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Fluid biomarkers of the neurovascular unit in cerebrovascular disease and vascular cognitive disorders: A systematic review and meta-analysis

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ABSTRACT

Background: The disruption of the neurovascular unit (NVU), which maintains the integrity of the blood brain barrier (BBB), has been identified as a critical mechanism in the development of cerebrovascular and neurodegenerative disorders. However, the understanding of the pathophysiological mechanisms linking NVU dysfunction to the disorders is incomplete, and reliable blood biomarkers to measure NVU dysfunction are yet to be established. This systematic review and meta-analysis aimed to identify biomarkers associated with BBB dysfunction in large vessel disease, small vessel disease (SVD) and vascular cognitive disorders (VCD).

Methods: A literature search was conducted in PubMed, EMBASE, Scopus and PsychINFO to identify blood biomarkers related to dysfunction of the NVU in disorders with vascular pathologies published until 20 November 2023. Studies that assayed one or more specific markers in human serum or plasma were included. Quality of studies was assessed using the Newcastle-Ottawa Quality Assessment Scale. Effects were pooled and methodological heterogeneity examined using the random effects model.

Results: A total of 112 studies were included in this review. Where study numbers allowed, biomarkers were analysed using random effect meta-analysis for VCD (1 biomarker; 5 studies) and cerebrovascular disorders, including stroke and SVD (9 biomarkers; 29 studies) while all remaining biomarkers ($n = 17$ biomarkers; 78 studies) were examined through qualitative analysis. Results of the meta-analysis revealed that cerebrospinal fluid/serum albumin quotient (Q-Alb) reliably differentiates VCD patients from healthy controls (MD = 2.77; 95 % CI = 1.97–3.57; $p < 0.0001$) while commonly measured biomarkers of endothelial dysfunction (VEGF, VCAM-1, ICAM-1, vWF and E-selectin) and neuronal injury (NfL) were significantly elevated in vascular pathologies. A qualitative assessment of non-meta-analysed biomarkers revealed NSE, NfL, vWF, ICAM-1, VCAM-1, lipocalin-2, MMP-2 and MMP-9 levels to be upregulated in VCD, although these findings were not consistently replicated.

Conclusions: This review identifies several promising biomarkers of NVU dysfunction which require further validation. A panel of biomarkers representing multiple pathophysiological pathways may offer greater discriminative power in distinguishing possible disease mechanisms of VCD.

Introduction

Vascular cognitive disorders (VCD), also referred to as vascular cognitive impairment (VCI) or sometimes vascular cognitive impairment and dementia (VCID), are the second most common cause of dementia after Alzheimer's disease (AD), affecting at least 7.2 million people worldwide [1]. VCD represent a heterogeneous group of disorders with multiple pathogenetic mechanisms, with the fundamental characteristic attributable to brain injury arising from cerebrovascular disorders that affect the small and large vessels of the brain [2]. One important

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mechanism is the breakdown of the blood brain barrier (BBB) owing to the disruption of the neurovascular unit (NVU), a mechanism shared between VCD and neurodegenerative disorders [3].

This paper focuses on the NVU as the basic structural and functional subunit of the BBB. At the cellular level, the NVU is the building block of the brain parenchyma and comprises a basement membrane, endothelial cells, pericytes, vascular smooth muscle cells, glial cells (astrocytes, microglia, oligodendrocytes) and neurons [3]. The NVU is responsible for the regulation of cerebral blood flow, protection of the brain from blood borne toxins, and delivery of nutrients to, and clearance of waste products from, the brain [4]. Dysfunction of the NVU has been attributed to the degradation of endothelial cells, pericytes and loss of tight junction proteins [4]. Even though some BBB breakdown occurs with normal ageing [5], it has been found to be more pronounced in individuals with mild cognitive impairment, suggesting its association with early cognitive impairment [6]. Disruption of the NVU occurs in small and large cerebral vessel disease, following stroke [7], and in neurodegenerative disease [2], making it a key area of interest in the pathogenesis of VCD and neurodegenerative dementias.

Activation or disruption of the NVU induces release of molecules, such as soluble platelet derived growth factor receptor β (sPDGFRβ) [8], occludin and claudin-5 [9] into the circulation, characteristic for specific cellular components [10]. The detection of these molecules as potential biomarkers in both CSF and blood could therefore serve as an indicator of the integrity of the NVU, and thereby the maintenance of the blood-brain barrier (BBB), cerebral homeostasis and cerebral blood flow [11]. While there are a number of reviews on biomarkers associated with VCD in general [2,12-14], none has solely categorised them as activated components of the NVU. The focal points of this review, aim to address gaps in the literature, and include; ***(1)*** a focus on blood and other fluid biomarkers, since the literature has mainly been on CSF, ***(2)*** a focus on blood testing would provide for an economical, minimally invasive, and accessible alternative that would allow clinicians to screen for VCD readily, ***(3)*** to date there has been no meta-analysis of NVU biomarkers in blood. This review provides an updated summary of existing blood biomarkers related to NVU pathology in large vessel disease, SVD and VCD. Though the primary focus of the biomarkers was to assist with diagnosis and mechanistic understanding of VCD, data were incorporated from the stroke literature as stroke is closely related to VCD and has been the subject of significant investigation in this regard. We examined all published literature on blood biomarkers of the NVU and performed meta-analyses on those with three or more published studies with relevant data format.

Methods

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Supplementary Table S1) [15]. A protocol was registered with PROSPERO (ID: CRD42023389103).

Database search strategy

A systematic search was conducted to identify blood-based biomarkers along the spectrum of VCD and cerebrovascular pathologies. The search was conducted in PubMed, Scopus, Embase (via Ovid) and PsychINFO (via ProQuest) for studies from inception until 20 November 2023. Search terms included combinations of the Medical Subject Headings and keywords for three themes: VCD, NVU and blood biomarkers (Supplementary Table S2). No restriction for publication period was set. Filters were applied for language and to exclude non-journal publications. Two authors (G.K.H. and T.J.) independently performed a search of the terms and evaluated all titles and abstracts using the prespecified eligibility criteria (see section below). Removal of duplicates and screening was performed via Rayyan software [16]. During the screening phase, bibliography lists of nine review articles were checked for additional primary studies using the snowball sampling design. In the event of any disagreement, a third author (S.H.) was consulted to reach a consensus.

