Laboratory biomarkers of delayed cerebral ischemia following subarachnoid hemorrhage: A systematic review

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ABSTRACT

Delayed cerebral ischemia (DCI) substantially contributes to disability and death in subarachnoid hemorrhage (SAH) patients; however, its pathophysiology is incompletely understood and diagnostic and therapeutic strategies are lacking. Biomarkers may help to elucidate the pathophysiology, optimize early diagnosis, or provide treatment targets. We systematically searched PubMed and Embase on October 13, 2021, for studies that evaluated at least one laboratory biomarker in patients with DCI, using the most up-to-date definition of DCI as proposed by a panel of experts in 2010. Quality of studies was assessed using the Newcastle-Ottawa Scale or Cochrane Collaboration's risk of bias assessment tool. Biomarkers of clinical and radiological DCI were analyzed separately. Results were meta-analyzed if possible, otherwise narratively reviewed. Biomarkers were classified as significant, inconclusive, or nonsignificant. We defined validated biomarkers as those with significant results in meta-analyses, or in at least two studies using similar methodologies within the same time interval after SAH. The search yielded 209 articles with 724 different biomarkers; 166 studies evaluated 646 biomarkers of clinical DCI, of which 141 were significant and 7 were validated biomarkers (haptoglobulin 2-1 and 2-2, ADAMTS13, vWF, NLR, P-selectin, F2-isoprostane); 78 studies evaluated 165 biomarkers of radiological DCI, of which 63 were significant and 1 was a validated biomarker (LPR). Hence, this review provides a selection of seven biomarkers of clinical DCI and one biomarker of radiological DCI as most promising biomarkers of DCI. Future research should focus on determining the exact predictive, diagnostic, and therapeutic potentials of these biomarkers.

Keywords: Biomarker, Delayed cerebral ischemia, Subarachnoid hemorrhage

Introduction

Delayed cerebral ischemia (DCI) is an important and potentially preventable contributor to disability and death in subarachnoid hemorrhage (SAH) patients in whom the

causative aneurysm has been obliterated (1,2). The pathophysiology of DCI is complex and multifactorial; however, it is not yet fully understood. As a result, an accurate diagnostic test and effective treatment are both lacking.

Biomarkers may not only help to further elucidate the pathophysiology of DCI, but could also aid in optimizing early diagnosis and prompt treatment. Even though the present literature is brimmed with biomarker studies of DCI, accurate biomarkers of DCI have not yet been established. In 2018, an extensive systematic review proposed a panel analysis of 6 selected genetic and 15 protein biomarker candidates for further prospective validation of DCI prediction (3). However, this review used a very broad definition of DCI, including also DCI defined solely as angiographic vasospasm on digital subtraction angiography or increased flow velocities on transcranial Doppler (TCD) ultrasonography. Historically, angiographic vasospasm was considered the sole cause of DCI; however, in the past decades research has

shown that DCI and vasospasms are two different entities (4). Therefore, the combined use of both vasospasm and DCI in the 2018 review may have misguided the selected panel of biomarkers.

In 2010, a panel of experts proposed a strict definition of DCI, divided into a clinical and radiological definition, to be used as outcome measure and to enable more reliable meta-analyses of future clinical trials and observational studies (4). We used these definitions of DCI to systematically review the current literature on laboratory biomarkers of DCI and selected a new panel of the most promising biomarkers. The selected biomarkers may be useful for the prediction or diagnosis of DCI, either individually or combined.

Methods

The Preferred Reported Items for Systematic Review and Meta-analysis (PRISMA) 2020 guidelines were followed. This review was not registered and a review protocol was not prepared.

