misslitz, A. C., & Rot, A. (2008). CCR7 and its ligands: balancing immunity and tolerance. *Nature Reviews Immunology*, *8*(5), 362-371. https://doi.org/10.1038/nri2297

Fuentes, A., Deotto, A., Desrocher, M., deVeber, G., & Westmacott, R. (2016). Determinants of cognitive outcomes of perinatal and childhood stroke: A review. *Child Neuropsychology*, *22*(1), 1-38. https://doi.org/10.1080/09297049.2014.969694 García-Berrocoso, T., Giralt, D., Bustamante, A., Llombart, V., Rubiera, M., Penalba, A., ... & Montaner, J. (2014). Role of beta-defensin 2 and interleukin-4 receptor as stroke outcome biomarkers. *Journal of neurochemistry*, *129*(3), 463-472. https://doi.org/10.1111/jnc.12649

Gelderblom, M., Gallizioli, M., Ludewig, P., Thom, V., Arunachalam, P., Rissiek, B., ... & Magnus, T. (2018). IL-23 (interleukin-23)–producing conventional dendritic cells control the detrimental IL-17 (interleukin-17) response in stroke. *Stroke*, *49*(1), 155-164. https://doi.org/10.1161/STROKEAHA.117.019101

Gould, T. D., Dao, D. T., & Kovacsics, C. E. (2009). The open field test. *Mood and anxiety related phenotypes in mice*, 1-20.

Greenham, M., Hearps, S., Gomes, A., Rinehart, N., Gonzalez, L., Gordon, A., ... & Anderson, V. (2015). Environmental contributions to social and mental health outcomes following pediatric stroke. *Developmental neuropsychology*, *40*(6), 348-362. https://doi.org/10.1080/87565641.2015.1095191

Jaillard, A., Grand, S., Le Bas, J. F., & Hommel, M. (2010). Predicting cognitive dysfunctioning in nondemented patients early after stroke. *Cerebrovascular Diseases*, *29*(5), 415-423. https://doi.org/10.1159/000289344

Jin, R., Yang, G., & Li, G. (2010). Inflammatory mechanisms in ischemic stroke: role of inflammatory cells. *Journal of leukocyte biology*, *87*(5), 779-789. https://doi.org/10.1189/jlb.1109766

Johansson, Å., Ahren, B., Näsman, B., Carlström, K., & Olsson, T. (2000). Cortisol axis abnormalities early after stroke–relationships to cytokines and leptin. *Journal of internal medicine*, *247*(2), 179-187. https://doi.org/10.1046/j.1365-2796.2000.00600.x

Kliper, E., Bashat, D. B., Bornstein, N. M., Shenhar-Tsarfaty, S., Hallevi, H., Auriel, E., ... & Assayag, E. B. (2013). Cognitive decline after stroke: relation to inflammatory biomarkers and hippocampal volume. *Stroke*, *44*(5), 1433-1435. https://doi.org/10.1161/STROKEAHA.111.000536

Kriz, J. (2006). Inflammation in ischemic brain injury: timing is important. *Critical reviews™ in Neurobiology*, *18*(1-2). https://doi.org/10.1615/CritRevNeurobiol.v18.i1-2.150

Krueger, H., Koot, J., Hall, R. E., O'Callaghan, C., Bayley, M., & Corbett, D. (2015). Prevalence of individuals experiencing the effects of stroke in Canada: trends and projections. *Stroke*, *46*(8), 2226-2231. https://doi.org/10.1161/STROKEAHA.115.009616

Kulesh, A., Drobakha, V., Kuklina, E., Nekrasova, I., & Shestakov, V. (2018). Cytokine response, tract-specific fractional anisotropy, and brain morphometry in post-stroke cognitive impairment. *Journal of Stroke and Cerebrovascular Diseases*, *27*(7), 17521759. https://doi.org/10.1016/j.jstrokecerebrovasdis.2018.02.004

Kurlowicz, L., & Wallace, M. (1999). The mini-mental state examination (MMSE).