Inclusion and exclusion criteria

Eligible studies met the following inclusion criteria: (1) conducted in individuals with vascular neurocognitive disorders (VCD) or cerebrovascular disorders (large vessel stroke or small vessel disease); (2) conducted in humans; (3) assayed one or more specific markers in serum or plasma; (4) assessed a biomarker relevant to a component of the NVU (extracellular matrix, tight junctions, pericytes, neuroglia and endothelial cells); (5) English language only and (6) original, primary manuscripts. In addition to the mentioned inclusion criteria, studies shortlisted for the meta-analysis had to have a case-control study design and include a healthy control group.

Studies were excluded from both the meta-analysis and systematic review if they belonged to any of the following categories: (1) animal studies; (2) non-cerebrovascular based studies, (3) studies involving vascular surgery or aneurysms, (4) studies conducted on other neurological diseases that may cause cognitive impairment such as Alzheimer's disease, Parkinson's disease, encephalopathy, traumatic brain injury and depression, (5) studies on biomarkers not related to a NVU component, (6) studies which only analysed biomarkers in tissues other than blood or CSF (e.g. Urine and saliva); and (7) other publication types (reviews, editorials, comments etc.). Full text of shortlisted studies was obtained for further review and data extraction.

Data extraction

Data extraction was performed by two authors (G.K.H. and T.J.). Data indices included the primary author's name, year of publication, mean age of subjects, sample size for cases and/or controls, number (or %) of female subjects, specimen type (serum or plasma), method of measurement, name of study or country or place of recruitment (where applicable), assessed blood biomarker(s), association measure and outcomes pertaining to the biomarker of interest. In case of missing or unclear data, authors were contacted by email. Meta-analyses were performed when data (expressed as mean ± SD) were available for a minimum of three studies per biomarker to obtain reliable estimates. Studies without a healthy control group were excluded from the meta-analysis. Extracted values for stroke case groups were from baseline scores and if not provided, values close to the onset of stroke were extracted.

Qualitative analysis

To perform a comprehensive review of the topic, shortlisted studies that met the general inclusion criteria for the review but not the meta-analysis were summarised qualitatively. This was the case for most studies on VCD as there were insufficient articles on biomarker measurements related to the NVU. Studies on cerebrovascular disorders lacking the statistical reporting values of interest, healthy controls or if they were present in a count of less than 3 for a biomarker, were also summarised qualitatively.

Quantitative analysis

The test for skewness was performed using the method described in Wan et al. [17] as implemented in the R package 'metamedian' for studies reporting median, first and third quartiles. Means and SDs were estimated based on quartiles, minimum, maximum and sample sizes using two methods [17] (1) under the normality assumption for the biomarkers by Wan et al. [17,18] (2) under non-normal distributions for the biomarkers by McGrath et al. [19], as implemented in the R package 'estmeansd'.

Meta-analysis was performed using raw mean difference (MD) between cases and controls. Due to differences in biomarker measures and large variability across studies, studies were removed from the meta-analysis if their 95 % confidence intervals (CI) do not overlap with the CI of the pooled effect size (outliers). Random effects model was selected to address known methodological and analytical heterogeneity. Statistical heterogeneity was assessed using the I^2 statistic (values of 25 %, 50 % and 75 % indicate small, moderate and large heterogeneity, respectively).

Considering the large variations in estimated and reported means, SDs and MDs within each biomarker, the meta-analysis was repeated using the unit-free standardised mean difference (SMD), effect size measure and sensitivity of statistical inference on the pooled results were assessed.

Publication bias within the meta-analysed studies was examined using the Egger's regression test for funnel plot asymmetry as implemented in R package 'metafor'. The effect size calculations, meta-analyses and forest plots were done using the appropriate functions in the R packages 'metafor' [20] and 'dmetar' [21].

Quality evaluation

The quality of studies was assessed using a modified version of the Newcastle-Ottawa Quality Assessment Scale (NOS) (Supplementary Table S6–7). The adaptation of questions was validated by consultation with senior authors (P.S. and A.P.). Two authors (G.K.H. and T.J.) independently appraised three aspects of the scale: selection of study groups, comparability of the groups and the outcome of interest. The maximum number of points awarded to each section was three, one and two for case-control studies respectively and two for each section for all other study types. Final NOS score for each study ranged from 0 (lowest quality) to 6 (highest quality). Studies with a score of 0–2 were identified as low quality, 3–4 as medium quality and those between 5 and 6 considered to be of high quality. Discrepancies in the quality assessment were resolved by consensus.