Search strategy and selection criteria

PubMed and Embase were searched for relevant studies from January 1, 1985, to October 13, 2021. The search strategy can be found in the supplemental data (Supplementary material, page 2-3). Two authors (MAT and HL) independently selected eligible studies. Titles and abstracts were screened for potential eligibility when covering primary studies on biomarkers of DCI in SAH patients either written in Dutch or English. Of the selected studies, full texts were screened and studies were considered eligible if they met the following criteria: (1) patients with SAH of whom (2) at least 95% were diagnosed with a causative aneurysm, (3) measurement of at least one laboratory biomarker (4) during hospital admission, (5) using either the radiological or clinical definition of DCI as proposed in 2010 (criteria listed in Tab. I), and (6) the studies had to perform, or allow for, statistical analysis on the biomarker in question and DCI. Exclusion criteria were: (1) studies with mixed clinical and radiological DCI cohorts, in which patients with either clinical or radiological DCI could not be distinguished from the mixed cohort, (2) biomarker levels in patients with and without DCI were inconsistent (e.g., different numbers in tables/figures and text), (3) no level of statistical significance was given, nor could be calculated, (4) studies in children only, (5) the same patient population (similar years and hospital of patient inclusion) was used by more than one study and, within those studies, the same biomarker was measured and compared similarly between DCI and no DCI patients. In this case, the study with the smallest sample size, and if sample sizes were equal the most outdated study, was excluded. Lastly, we checked studies on nimodipine administration. In 1988 and 1989, two randomized controlled trials showed efficacy of nimodipine in preventing DCI, resulting in a shift in SAH management (5,6). Therefore, we excluded studies with SAH patients before 1985. SAH cohorts between 1985 and 1990 were only included if nimodipine administration was explicitly mentioned. All papers after 1990 were included, unless nimodipine was described explicitly as being not part of the treatment protocol.

TABLE I - Criteria of the clinical and radiological definition of DCI

Clinical DCI	
Defined as:	*Excluded if:*

• A decrease in level of consciousness (described by a decrease of the Glasgow Coma Scale score or an increase of the National Institutes of Health Stroke Scale score) *or*
• Focal neurological impairment (e.g., aphasia, motor impairment, sensory deficits, neglect)
	• Vague definitions of DCI, e.g., "clinical deterioration," "neurological deterioration," "worsening of neurological condition," without specifically mentioning either decreased level of consciousness or focal neurological impairment
	• The DCI cohort also includes patients with solely signs of vasospasm without clinical symptoms of DCI. For example, patients with:
	  • Arterial narrowing on CT-A or DSA
	  • Increased flow velocities on TCD

Radiological DCI	
Defined as:	*Excluded if:*
• New ischemia/infarction/stroke or • Secondary ischemia/infarction/stroke or • Ischemia/infarction/stroke due to DCI (or associated DCI terms, including delayed ischemic/neurological deficit, [clinical] vasospasm, secondary ischemia/infarction)	• Defined as "presence of ischemia/infarction/stroke" without defining "new," "secondary," or "due to DCI/associated terms of DCI" • Presence of ischemia/infarction/stroke determined by an imaging modality other than noncontrast CT or MRI, e.g., CT perfusion, CT-A) • Other nonimaging methods used to assess ischemia/infarction/stroke, e.g., brain tissue oxygenation monitoring and microdialysate biomarkers

CT = computed tomography; CT-A = CT-angiography; DCI = delayed cerebral ischemia; DSA = digital subtraction angiography; MRI = magnetic resonance imaging; TCD = transcranial Doppler.

Data extraction

The same authors (MAT and HL) independently extracted baseline SAH characteristics (age, gender, World Federation of Neurological Societies [WFNS] grade and Fisher grade), the study's definition of DCI, the number of patients with and without DCI, and biomarker-related data.

If studies addressed both clinical and purely radiological DCI separately, biomarker-related data were extracted for both definitions. The biomarker-related data concerned laboratory biomarkers only (clinical and radiological biomarkers [heart rate, blood pressure, temperature, TCD velocities, computed tomography (CT) perfusion variables etc.] were left out of consideration). Biomarker data had to concern levels of individual biomarkers or ratios of two biomarkers, that is, combinations of three or more biomarkers, such as decision tree analysis or a self-made calculated score based on multiple biomarkers, were left out of consideration. Data included the biomarker medium (blood, cerebrospinal fluid [CSF], microdialysate [MD], urine, or other), timing of measurement(s), and all statistical analyses regarding the biomarker and the occurrence of DCI. If the biomarker medium was not mentioned, it was assumed to be blood. A biomarker measured in multiple media, for example, in blood and CSF, was considered as two separate biomarkers.

Nongenetic biomarkers were stratified into biomarker groups, which were based on the multifactorial pathophysiology of DCI as described by a previously published systematic review (7). Of biomarkers with multiple functions, we aimed to select the function which the authors of the study considered as DCI-related and subsequently categorized the biomarker into that specific biomarker group. Nongenetic biomarkers which could not be stratified to any biomarker group related to the pathophysiology of DCI were categorized as "other." Within the "other" group, we aimed to cluster biomarkers with similar functions. Genetic biomarkers were categorized as a separate group. The extracted data were compared and discrepancies were discussed with a third author (DV) and solved.