Lansing, A. E., Max, J. E., Delis, D. C., Fox, P. T., Lancaster, J., Manes, F. F., & Schatz, A. (2004). Verbal learning and memory after childhood stroke. *Journal of the International Neuropsychological Society*, *10*(5), 742-752. https://doi.org/10.10170S1355617704105122

Lee, S., Kim, Y. O., & Ryu, J. A. (2020). Clinical usefulness of early serial measurements of Creactive protein as outcome predictors in patients with subarachnoid hemorrhage. *BMC neurology*, *20*, 1-10. https://doi.org/10.1186/s12883-020-01687-3

Lindenstrøm, E., Boysen, G., Christiansen, L. W., & Nielsen, P. W. (1991). Reliability of Scandinavian neurological stroke scale. *Cerebrovascular Diseases*, *1*(2), 103-107. https://doi.org/10.1159/000108825

Liu, Xinjing, Beng Wang, Xiao Wang, Mengke Tian, Xin Wang, and Yan Zhang. "Elevated plasma high-sensitivity C-reactive protein at admission predicts the occurrence of poststroke fatigue at 6 months after ischaemic stroke." *European Journal of Neurology* 27, no. 10 (2020): 2022-2030. https://doi.org/10.1111/ene.14430

Max, J. E., Mathews, K., Lansing, A. E., Robertson, B. A., Fox, P. T., Lancaster, J. L., … Smith, J. (2002). Psychiatric disorders after childhood stroke. *Journal of the American Academy of Child & Adolescent Psychiatry*, *41*(5), 555–562. https://doi.org/10.1097/00004583200205000-00013

Michaud, M., Balardy, L., Moulis, G., Gaudin, C., Peyrot, C., Vellas, B., ... & Nourhashemi, F. (2013). Proinflammatory cytokines, aging, and age-related diseases. Journal of the American Medical Directors Association, 14(12), 877-882. https://doi.org/10.1016/j.jamda.2013.05.009

Moher, D., Liberati, A., Tetzlaff, J., Altman, D., & The PRISMA Group. (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement, *6*(7), e1000097. https://doi.org/10.1371/journal.pmed.1000097

Molad, J., Ben-Assayag, E., Korczyn, A. D., Kliper, E., Bornstein, N. M., Hallevi, H., & Auriel, E. (2018). Clinical and radiological determinants of transient symptoms associated with infarction (TSI). *Journal of the neurological sciences*, *390*, 195-199.

https://doi.org/10.1016/j.jns.2018.04.038

Moser, B., Wolf, M., Walz, A., & Loetscher, P. (2004). Chemokines: multiple levels of leukocyte migration control☆. *Trends in immunology*, *25*(2), 75-84. https://doi.org/10.1016/j.it.2003.12.005

Napoli, I., Kierdorf, K., & Neumann, H. (2009). Microglial precursors derived from mouse embryonic stem cells. *Glia*, *57*(15), 1660-1671. https://doi.org/10.1002/glia.20878

Narasimhalu, K., Lee, J., Leong, Y. L., Ma, L., De Silva, D. A., Wong, M. C., ... & Chen, C. (2015). Inflammatory markers and their association with post stroke cognitive decline. *International Journal of Stroke*, *10*(4), 513-518. https://doi.org/10.1111/ijs.12001

Nasreddine, Z. S., Phillips, N. A., Bédirian, V., Charbonneau, S., Whitehead, V., Collin, I., ... & Chertkow, H. (2005). The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *Journal of the American Geriatrics Society*, *53*(4), 695699. https://doi.org/10.1111/j.1532-5415.2005.53221.x

Nguyen, V. A., Carey, L. M., Giummarra, L., Faou, P., Cooke, I., Howells, D. W., ... & Crewther, S. G. (2016). A pathway proteomic profile of ischemic stroke survivors reveals innate immune dysfunction in association with mild symptoms of depression–a pilot study. *Frontiers in neurology*, *7*, 85. https://doi.org/10.3389/fneur.2016.00085

Nys, G. M. S., Van Zandvoort, M. J. E., De Kort, P. L. M., Jansen, B. P. W., De Haan, E. H. F., & Kappelle, L. J. (2007). Cognitive disorders in acute stroke: prevalence and clinical determinants. *Cerebrovascular Diseases*, *23*(5-6), 408-416. https://doi.org/10.1159/000101464

O'Keeffe, F., Liégeois, F., Eve, M., Ganesan, V., King, J., & Murphy, T. (2014). Neuropsychological and neurobehavioral outcome following childhood arterial ischemic stroke: attention deficits, emotional dysregulation, and executive dysfunction. *Child Neuropsychology*, *20*(5), 557-582. https://doi.org/10.1080/09297049.2013.832740