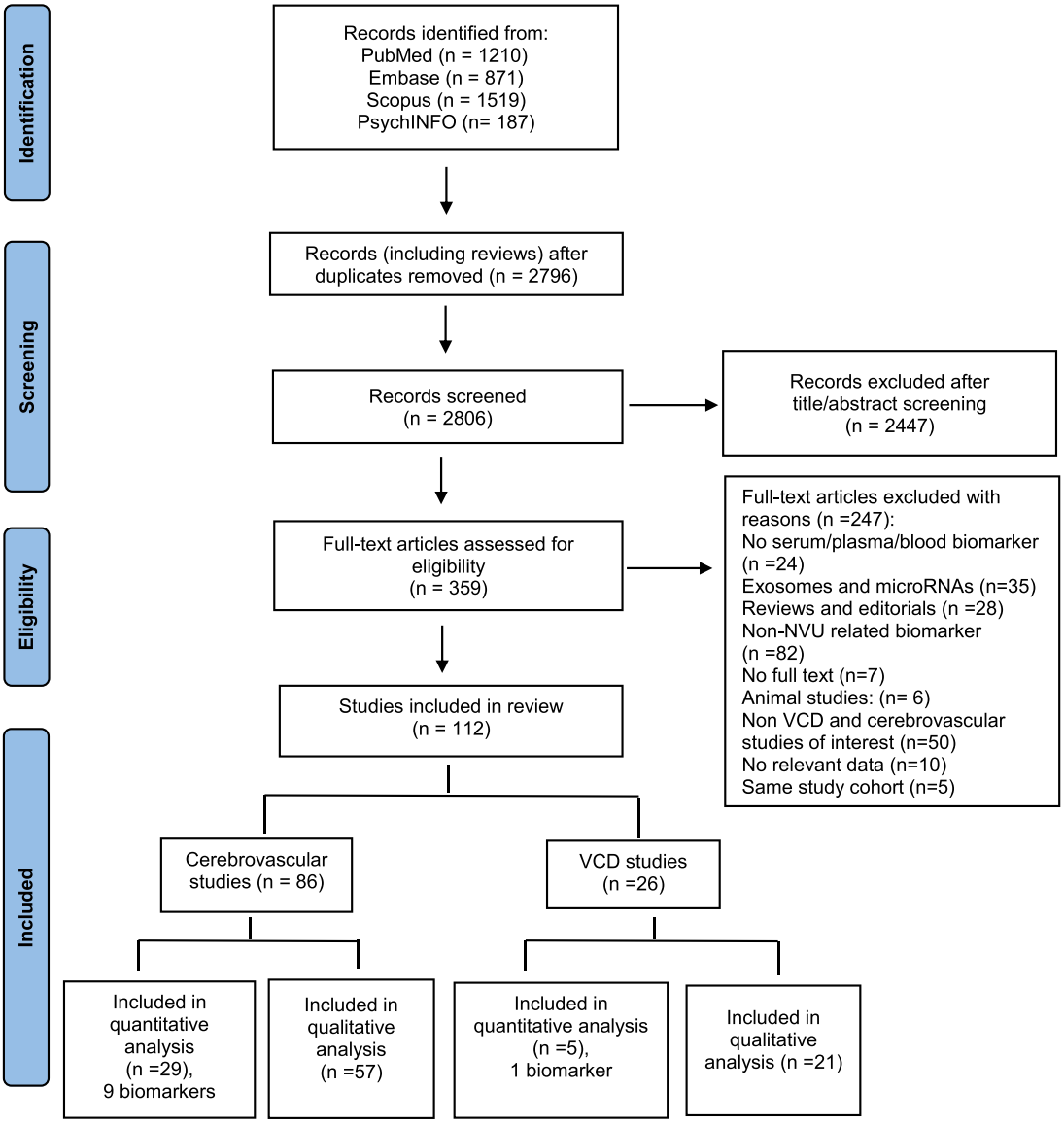

Fig. 1. PRISMA flowchart of Identification and Selection of studies based on the eligibility criteria.

Table 1
Classification of identified blood fluid biomarkers based on NVU component.

NVU Component	Blood Biomarker	Number of VCD Studies		Number of Cerebrovascular Studies	
		Plasma	Serum	Plasma	Serum
BBB Permeability	Q-Alb*	CSF/Plasma: 2 [22,24]	CSF/Serum: 4 [23,25,26,87]		CSF/Serum:1 [55]
Endothelial Dysfunction	vWF	4 [67,72-74]	–	14 [27-30,36,110-118]	–
	PECAM-1	–	–	1 [116]	1 [119]
	Endothelin-1	–	–	1 [76]	–
	ICAM-1	2 [67,68]	1 [120]	12 [36,38,41,43,113,116,117,121-125]	5 [39,42,64,126,127]
	VCAM-1	2 [37,67]	1 [66]	11 [36,38,40,41,46,113,122-125,128]	6 [37,39,42,64,126,129]
	E-selectin	2 [37,67]	–	15 [27,28,36,38,40,41,45-47,65,86,116,122,124,125]	6 [37,39,42,44,64,129]
	P-selectin	1 [68]	–	9 [28,40,45,47,86,111,114,116,128]	2 [42,64]
	VEGF	–	1 [70]	6 [31,86,113,130-132]	12 [32-35,51,64,133-138]
Tight junction proteins	VE-Cadherin	–	–	–	1 [139]
	Claudin-5	–	–	–	4 [9,138,140,141]
	Occludin	–	–	–	7 [9,79,138,140-143]
	ZO-1	–	–	–	3 [9,79,140]
Neuronal Injury	NSE	–	2 [91,144]	3 [54,112,114]	8 [32,52,53,138,145-148]
	NfL	–	3 [105–107]	4 [46,149-151]	7 [11,48,49,152-155]
	NFH	–	–	–	2 [156,157]
	Total Tau	–	–	1 [158]	1 [147]
	Neurogranin	–	–	1 [158]	–
	Neuronal Pentraxin 2	–	1 [159]	–	–
Neuroglial Injury	Lipocalin 2	2 [94,95]	–	–	–
	GFAP	–	1 [106]	–	2 [93,134]
	S100β	–	2 [91,108]	2 [46,112]	12 [32,33,50,51,129,134,138,145,147,156,160,161]
	Galectin-3	–	1 [162]	–	–
	MgAb	–	1 [163]	–	–
Extracellular Matrix	MMP-2	–	1 [109]	2 [86,123]	–
	MMP-3	–	–	1 [123]	1 [135]
	MMP-9	1 [85]	–	8 [55,86,112,122-124,164,165]	5 [64,79,134,135,138]

* Both CSF and plasma samples are required for the measurement of the CSF/Plasma albumin quotient. The numbers represent the quantity of studies, with the respective references in superscript.

Results

Search results and study characteristics

The search strategy from four databases yielded 2796 results (Fig. 1). An additional 10 studies were included from reviews and manual searching. We screened 2806 titles and abstracts and reviewed 359 full-text articles, finally including 112 studies. In total, 27 biomarkers were identified as indicators of NVU dysfunction (Table 1). Five out of the 26 studies met the inclusion criteria for VCD and were included in the meta-analysis (Fig. 1& 2), while the remaining 21 were included in the qualitative synthesis (Fig. 1& Supplementary Table S3). Eighty-six studies on cerebrovascular disorders were shortlisted out of which, 29 were meta-analysed and 57 summarised qualitatively (Fig. 1). A list of all included studies is provided in the Supplementary section (Supplementary Tables S3–5, S8).

Quality assessment and publication bias

Assessment of technical aspects of the available data, such as quality of individual manuscripts, publication bias and qualitative analyses are provided in Supplementary Tables S6–7.

Quantitative analysis

For those studies reporting quartiles, means and SDs were estimated assuming both normally and non-normally distributed outcome variables. Some biomarkers were found to have skewed distributions