Quality assessment

Two authors (MAT and DV) independently assessed the quality of included studies using the Newcastle-Ottawa Scale (NOS) for case control and cohort studies and the Cochrane Collaboration's risk of bias assessment tool for randomized trials. Studies could obtain a maximum of eight or nine points, depending on the use of a nonexposed cohort. The Cochrane Collaboration's risk of bias assessment tool comprises seven criteria, which can be scored as high, low, or unclear risk of bias. Discrepancies were discussed with a third opinion (WPV) and solved.

Data interpretation and analysis

Biomarkers of clinical DCI (primary outcome) were analyzed separately from biomarkers of radiological DCI (secondary outcome). We categorized biomarkers into significant and nonsignificant biomarkers. Biomarkers, which were studied by one study only, were considered significant if at least one measurement was significantly associated with DCI (p < 0.05) and nonsignificant if all measurements yielded nonsignificant results. If a biomarker was investigated by more than one study, the classification into significant and nonsignificant was either based on a biomarker-specific meta-analysis, if methodologically possible (similar type of analyses and timing of measurement), or by descriptive comparison. Meta-analyses were performed only if all relevant studies, which investigated the biomarker in question on a specific point in time after SAH, could be included, using Review Manager 5.4. For continuous data we used the inverse variance method with random effects model to calculate weighted mean differences with 95% confidence intervals. For dichotomous data we used the Mantel-Haenszel method with random effects model to calculate estimated odds ratio with 95% confidence intervals. A pooled effect size was estimated for each specific timing of biomarker measurement. Descriptive comparison of the studies was done by summarizing the results of all relevant studies in a biomarker-specific figure, which was then used to classify the biomarkers into significant, inconclusive, and nonsignificant. The biomarker-specific figures display the author, year, number of patients with and without DCI, the type of analyses, and the results divided into categories of sampling timing (day 0-3, 4-8, 9-13, and >14 after SAH). The method used for classification of biomarkers into significant, inconclusive, and nonsignificant based on the biomarker-specific figures is explained in the supplemental data (Supplementary material, page 4).

In order to select the most promising biomarkers of DCI, we evaluated whether significant biomarkers were validated by a second study. A validated biomarker was defined as a biomarker with significant results in at least two studies using similar methodologies within the same time interval after SAH, without any other study showing contradictory results. Biomarkers of which the meta-analysis of all relevant studies yielded a significant association were considered validated, too. Additionally, biomarkers that had only been investigated by one study were differentiated from those biomarkers that were investigated by a high-quality study. We defined high quality as a maximum (eight or nine) or maximum minus one point (seven out of eight or eight out of nine) quality assessment score.

Data have been reported according to the PRISMA reporting guidelines for systematic reviews and meta-analyses.