Ormstad, H., Aass, H. C. D., Lund-Sørensen, N., Amthor, K. F., & Sandvik, L. (2011). Serum levels of cytokines and C-reactive protein in acute ischemic stroke patients, and their relationship to stroke lateralization, type, and infarct volume. *Journal of neurology*, *258*(4), 677-685. https://doi.org/10.1007/s00415-011-6006-0

Ortiz, G. A., & L. Sacco, R. (2014). National institutes of health stroke scale (nihss). *Wiley StatsRef: statistics reference online*. https://doi.org/10.1002/9781118445112.stat06823

Oto, J., Suzue, A., Inui, D., Fukuta, Y., Hosotsubo, K., Torii, M., ... & Nishimura, M. (2008). Plasma proinflammatory and anti-inflammatory cytokine and catecholamine concentrations as predictors of neurological outcome in acute stroke patients. *Journal of anesthesia*, *22*(3), 207-212. https://doi.org/10.1007/s00540-008-0639-x

Ovbiagele, B., & Nguyen-Huynh, M. N. (2011). Stroke epidemiology: advancing our understanding of disease mechanism and therapy. *Neurotherapeutics*, *8*(3), 319. https://doi.org/10.1007/s13311-011-0053-1

Peterson, R. K., Williams, T. S., McDonald, K. P., Dlamini, N., & Westmacott, R. (2019). Cognitive and Academic Outcomes Following Childhood Cortical Stroke. *Journal of child neurology*, *34*(14), 897-906. https://doi.org/10.1177/0883073819866609

Phani, S., Loike, J. D., & Przedborski, S. (2012). Neurodegeneration and inflammation in Parkinson's disease. *Parkinsonism & related disorders*, *18*, S207-S209. https://doi.org/10.1016/S1353-8020(11)70064-5

Planton, M., Peiffer, S., Albucher, J. F., Barbeau, E. J., Tardy, J., Pastor, J., ... & Demonet, J. F. (2012). Neuropsychological outcome after a first symptomatic ischaemic stroke with 'good recovery'. *European Journal of Neurology*, *19*(2), 212-219. https://doi.org/10.1111/j.1468-1331.2011.03450.x

Protti, G. G., Gagliardi, R. J., Forte, W. C., & Sprovieri, S. R. S. (2013). Interleukin-10 may protect against progressing injury during the acute phase of ischemic stroke. *Arquivos de neuro-psiquiatria*, *71*(11), 846-851. https://doi.org/10.1590/0004-282X20130168

Roach, E. S., Golomb, M. R., Adams, R., Biller, J., Daniels, S., deVeber, G., … Smith, E. R. (2008). Management of Stroke in Infants and Children. *Stroke*, *39*(9), 2644–2691. https://doi.org/10.1161/STROKEAHA.108.189696

Rothenburg, L. S., Herrmann, N., Swardfager, W., Black, S. E., Tennen, G., Kiss, A., ... & Lanctôt, K. L. (2010). The relationship between inflammatory markers and post stroke cognitive impairment. *Journal of geriatric psychiatry and neurology*, *23*(3), 199-205. https://doi.org/10.1177/0891988710373598

Rothenburg, L. S., Herrmann, N., Swardfager, W., Black, S. E., Tennen, G., Kiss, A., ... & Lanctôt, K. L. (2010). The relationship between inflammatory markers and post stroke cognitive impairment. *Journal of geriatric psychiatry and neurology*, *23*(3), 199-205. https://doi.org/10.1177/10.1177/0891988710373598

Runchey, S., & McGee, S. (2010). Does this patient have a hemorrhagic stroke?: clinical findings distinguishing hemorrhagic stroke from ischemic stroke. *Jama*, *303*(22), 22802286. https://doi.org/10.1001/jama.2010.754

Sacco, R. L., Kasner, S. E., Broderick, J. P., Caplan, L. R., Connors, J. J., Culebras, A., ... & Vinters, H. V. (2013). An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*, *44*(7), 2064-2089. https://doi.org/10.1161/STR.0b013e318296aeca

Sachdev, P. S., Brodaty, H., Valenzuela, M. J., Lorentz, L., Looi, J. C. L., Wen, W., & Zagami, A. S. (2004). The neuropsychological profile of vascular cognitive impairment in stroke and TIA patients. *Neurology*, *62*(6), 912-919. https://doi.org/10.1212/01.WNL.0000115108.65264.4B