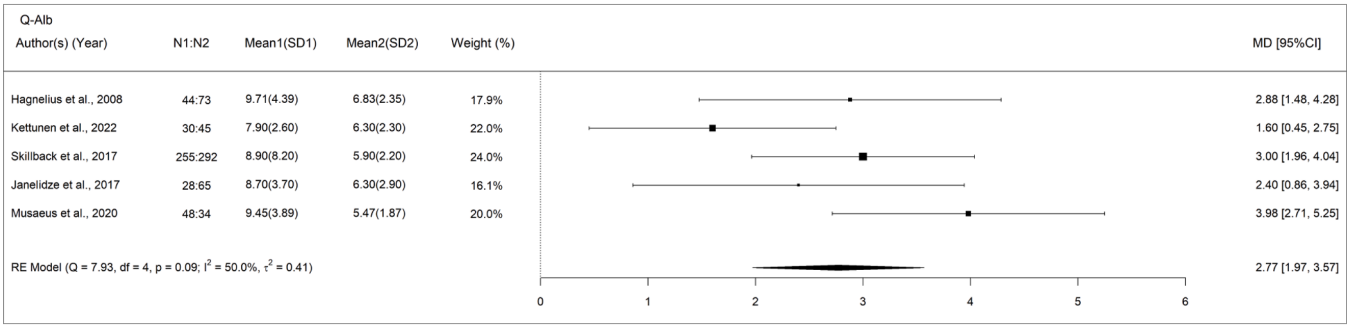

Fig. 2. Meta-analysis plot for CSF-Serum albumin quotient (Q-Alb) in vascular neurocognitive disorders (VCD).
Abbreviations - N1: Number of case subjects; N2: Number of control subjects; Mean 1: Mean of case subjects; SD 1: Standard deviation of case subjects; Mean 2: Mean difference of controls; SD 2: Standard deviation of controls.
The summary results within parentheses followed by the RE model correspond to the test of heterogeneity among the studies. P-value for significance of the MD is shown in supplementary table S9.

(Supplementary Table S8). Both MD and SMD measures were meta-analysed, with comprehensive results including p values reported within the text shown in supplementary tables S9-S10. The meta-analysis of MD with means and SDs estimated assuming non-normal distribution are shown in Forest plots (Figs. 2 and 3).

Meta-analysis of VCD biomarkers of BBB integrity

The Q-Alb quotient was the only biomarker of VCD with sufficient replicate studies ($n = 5$) that it could be meta-analysed (Supplementary Table S9 and Fig. 2). Q-Alb quotient was upregulated in VCD patients ($n = 405$) relative to healthy controls ($n = 509$) [22–26] (MD = 2.77; 95 % CI = 1.97–3.57; $p < 0.0001$, moderate heterogeneity across studies; $I^2 = 50.0$ %).

Meta- analysis of NVU component biomarkers in cerebrovascular disorders

Endothelial dysfunction

Four of 14 studies on von Willebrand factor (vWF), a glycoprotein crucial to hemostasis, involving stroke and healthy controls were meta-analysed (Fig. 3.1A). The vWF levels were significantly upregulated in people with cerebrovascular disease compared to healthy controls (370 stroke and 3513 controls; MD = 21.77; 95% CI = 12.07 to 31.48; $p = <0.001$, with moderate heterogeneity across studies; $I^2 = 58.0\%$) [27–30]. Five of 18 studies on vascular endothelial growth factor (VEGF), a master regulator of angiogenesis, were meta-analysed (Fig. 3.1B), with VEGF elevated in stroke patients ($n = 365$) relative to healthy controls ($n = 315$) (MD = 132.08; 95 % CI = 47.75–216.41; $p = 0.002$, $I^2 = 99.4$ %) [31–35].

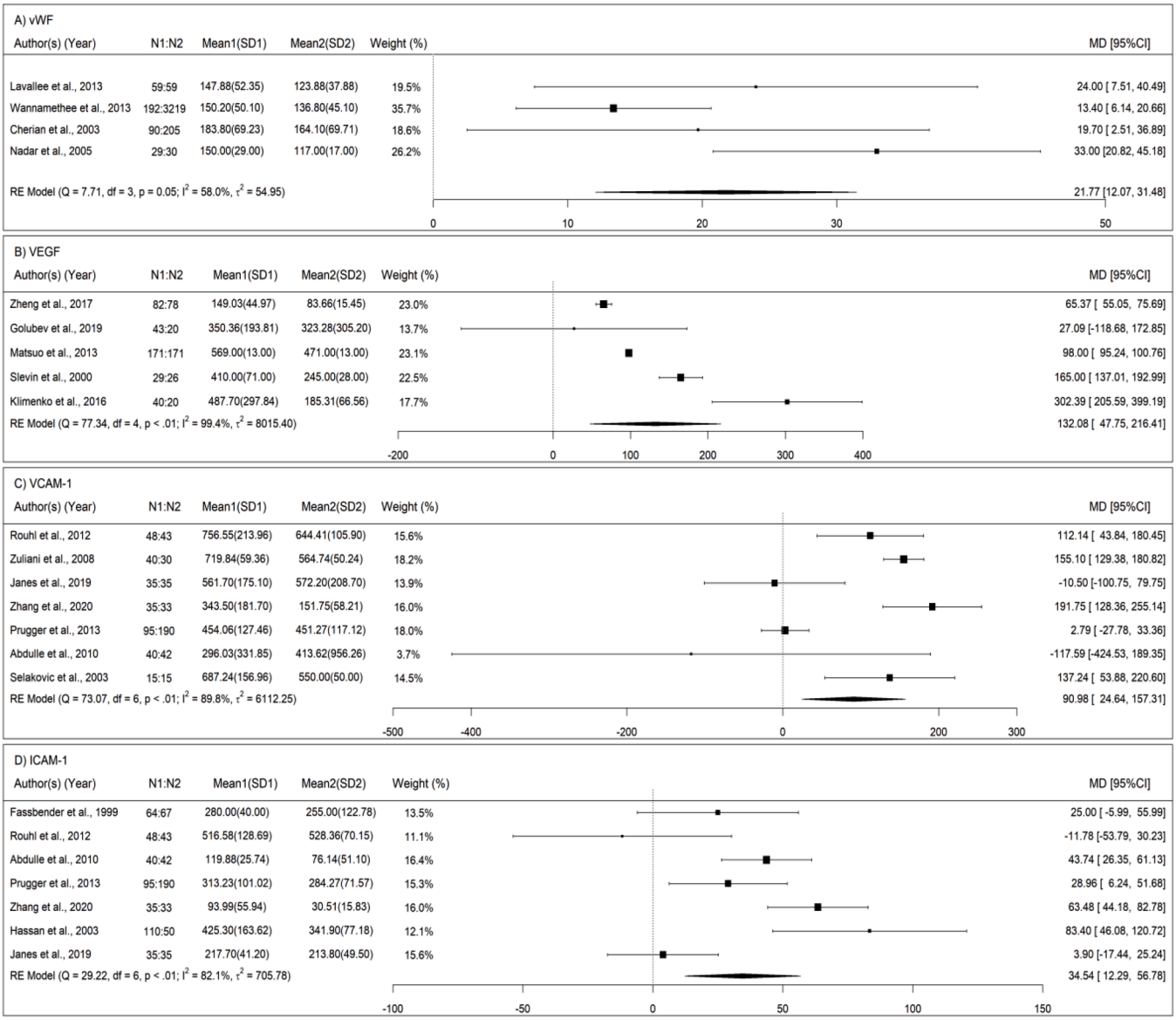

Fig. 3.1. Meta-analyses of biomarkers in cerebrovascular disorders.
Abbreviations – N1: Number of case subjects; N2: Number of control subjects; Mean 1: Mean of case subjects; SD 1: Standard deviation of case subjects; Mean 2: Mean difference of controls; SD 2: Standard deviation of controls.
The summary results within parentheses followed by the RE model correspond to the test of heterogeneity among the studies. P-value for significance of the MD is shown in supplementary table S9.