Results

Included studies

After removing duplicates, the search yielded a total of 5,820 studies. We excluded 3,900 studies during abstract screening and 1,711 studies during full-text screening, after which 209 articles (204 cohort and 4 case-control studies, 1 randomized controlled trial) remained (Fig. 1). Baseline characteristics of all included studies are listed in Table S1 of the supplemental data (Supplementary material, page 5-12). Altogether, the 209 studies measured 724 different biomarkers in 25,933 SAH patients (not corrected for overlapping
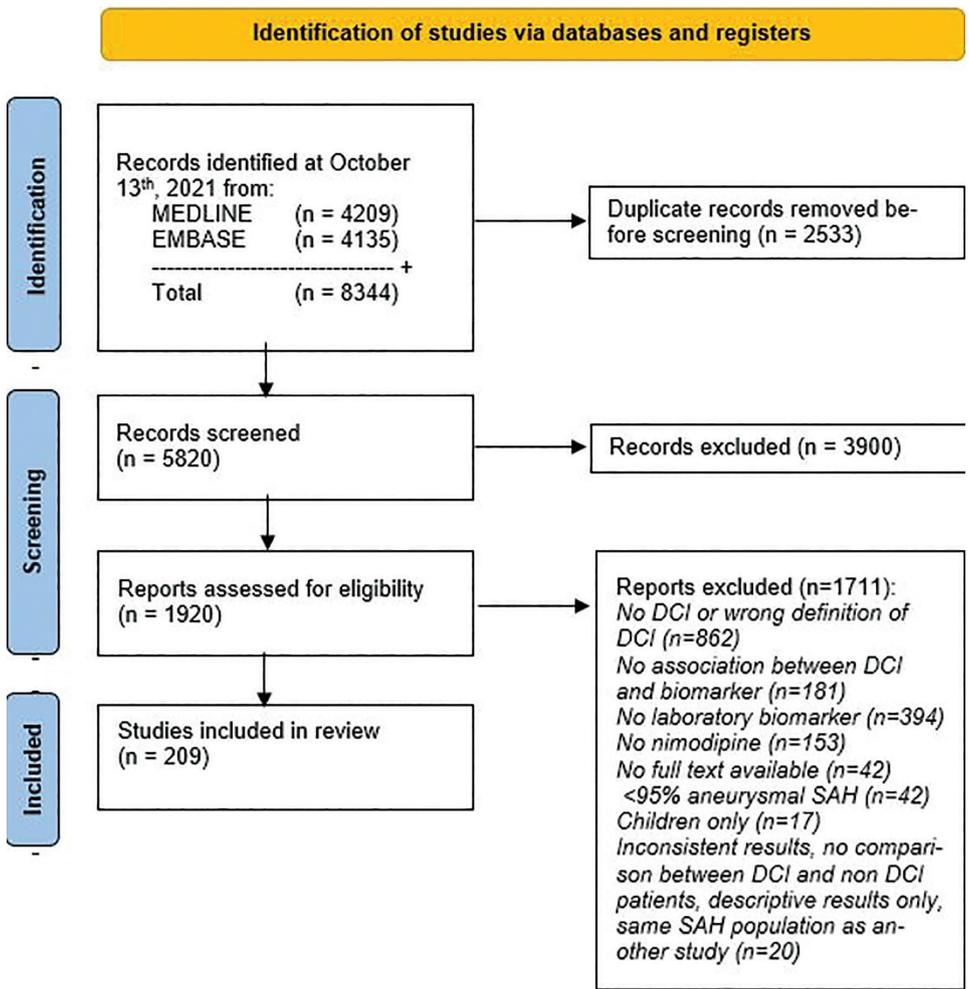
Fig. 1 - PRISMA 2020 flow diagram for systematic reviews.

patient cohorts). A summary of the NOS quality scores is listed in Table II, and the quality scores of individual studies are displayed in the baseline characteristics table (Table S1, page 5-12). The four case-control studies scored three, four (n = 2) and seven of nine points. The randomized controlled trial scored low risk on three of seven items.

Clinical DCI

Biomarkers of clinical DCI were studied by 166 studies comprising 646 different biomarkers (Fig. 2) in 20,983 SAH patients of whom 5,810 (28%) developed DCI. Most biomarkers (588 of 646, 91%) were investigated by one study and 58 (9%) by more than one study (range 2 to 14, median 3). The distribution of the biomarkers among the biomarker groups is shown in Table III.

In total, 141 biomarkers (n = 88 nongenetic, n = 53 genetic) were classified as significantly associated with clinical DCI (Table S2, page 13-34). A summary of studied and significant biomarkers and specific trends observed within each biomarker group are displayed in Table III. Of the significant biomarkers, 121 were investigated by one study and 20 by more than one study. Meta-analyses were possible for five biomarkers (haptoglobin 1-1, 2-1, and 2-2, ADAM metallopeptidase with thrombospondin type 1 motif 13 [ADAMTS13] and

TABLE II - Summary of the Newcastle-Ottawa Scale quality assessment scores of 204 cohort studies