Shaheen, H. A., Daker, L. I., Abbass, M. M., & Abd El Fattah, A. A. (2019). Post-stroke executive dysfunction and verbal fluency negatively correlated to IL8. *The Egyptian Journal of Neurology, Psychiatry and Neurosurgery*, *55*(1), 1-8. https://doi.org/10.1186/s41983-019-0090-y

Sharp, F. R., & Jickling, G. C. (2014). Modeling immunity and inflammation in stroke: differences between rodents and humans?. *Stroke*, *45*(9), e179-e180. https://doi.org/10.1161/STROKEAHA.114.005639

Shiber, J. R., Fontane, E., & Adewale, A. (2010). Stroke registry: hemorrhagic vs ischemic strokes. *The American journal of emergency medicine*, *28*(3), 331-333. https://doi.org/10.1016/j.ajem.2008.10.026

Sierra, C., Coca, A., & Schiffrin, E. L. (2011). Vascular mechanisms in the pathogenesis of stroke. *Current hypertension reports*, *13*(3), 200-207. https://doi.org/10.1007/s11906011-0195-x

Smith, C. J., Emsley, H. C., Gavin, C. M., Georgiou, R. F., Vail, A., Barberan, E. M., ... & Tyrrell, P. J. (2004). Erratum to: Peak plasma interleukin-6 and other peripheral markers of inflammation in the first week of ischaemic stroke correlate with brain infarct volume, stroke severity and long-term outcome. *BMC neurology*, *4*(1), 5.

Sproston, N. R., & Ashworth, J. J. (2018). Role of C-reactive protein at sites of inflammation and infection. *Frontiers in immunology*, *9*, 754. https://doi.org/10.3389/fimmu.2018.00754

Srikanth, V. K., Thrift, A. G., Saling, M. M., Anderson, J. F., Dewey, H. M., Macdonell, R. A., & Donnan, G. A. (2003). Increased risk of cognitive impairment 3 months after mild to moderate first-ever stroke: a Community-Based Prospective Study of Nonaphasic English-Speaking Survivors. *Stroke*, *34*(5), 1136-1143. https://doi.org/10.1161/01.STR.0000069161.35736.39

Streit, W. J., & Xue, Q. S. (2009). Life and death of microglia. *Journal of neuroimmune pharmacology*, *4*(4), 371. https://doi.org/10.1007/s11481-009-9163-5

Swardfager, W., Herrmann, N., Andreazza, A. C., Swartz, R. H., Khan, M. M., Black, S. E., & Lanctôt, K. L. (2014). Poststroke neuropsychiatric symptoms: relationships with IL-17 and oxidative stress. *BioMed Research International*, *2014*. https://doi.org/10.1155/2014/245210

Tang, E. Y., Price, C., Stephan, B., Robinson, L., & Exley, C. (2020). Impact of Memory Problems Post-stroke on Patients and Their Family Carers: A Qualitative Study. *Frontiers in medicine*, *7*, 267. https://doi.org/10.3389/fmed.2020.00267

Tarkowski, E., Rosengren, L., Blomstrand, C., Wikkelsö, C., Jensen, C., Ekholm, S., & Tarkowski, A. (1995). Early intrathecal production of interleukin-6 predicts the size of brain lesion in stroke. *Stroke*, *26*(8), 1393-1398. https://doi.org/10.1161/01.STR.26.8.1393

Tatemichi, T. K., Desmond, D. W., Stern, Y., Paik, M., Sano, M., & Bagiella, E. (1994). Cognitive impairment after stroke: frequency, patterns, and relationship to functional abilities. *Journal of Neurology, Neurosurgery & Psychiatry*, *57*(2), 202-207. http://dx.doi.org/10.1136/jnnp.57.2.202

Vila, N., Castillo, J., Dávalos, A., & Chamorro, A. (2000). Proinflammatory cytokines and early neurological worsening in ischemic stroke. *Stroke*, *31*(10), 2325-2329. https://doi.org/10.1161/01.STR.31.10.2325

Viscogliosi, C., Belleville, S., Desrosiers, J., Caron, C. D., Ska, B., & BRAD group. (2011). Participation after a stroke: Changes over time as a function of cognitive deficits. *Archives of Gerontology and Geriatrics*, *52*(3), 336-343. https://doi.org/10.1016/j.archger.2010.04.020