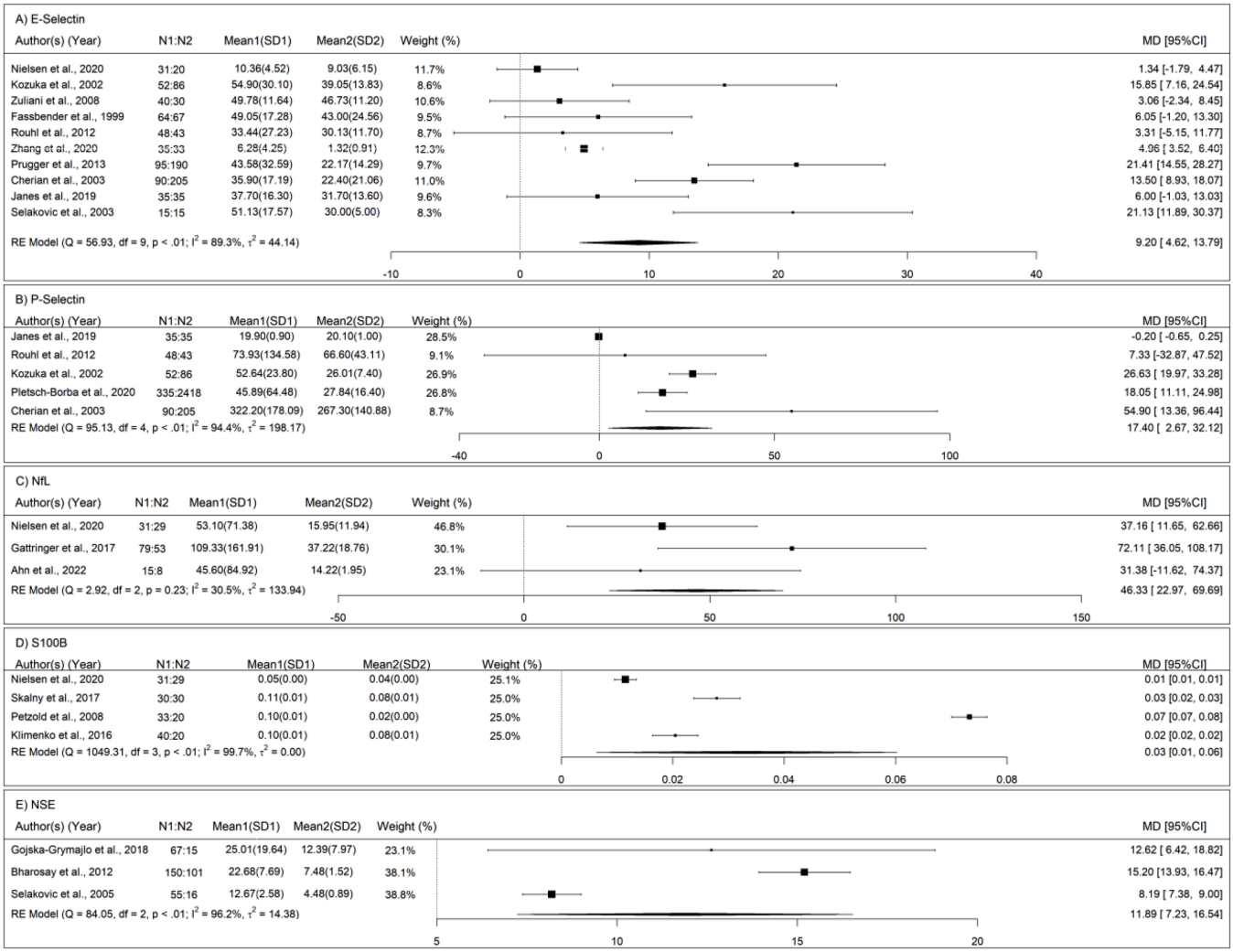

Fig. 3.2. Meta-analyses of biomarkers in cerebrovascular disorders.
Abbreviations – N1: Number of case subjects; N2: Number of control subjects; Mean 1: Mean of case subjects; SD 1: Standard deviation of case subjects; Mean 2: Mean difference of controls; SD 2: Standard deviation of controls.
The summary results within parentheses followed by the RE model correspond to the test of heterogeneity among the studies. P-value for significance of the MD is shown in supplementary table S9.

Neuroglial and neuronal injury

Patients with cerebrovascular diseases showed increased levels of vascular cellular adhesion molecule-1 (VCAM-1) (7 studies; 308 stroke patients and 388 neurologically normal controls; MD = 90.98; 95 % CI = 24.64 to 157.31; $p = 0.007$; $I^2 = 89.8$ %) (Fig. 3.1C) [36–42] as well as upregulated intercellular adhesion molecule-1 (ICAM-1) levels (427 subjects and 460 controls; MD = 34.54; 95 % CI = 12.29–56.78; $p = 0.002$; $I^2 = 82.1$ %) (Fig. 3.1D) [36,38-40,42-44]. Blood levels of E-selectin (10 studies; 505 subjects with stroke and 724 controls; MD = 9.20; 95 % CI = 4.62–13.79; $p < 0.001$, $I^2 = 89.3$ %) (Fig. 3.2A) [28,36, 37,39-42,44-46] and P-selectin (5 studies; 560 subjects with stroke or SVD and 2787 controls; MD = 17.4; 95 % CI = 2.67–32.12; $p = 0.02$, $I^2 = 94.4$ %) were increased in cerebrovascular diseases compared to healthy controls [28,40,42,45,47] (Fig. 3.2B).

NfL, a major component of the neuronal cytoskeleton, was significantly higher in subjects with stroke or SVD (3 studies; 125 subjects) compared to 90 healthy controls (MD = 46.33; 95 % CI = 22.97–69.69; $p = 0.0001$; $I^2 = 30.5$ %) [46,48,49](Fig. 3.2C).