Quality score	134 studies without control group (maximum 8 points)	70 studies with control group (maximum 9 points)
1 point	None	None
2 points	7 studies	2 studies
3 points	24 studies	8 studies
4 points	20 studies	16 studies
5 points	35 studies	20 studies
6 points	34 studies	14 studies
7 points	10 studies	7 studies
8 points	4 studies	3 studies
9 points	–	None

von Willebrand factor [vWF]). The meta-analyses showed that SAH patients with haptoglobin polymorphism 2-1 were less likely to develop DCI and patients with haptoglobin polymorphism 2-2 were more likely to develop DCI (8-10). DCI patients had lower ADAMTS13 levels on day 1 and higher levels of vWF on day 4 after SAH, compared to patients without
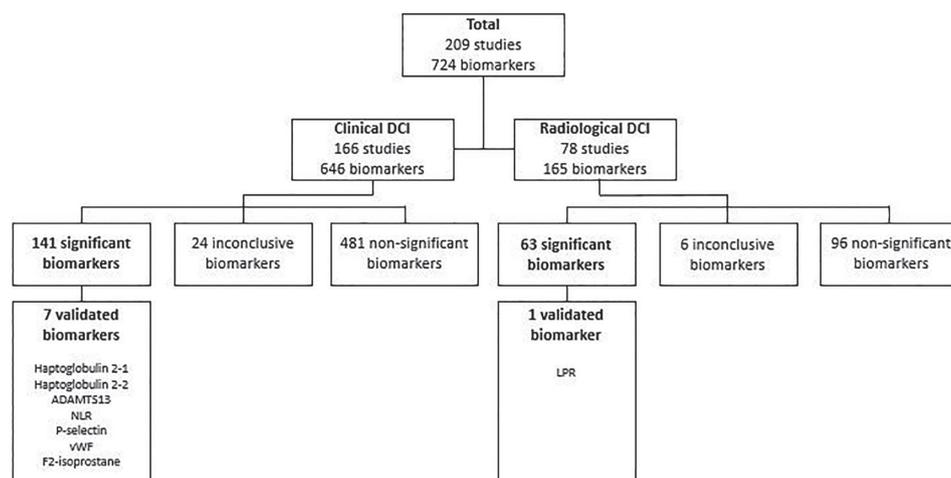
Fig. 2 - Flowchart of all biomarkers, divided into clinical and radiological DCI. ADAMTS13 = ADAM metallopeptidase with thrombospondin type 1 motif 13; LPR = lactate/pyruvate ratio; NLR = neutrophil/lymphocyte ratio; vWF = von Willebrand factor.

TABLE III - Number of studied and significant biomarkers and specific trends observed within each biomarker group of clinical DCI

Biomarker group	Biomarkers of clinical DCI		Specific trends observed among significant biomarkers within biomarker group
	Studied	Significant	
Nongenetic biomarkers	**225**	**88**	
Brain injury	16	8	All indicated more brain injury in patients with DCI. No specific trend in time.
Coagulation cascade	33	15	All indicated increased platelet activity, hypercoagulability, or hyperfibrinolysis. No specific trend in time.
Cortical spreading depressions	2	1	Excitotoxicity in first 48 h after SAH.
Endothelial injury	3	2	Both indicated more endothelial injury in DCI.
Inflammation and immune system	83	29	25 of 29 biomarkers indicated enhanced inflammation or immune response. Most frequently observed in first couple of days following SAH.
Oxidative stress	18	7	5 of 7 biomarkers indicated increased oxidative stress in patients with DCI. No specific trend in time.
Vascular tone	22	9	6 of 9 biomarkers indicated vasoconstriction, 2 indicated vasodilation, 1 was significant with unknown point estimate.
Volemic status	10	2	Both increased and decreased diuresis and natriuresis were observed in DCI.
Other	38	14	Subcategories were: cerebral metabolism, gender-specific growth factors, lipid metabolism, oxygen-carrying capacity, and stress response.
Genetic biomarkers	**421**	**53**	
Genomic	5	1	Function often unclear, some were involved in processes of oxidative stress, vascular tone, volemic status, stress response, inflammation and coagulation, among others.
MicroRNA	51	0	
Methylation	44	36	
Polymorphism	13	3	
RNA	15	6	
Single nucleotide polymorphism	293	7	

DCI = delayed cerebral ischemia; RNA = ribonucleic acid; SAH = subarachnoid hemorrhage.