Von Elm, E., Altman, D. G., Egger, M., Pocock, S. J., Gøtzsche, P. C., & Vandenbroucke, J. P. (2007). The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Annals of internal medicine*, *147*(8), 573-577. https://doi.org/10.7326/0003-4819-147-8-200710160-00010

Wang, B., & Jin, K. (2015). Current perspectives on the link between neuroinflammation and neurogenesis. *Metabolic brain disease*, *30*(2), 355-365. https://doi.org/10.1007/s11011014-9523-6

Wardlaw, J. M., Doubal, F., Armitage, P., Chappell, F., Carpenter, T., Muñoz Maniega, S., ... & Dhillon, B. (2009). Lacunar stroke is associated with diffuse blood–brain barrier dysfunction. *Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society*, *65*(2), 194-202. https://doi.org/10.1002/ana.21549

Westmacott, R., McDonald, K. P., deVeber, G., MacGregor, D., Moharir, M., Dlamini, N., ... & Williams, T. S. (2018a). Neurocognitive outcomes in children with unilateral basal ganglia arterial ischemic stroke and secondary hemidystonia. *Child Neuropsychology*, *24*(7), 923-937. https://doi.org/10.1080/09297049.2017.1353073

Westmacott, R., McDonald, K. P., Roberts, S. D., deVeber, G., MacGregor, D., Moharir, M., ... & Williams, T. S. (2018b). Predictors of cognitive and academic outcome following childhood subcortical stroke. *Developmental neuropsychology*, *43*(8), 708-728. https://doi.org/10.1080/87565641.2018.1522538

Wilson, J. L., Hareendran, A., Hendry, A., Potter, J., Bone, I., & Muir, K. W. (2005). Reliability of the modified Rankin Scale across multiple raters: benefits of a structured interview. *Stroke*, *36*(4), 777-781. https://doi.org/10.1161/01.STR.0000157596.13234.95

Ziegler-Heitbrock, L. (2015). Blood monocytes and their subsets: established features and open questions. *Frontiers in immunology*, *6*, 423.https://doi.org/10.3389/fimmu.2015.00423

Appendix A

Description of Key terms

Key term	Description
Adhesion molecules	Adhesion molecules are molecules localized at synaptic sites in neural axons and dendrites. They have the role of facilitating pre and post synaptic specialization. They also play a role in leukocyte migration; they are leukocyte attractants (Dalva, McClelland, & Kayser, 2007).
Chemokines	Inflammatory chemokines play an important role in recruiting of effector leukocytes in inflammation, injury, and infection. (Moser, Wolf, Walz, & Loetscher, 2004).
C-reactive protein (CRP)	CRP is a peripheral, acute inflammatory marker, primarily synthesized in liver. It plays an important role in acute phase response to inflammation (Sproston, & Ashworth, 2018).
Hemorrhagic Stroke	Hemorrhagic stroke is caused by ruptured blood vessels. Hypertensive small vessel disease is the most common underlying mechanism; causing lipohyalinosis of the small arteries (Sierra, Coca, & Schiffrin, 2011).
Ischemic stroke	Ischemic stroke is defined as the interruption of blood flow which deprives the affected brain regions of oxygen and nutrients which leading to permanent damage of brain tissue, called infarction (Festa, Lazar, & Marshall, 2008).
Leukocytes	Leukocytes are more commonly called white blood cells. They play a role in counteracting foreign substances. Leukocytes and chemokines are controllers of migration in the instance of an injury (Moser, Wolf, Walz, & Loetscher, 2004).

Microglia	Microglia become particularly active after injury, depending on the nature or severity of
	the injury. They play a very important and central role in acute neuroinflammation by facilitating the release of pro-inflammatory cytokines (Streit & Xue, 2009).
Monocytes	Blood monocytes are bone marrow-derived leukocytes that are characterized by the ability to produce cytokines (Ziegler-Heitbrock, 2015).
Pro-inflammatory cytokines	Cytokines are regulators of host response to infection. Pro-inflammatory molecules are part of the body's immune response. However, they can have an adverse effect on recovery. High levels of pro-inflammatory cytokines can produce fever, inflammation, tissue destruction, and neurodegeneration (Dinarello, 2000).