Four studies analysed differences in S100 calcium-binding protein B (S100B), a commonly used astrocyte marker, levels between 134 patients with stroke and 99 healthy controls. S100B levels were elevated in stroke patients relative to controls (MD = 0.03; 95 % CI = 0.01–0.06; $p = 0.02$, $I^2 = 99.7$ %) (Fig. 3.2D) [33,46,50,51]. Three studies comparing circulating neuron specific enolase (NSE) concentrations, an enzyme released from neurons during injury, between 272 stroke patients and 132 controls, and reported significantly upregulated levels in stroke subjects (MD =11.89; 95 % CI = 7.23–16.54; $p < 0.001$, $I^2 = 96.2$ %) (Fig. 3.2E) [52–54].

Publication bias

Statistical examination using the Egger's regression test revealed no publication bias for the list of studies included in the final meta-analysis (Supplementary Table S9, column 0).

Discussion

This review summarises the evidence on biomarkers associated with NVU pathology and identifies altered markers in patients with VCD or cerebrovascular disorders such as stroke. The data indicates a diversity of blood biomarkers associated with cerebrovascular disease with or without cognitive impairment. The biomarkers can be theoretically linked to multiple disease mechanisms, including increased BBB permeability caused by endothelial dysfunction or disruption of tight

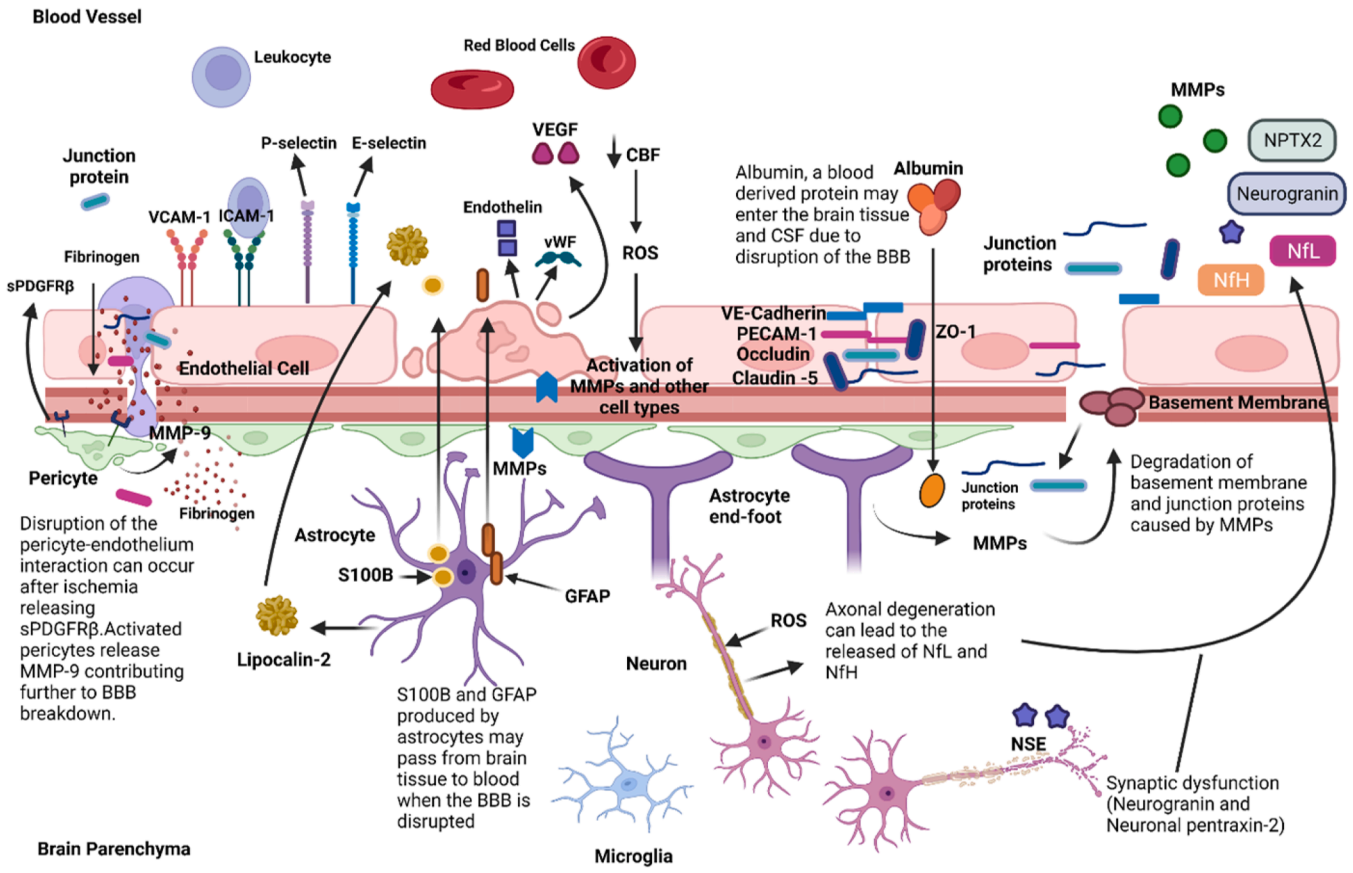

Fig. 4. Overview of the NVU and its associated blood biomarkers.
The NVU is comprised of endothelial cells, a basement membrane, pericytes, glial cells and neurons. It is postulated that hypoperfusion and reduced cerebral blood flow arising from vascular pathologies trigger a sequence of events, such as the release of ROS which can activate pericytes and astrocytes to secrete MMPs as well as other cellular components. MMPs have been linked to the degradation of the basement membrane and junction proteins, which can be detected in the brain tissue or peripheral circulation. Additionally, ischemic conditions can disrupt pericyte-endothelium interaction causing the release of soluble PDGFRβ and disruption of junction proteins. Activated pericytes release MMP-9 further contributing to the breakdown of the BBB. Increase in activated MMPs, ROS and cytokines can potentially induce neuronal dysfunction and damage. With the disruption of the BBB, blood proteins such as albumin enter the brain tissue and CSF. Additionally, proteins indicative of neuronal injury (NfL, NfH, NSE), synaptic dysfunction (neurogranin, neuronal pentraxin-2), astrocyte injury (S100B, GFAP and lipocalin-2) and pericyte dysfunction (sPDGFRβ) may enter the bloodstream. In response to inflammation, endothelial cells release various molecules such as VCAM-1, ICAM-1, P-selectin, E-selectin, endothelin, VEGF and vWF into the blood. Most of the derived biomarkers apart from Tau, microglial antibodies and galectin-3 are included here. Image created by first author GKH using the program BioRender.com.

and adherens junctions, as well as injury to neurons, neuroglia and the interstitial matrix (Table 1, Fig. 4).