DCI, in two studies (11,12). The results of the remaining 53 significant biomarkers that were investigated by multiple studies that could not be meta-analyzed were summarized in biomarker-specific figures. Based on the biomarker-specific figures, three other biomarkers (neutrophil/lymphocyte ratio [NLR] and P-selectin in blood and F2-isoprostane in urine) had significant results in two or more studies using similar methodologies and timing of measurement, and were considered validated biomarkers. Four studies on NLR showed a proinflammatory state on admission and preoperatively in patients with DCI compared to patients without DCI (13-16). P-selectin, a marker of endothelial activation, was found to have a significantly larger increase during DCI onset, compared to paired samples in the non-DCI group in two studies

TABLE IV - Quality of relevant studies of validated biomarkers

Validated biomarker	Studies	Quality of studies
Clinical DCI		
ADAMTS13	Li, 2017 (11)	3/8
	Tang, 2015 (12)	4/9
F2-isoprostane	Wiśniewski, 2020 (19)	6/9
	Wiśniewski, 2017 (20)	6/9
Haptoglobulin 2-1	Kim, 2018 (8)	3/8
	Leclerc, 2015 (9)	5/8
	Ohnishi, 2014 (10)	6/8
Haptoglobulin 2-2	Kim, 2018 (8)	3/8
	Leclerc, 2015 (9)	5/8
	Ohnishi, 2014 (10)	6/8
NLR	Liu, 2020 (13)	6/8
	Al-Mufti, 2019 (14)	6/8
	Wu, 2019 (16)	7/8
	Tao, 2017 (15)	5/8
P-selectin	Wang, 2011 (17)	7/9
	Frijns, 2006 (36)	5/8
vWF	Li, 2017 (11)	3/8
	Tang, 2015 (12)	4/9
Radiological DCI		
LPR	Kofler, 2020 (26)	4/8
	Torné, 2020 (27)	2/8

ADAMTS13 = ADAM metallopeptidase with thrombospondin type 1 motif 13; DCI = delayed cerebral ischemia; LPR = lactate/pyruvate ratio; NLR = neutrophil/lymphocyte ratio; vWF = von Willebrand factor.

(17,18). F2-isoprostane in urine on day 3 after SAH was significantly associated with the occurrence of DCI in two studies (19,20). The quality of studies from which we found the seven validated biomarkers is listed in Table IV. Both meta-analyses and biomarker-specific figures can be found in the supplemental data (Supplementary material, Figure S1-S58, page 35-45).

Among the 121 significant biomarkers investigated by one study only, 5 (n = 4 nongenetic, n = 1 genetic) biomarkers were investigated by high-quality studies: brain natriuretic peptide (21), osteopontin (22), tenascin C (23), and neutrophil/albumin ratio (24) in blood and endothelial nitric oxide synthase (SNP rs2070744 T-786C) using buccal swabs (25).

Radiological DCI

Biomarkers of radiological DCI were studied by 78 studies comprising 165 different biomarkers (Fig. 2) in 10,282 SAH patients of whom 2,254 (22%) developed DCI. Most biomarkers (146 of 165, 88%) were investigated by one study and 19 (12%) by more than one study (range 2 to 8, median 2). The distribution of the biomarkers among the biomarker groups is shown in Table V.

In total, 63 biomarkers (n = 39 nongenetic, n = 24 genetic) were classified as significantly associated with radiological DCI

(Supplementary material, Table S2, page 13-34). A summary of the studied and significant biomarkers and specific trends observed within each biomarker group is given in Table V. Of the significant biomarkers, 56 were investigated by one study and 7 by multiple studies. Meta-analyses were not possible. Based on the biomarker-specific figures, one biomarker, lactate/pyruvate ratio (LPR) in blood, was considered validated as two independent studies showed that an LPR higher than 40 was associated with DCI, measured during the first weeks following SAH (26,27). The quality of the two studies on LPR was 4/8 and 2/8 (Table 4). The biomarker-specific figures can be found in the supplemental data (Supplementary material, Figure S59-S77, page 46-48).

Among the 56 significant biomarkers investigated by one study, 7 nongenetic blood biomarkers were investigated by a high-quality study: monocyte LFA-1, monocyte Mac-1, monocyte PSGL-1, neutrophil LFA-1, neutrophil Mac-1, neutrophil PSGL-1, and osteopontin (22,28).

Clinical vs. Radiological DCI

Of all biomarkers, 89 were studied for both clinical and radiological DCI (Supplementary material, Table S2, page 13-34). Eight blood biomarkers were significantly associated with both clinical and radiological DCI (d-dimer, platelet activating factor, interleukin-17, lectin complement pathway activity, osteopontin, brain natriuretic peptide, urea/creatinine ratio and serine proteinase inhibitor family E member 1 SNP rs2227631 + rs1799889 + rs6092 + rs6090 + rs2227684 + rs7242). Forty-five biomarkers were classified as nonsignificant for both clinical and radiological DCI. Of the remaining 36 biomarkers, the classification into significant, inconclusive, or nonsignificant differed between clinical and radiological DCI.

Discussion

This review has selected seven biomarkers of clinical DCI (haptoglobin polymorphisms 2-1 and 2-2, ADAMTS13, NLR, P-selectin, and vWF in blood and F2-isoprostane in urine) and one biomarker of radiological DCI (LPR in MD) as most promising biomarkers of DCI. Of note, the majority of significant biomarkers (121/141 of clinical DCI and 56/63 of radiological DCI) were only evaluated by one study, and although being potential biomarkers, especially the 12 biomarkers from high-quality studies, are in need of validation.

In 2018, a review on biomarkers of DCI yielded a panel of 21 predictive biomarkers (3); however, this review had three substantial limitations, which may have misguided the selected panel of biomarkers: (1) patients with solely angiographic vasospasm and increased flow velocities on TCD ultrasound, as indication of DCI, were also included, (2) the results of biomarkers measured in different media (CSF and blood) were combined, and (3) no differentiation between predictive and diagnostic biomarkers was made. In our present review, the most up-to-date definition of DCI was strictly applied during the selection of eligible articles and a biological substance measured in multiple media was considered a separate biomarker for each medium. As a result, our review yielded less studies (209 vs. 270). Although we found more biomarkers (724 vs. 257), our review yielded

TABLE V - Number of studied and significant biomarkers and specific trends observed within each biomarker group of radiological DCI.

Biomarker group	Biomarkers of radiological DCI		Specific trends observed among significant biomarkers within biomarker group
	Studied	Significant	
Nongenetic biomarkers	**100**	**39**	
Brain injury	6	2	All indicated more brain injury in patients with DCI. No specific trend in time.
Coagulation cascade	16	9	All four biomarkers of primary hemostasis indicated increased platelet activation/aggregation, three of four secondary hemostasis biomarkers showed hypercoagulability, one biomarker showed hyperfibrinolysis in patients with DCI. No specific trend in time.
Cortical spreading depressions	–	–	–
Endothelial injury	4	2	Both biomarkers indicated increased endothelial injury in DCI.
Inflammation and immune system	33	15	12 of 15 inflammation and immune system markers indicated increased inflammation and elevated immune response in patients with DCI. No specific trend in time.
Oxidative stress	4	2	Both biomarkers indicated increased oxidative stress in patients with DCI.
Vascular tone	8	1	Vasoconstriction between days 0 and 14 after SAH in DCI.
Volemic status	2	2	More diuresis and natriuresis were observed in DCI. More DCI in hyponatremia vs. no hyponatremia.
Other	27	6	Subcategories were: angiogenesis, cerebral metabolism, lipid metabolism, stress response, and protein metabolism.
Genetic biomarkers	**63**	**24**	
Genomic	3	0	Function often unclear; however, four biomarkers were involved in processes of coagulation, inflammation, and vascular tone.
MicroRNA	28	19	
Methylation	–	–	
Polymorphism	5	1	
RNA	–	–	
Single nucleotide polymorphism	27	4	

DCI = delayed cerebral ischemia; RNA = ribonucleic acid; SAH = subarachnoid hemorrhage.

only eight validated biomarkers, as opposed to 21 by Jabbarli et al., of which two (ADAMTS13 and NLR) were in agreement (3). The discrepancy between the panels of biomarkers selected by both reviews emphasizes the importance of a uniform definition of DCI, especially in the absence of solid diagnostic criteria.

The eight validated biomarkers of DCI are all related to known pathways of the multifactorial pathophysiology of DCI. In clinical DCI, increased platelet aggregability, thereby potentially leading to the formation of microthrombi, was observed by decreased admission levels of ADAMTS13 and increased levels of vWF on day 4 after SAH. As DCI usually occurs between days 4 and 10 after SAH (4), the early onset of significantly differing levels makes these biomarkers potentially predictive of DCI. Notwithstanding, the quality of the studies was rather low (NOS scores of 3/8 and 4/9), therefore a high-quality study is necessary to further elucidate matters.