BBB integrity

The meta-analysis of plasma Q-Alb levels, as a marker of increased BBB permeability, showed an increase in VaD, subcortical small vessel disease and CADASIL patients when compared to healthy individuals [22–26] and were found to correlate with poor neurological outcomes in stroke [55]. Q-Alb levels were also elevated in other neurodegenerative disorders such as AD, Parkinson's disease dementia and frontotemporal dementia [24], but one study found that Q-Alb levels were highest in participants with VaD and mixed dementia compared to those with AD [25]. Furthermore, this association was not observed in AD cohorts without vascular risk factors [56,57]. Q-Alb may therefore be a useful biomarker of a compromised BBB and, by inference, NVU integrity, but more research is needed to determine its efficacy as a marker for differential diagnosis. Even though, it is the most widely used biomarker for BBB permeability, it is important to note that the calculation of Q-Alb levels requires the analysis of both serum and CSF samples.

Interestingly, Q-Alb has been found to correlate with sPDGFRβ levels [58,59]. Shed by pericytes, sPDGFRβ is another valuable biomarker of NVU disruption given its association with cognitive dysfunction in the CSF and serum of AD subjects [60,61].

The review also identified blood biomarkers of endothelial cells, junction proteins and neuronal injury, all key components of the NVU. While the evidence for most of these markers is limited, they may serve as potential avenues for future work to establish blood biomarkers for VCD in relation to other brain diseases.

Endothelial dysfunction

Significant elevation of all cell adhesion molecules (CAMs) in cerebrovascular disorders, (Fig. 3.1, Supplementary Table S8) were observed in the meta-analyses when MD was analysed. CAMs are essential for mediating leukocyte recruitment to sites of tissue damage across the vascular endothelium and can be released as soluble forms into the bloodstream as part of a feedback mechanism [62]. Studies that measured multiple CAMs found only one protein family, either VCAM-1, ICAM-1 or E-selectin to be associated with severity of SVD or lower cognitive scores (Supplementary Table S5). The association between ICAM-1 and poor cognition was particularly noteworthy being observed in a longitudinal study that followed up with participants for 16 years [63]. Furthermore, increased expression of CAMs in cerebrovascular

pathologies correlate with imaging markers such as lacunes (small areas of brain tissue damage/small subcortical infarcts), white matter hyperintensities (WMH) [64] and cerebral microbleeds suggesting potential use of these markers as indicators of cognitive impairment [65]. However, levels of these proteins in the blood of VCD and cerebrovascular disorders have been inconsistent. For example, VCAM-1 and E-selectin have been linked to poorer cognition and VCD in some studies [66,67] but the association with ICAM-1 and P-selectin is conflicting [68] (Supplementary Table S3).

Our meta-analysis also found upregulated blood vWF and VEGF levels in cerebrovascular disorders compared to healthy controls, with a large effect size for VEGF (Fig. 3.1). VEGF is a protein produced by vascular cells and neurons and is known to be a master regulator of angiogenesis involved in growth, maintenance and vascular repair; furthermore, VEGF mediates neuronal survival [31,69]'. One study found blood VEGF to be associated with VaD incidence [70] however, increased levels of circulating VEGF could also be a reflection of ageing [71]. Similarly, vWF levels were able to distinguish VCD subjects from healthy controls [72,73] and positively correlated with poor cognition and WMH [74]. Plasma vWF is derived mainly from endothelial cells rather than platelets; therefore, vWF is a gold standard measurement of endothelial damage [45]. Other less commonly studied proteins, such as PECAM-1 (CD31), which has been linked to worsening neurological outcome and endothelin-1, a predictor of VaD in cognitively intact adults [75], were also upregulated in the serum of stroke patients [76].

Tight and adherens junction proteins

Interestingly, qualitative analysis of results from our search found less commonly studied blood biomarkers such as the tight junctions (TJs) and adherens junctions to be present in the peripheral circulation of humans (Supplementary Table S5). Functional characteristics of TJs are attributed to various proteins, namely the claudins, occludin and cytoplasmic zonula occludens (ZO), which are responsible for regulating the permeability of endothelial cells in the cerebrovasculature. Disruption of these junctions may contribute to increased BBB leakage [77]. Claudin-5, occludin and ZO-1 were each upregulated in stroke patients compared to healthy controls. Specifically, increased levels of claudin-5 and ZO-1 were associated with worsening outcomes as a result of haemorrhagic transformation, while increased occludin levels were associated with severe cognitive impairment (Supplementary Table S5). The strength of correlation analyses between some of these proteins and stroke outcomes have been inconsistent in other studies. VE-cadherin, an adherens junction protein involved in regulating the adhesion of brain endothelial cells [78], was significantly upregulated in the blood of stroke patients [79], congruent with a recent study, where VE-cadherin levels were seen to be reduced in the brain and increased in the CSF of preclinical AD patients [80]. Though there are currently no studies measuring the levels of junction proteins in the blood of humans with VCD, BBB impairment resulting from degradation of TJs has been reported in endothelial cell culture models [81] and animal models of hypoxia-ischemia [82]. Analysing these structural proteins may provide possible insights into the pathophysiology of cognitive impairment associated with vascular pathologies as their degradation is an early indication of NVU dysfunction. The anatomical location of TJs and adherens junctions between adjacent endothelial cells of the BBB, may pose a challenge for their measurement in the systemic circulation. However, with the utilization of sensitive and specific assays, they may provide a novel avenue for monitoring the prognosis of vascular contributions to cognitive impairment.

Extracellular matrix proteins

Increased permeability of the BBB can be attributed to MMP related proteolytic degradation of the basal lamina and TJs [83]. MMP-9 is activated in hypoxic conditions [84], found to be elevated in VCD [85] and stroke patients [86] as well as associated with cognitive decline and worsening neurological outcomes. Though elevated blood MMP-2 levels have also been reported in VCD subjects with multiple infarcts and stroke [87], results for MMP-3 levels in cerebrovascular disorders were conflicting (Supplementary Table S5).

Neuroglial and neuronal injury

Findings from the meta-analysis revealed that subjects with cerebrovascular disorders have higher levels of NfL and NSE in their blood than do healthy controls (Fig. 3.2). NfL levels also correlated with neuroimaging lesions such as lacunes, microbleeds as well as, cognitive function in VCD and SVD. Notably, serum NfL successfully predicted 7-year changes in cognition in patients with a pure form of VaD. Similarly, a recent meta-analysis of 19 studies in 4237 patients with cerebrovascular events by Sanchez, Martirosian [88] found blood NfL levels to be a suitable diagnostic marker for distinguishing between cerebrovascular subtypes.