Most inflammation and immune system biomarkers seem to be significantly elevated early in the course of SAH. Accordingly, elevated NLR (a validated biomarker) in the first couple of days following SAH was found to be significantly associated with clinical DCI in four independent studies. But, the exact predictive ability, including determination of an optimal cut-off value with accompanying accuracy, specificity, and sensitivity, remains to be determined. Whether NLR could also serve as a preventive treatment target is debatable, as NLR is a highly nonspecific biomarker and nonspecific anti-inflammatory therapies have thus far proven disappointing for the prevention of DCI (29). P-selectin was found to significantly increase during clinical DCI onset in two studies, which suggests that P-selectin may be a potential candidate for diagnosis or therapeutic treatment, for example, P-selectin antagonism. Thus far, therapies targeting P-selectin have only been performed in experimental settings of ischemic stroke, showing a reduction in infarct volume and better clinical outcome (30), and myocardial infarction, showing significantly reduced myocardial damage after percutaneous coronary intervention (31). P-selectin antagonism has not been studied in SAH, yet.

Three validated biomarkers of oxidative stress were found for clinical DCI in our review: F2-isoprostane in urine and genetic biomarkers haptoglobin polymorphism 2-1 and 2-2. Genetic markers often require extensive processing time and

are therefore unsuitable for acute diagnosis; however, early determination of genetic profiles, for example, on admission, may aid in stratification of patients at high risk of clinical DCI. As such, the haptoglobin polymorphisms 2-1 and 2-2 may be useful for patient stratification, and could perhaps provide a potential preventive treatment target, for example, the administration of exogenous haptoglobulin (32). For F2-isoprostane, whether the observed increased urine levels have preceded the onset of clinical DCI in all patients is unknown; therefore, we cannot distinguish whether these biomarkers are predictive or diagnostic. Further research should be performed to explore the temporal relationship of these markers in regard to clinical DCI development.

The remaining validated biomarker, LPR in MD, allows for continuous neuromonitoring providing direct metabolic information, which can be used to detect an ischemic state, that is, radiological DCI. Since DCI currently is a clinical diagnosis per exclusion, LPR may be a helpful additive in comatose patients, as it may detect metabolic distress in an early phase already, before hypodensities are visible on noncontrast head CT and when ischemic brain injury may still be preventable. However, this invasive technique yields metabolic information only locally, resulting in a detection failure of at least 20% (27).

The difficulty of DCI is in the incomplete understanding of its pathophysiology and lack of hard diagnostic criteria. Currently, two definitions are used to identify patients with DCI: clinical and radiological DCI (4). Even though adherence to one definition yields a different selection of patients than the other, both are strongly related to poor clinical outcome at follow-up, therefore both seem to be relevant (33-35). Differences in the two definitions are clearly observed in this review, too, as 36 of 89 biomarkers studied for both definitions showed dissimilar results. The clinical definition seems to be the most relevant, given that early detection and correction of altered biomarkers may prevent the onset of clinical deficits. However, not all patients are neurologically assessable, therefore in comatose patients we currently rely on the radiological definition for DCI diagnosis. Considering that radiological appearance of ischemia or infarction is not immediately visible, once radiological DCI is diagnosed the treatment window for ischemic disease has often elapsed. Diagnosing radiological DCI based on biomarkers may lead to earlier detection of radiological DCI, perhaps even within the treatment window.

Limitations of this review are the heterogeneity in definitions used for DCI in literature, which complicates the inclusion of relevant studies, the methodological heterogeneity among included studies, which has resulted in a largely narrative review with a suboptimal method used for classification of biomarkers, and a high proportion of poor quality studies. The quality of studies was not implemented in our method used for classification. As a result, even though the results of studies of validated biomarkers have been reproduced by a second group, some of the selected validated markers rely on studies with relatively poor quality (e.g., ADAMTS13, vWF, and LPR). Strengths of this review are the strict use of the most up-to-date definition of DCI and the inclusion of all types of laboratory markers in blood as well as CSF.

Conclusion

In this review, seven biomarkers of clinical DCI (haptoglobin polymorphisms 2-1 and 2-2, ADAMTS13, NLR, P-selectin, and vWF in blood and F2-isoprostane in urine) and one biomarker of radiological DCI (LPR in MD) were selected as the most promising biomarkers of DCI. Future research should focus on determining the exact predictive or diagnostic abilities of these biomarkers, and exploring whether these biomarkers could serve as preventive or therapeutic treatment targets for DCI.

Disclosures

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