Qualitative evidence suggests similar patterns with neurofilament heavy chain (NfH) levels as it differentiated patients with neurological disorders from controls and correlated with infarct volume (Supplementary Table S5). There are fewer studies on NfH levels in VCD, but elevated levels have been seen in the CSF of VaD and AD patients in comparison to controls [89]. Neurofilaments with light, intermediate, and heavy chains are important for the maintenance of the cytoskeleton and together with NSE, have been widely recognised as markers of neuronal injury. In the event of hypoxia-ischemia, these molecules leak out of neurons, pass through the BBB and enter the peripheral circulation [90]. A positive correlation between serum NSE and WMH with NSE blood levels is a predictive marker in the progression of cognitive impairment [91].

S100B, glial fibrillary acidic protein (GFAP) and lipocalin-2 are proteins expressed in astrocytes, the most abundant glial cell type, and is critical for a healthy NVU. Therefore, elevation of these proteins serve as possible indicators of astrocyte injury [92]. A meta-analysis of studies revealed that S100B is upregulated in cerebrovascular disorders compared to controls (Fig. 3.2). S100B is not normally present in the peripheral circulation but is released following stroke and has been commonly implicated in brain injury. Elevated levels of serum GFAP have been found in ischemic stroke [93] and intracranial haemorrhage [e] [65] with lipocalin-2 increased in the blood of VaD [94] and AD patients [95]. Though activated astrocytes have been reported to contribute to the breakdown of the BBB [96], the exact pathogenic mechanisms involving lipocalin-2 and its diagnostic capability in cognitive impairment is unclear.

Many of these biomarkers were analysed in relatively few studies and with small sample sizes. As biomarkers such as GFAP and NfL are elevated in various brain disorders, their specificity for neurodegeneration needs to be evaluated in greater detail. The issue of whether NfL can be considered a primary marker of NVU integrity remains unresolved. As a major constituent of the neuro-axonal cytoskeleton, elevated NfL is typically reported in the CSF as a reflection of axonal damage, either primary or secondary to processes such as Wallerian degeneration [97–99]. Presence of elevated levels of NfL in the blood may therefore be a downstream effect of compromised BBB integrity, as has been reported in several brain diseases [100–103]. By contrast, others have failed to identify an association between NfL and BBB permeability [104]. Therefore, altered fluid levels of NfL in VCD, as identified in this review, cannot be regarded as a specific marker of NVU integrity. Further studies are warranted to validate the efficacy of these proteins as useful markers of BBB-related pathology and cognitive decline in the periphery.

Small vessel disease and cognitive impairment

There are only a limited number of studies investigating biomarkers of SVD and cognitive impairment. Out of these studies, vWF [67,72-74],

NSE [105], NfL [88,105-107], S100β [91,108] and Lipocalin-2 [94,95] appeared to be the most robust biomarkers across studies .

Strengths and limitations

To our knowledge, this is the first systematic review and meta-analysis on blood biomarkers pertaining to NVU pathology in both VCD and cerebrovascular disease. This study accounted for selection bias by having two independent reviewers perform screening of initial results. In addition, the extraction of eligible studies from reference lists maximised the inclusion of relevant studies. Various statistical tests were conducted using both SMD and MD measures (Supplementary Tables S8–10) before results were described based on non-normal estimation with MD measurements (Supplementary Table S9), therefore, allowing for the recognition of heterogeneity in biomarker levels. Also, there was limited disagreement (6%) among the three analysed domains when the quality of each study was assessed independently by two reviewers.

Our review has several limitations. Due to the limited number of studies related to NVU components in VCD subjects, we were unable to perform quantitative analysis to conclude statistical significance. Most of our meta-analyses have low study numbers which could have contributed to low statistical power. Some studies with wide deviations in measurements were removed from the meta-analyses. Additionally, the use of mean and SD values could have limited the inherent variance and not taken into account the skewness of the data. Some of the biomarkers were analysed in stroke cohorts but not in VCD patients. Hence, their actual potential as a diagnostic marker in VCD is not known. Despite exhaustive searches across four databases, we might have missed some eligible studies and data from a small number of studies had to be extrapolated from the bar graphs as there were no responses to requests for unprocessed data from authors. Apart from NfL and vWF, high heterogeneity was present in the analyses for all other biomarkers. This could have been attributed to a variety of factors including variability of fluid biomarkers, study subjects and sample size. It has also been argued that Egger's test on MD can lead to an overestimation of false positive outcomes [21]. Finally, as the biomarkers were analysed separately, it is unclear to what extent they are correlated.

Conclusion

Multiple blood biomarkers were quantitatively altered in VCD and cerebrovascular disorders. However, only nine biomarkers for cerebrovascular disorders and one for VCD could be meta-analysed, highlighting the limited research in VCD. Tight and adherens junctions (Claudin-5, Occludin and VE-cadherin), which have only been studied in animals and in a small number of human participants with stroke, should be analysed for their potential diagnostic role in VCD alongside other markers such as VEGF, NfL, vWF, Q-Alb and MMP-2/9. The diagnosis of VCD is likely to require a diverse panel of markers considering the heterogeneous nature of this disorder with multiple pathogenic mechanisms and more importantly, for the identification of various subtypes. In fact, one study found a panel of biomarkers associated with increased BBB permeability such as albumin quotient and MMP-2 amidst other inflammatory biomarkers to be the most predictive model for the diagnosis of subcortical ischemic vascular dementia [109]. As NVU is a hallmark of many neurological diseases, measuring its function could aid not only differential diagnosis but also prognosis and disease monitoring. Blood biomarkers of BBB permeability, pericytes and the integrity of endothelial cells, junction proteins, neurons and glia therefore deserve much greater enquiry.

CRediT authorship contribution statement

Gurpreet Kaur Hansra: Writing – original draft, Project administration, Methodology, Formal analysis, Data curation, Conceptualization. **Tharusha Jayasena:** Writing – review & editing, Data curation. **Satoshi Hosoki:** Writing – review & editing, Data curation. **Anne Poljak:** Writing – review & editing. **Ben Chun Pan Lam:** Writing – review & editing, Formal analysis. **Ruslan Rust:** Writing – review & editing. **Abhay Sagare:** Writing – review & editing. **Berislav Zlokovic:** Writing – review & editing. **Anbupalam Thalamuthu:** Writing – review & editing, Formal analysis. **Perminder S. Sachdev:** Writing – review & editing, Supervision.

Declaration of competing interest

None.

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Supplementary materials

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