

Magnetic resonance imaging and brain injury in the chronic phase after aneurysmal subarachnoid hemorrhage: A systematic review

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Abstract

Background: Case-fatality rates after aneurysmal subarachnoid hemorrhage have decreased over the past decades. However, many patients who survive an aneurysmal subarachnoid hemorrhage have long-term functional and cognitive impairments.

Aims: We sought to review all data on conventional brain MRI obtained in the chronic phase after aneurysmal subarachnoid hemorrhage to (1) analyze the proportion of patients with cerebral infarction or brain volume changes; (2) investigate baseline determinants predictive of MRI-detected damage; and (3) assess if brain damage is predictive of patient outcome.

Summary of review: All original data published between 1 January 2000 and 4 October 2017 was searched using the PUBMED, EMBASE, and Web of Science databases. Based on preset inclusion criteria, 15 from 5200 articles were included with a total of 996 aneurysmal subarachnoid hemorrhage patients. Quality assessment, risk of bias assessment, and level of evidence assessment were performed. The results according to aim, with levels of evidence, were: (1) 25 to 81% of aneurysmal subarachnoid hemorrhage patients show infarcts (strong); there is a higher ratio of cerebrospinal fluid-to-intracranial volume in patients compared to controls (strong); (2) there is a negative relation between age (moderate), DCI (low) and brain volume measurement outcomes; (3) lower brain parenchymal volume (strong) and the presence of infarcts or infarct volumes (moderate) are associated with a worse outcome.

Conclusion: Patients after aneurysmal subarachnoid hemorrhage may demonstrate brain infarcts and decreased brain parenchyma, which is related to worse outcome. Thereby, both brain infarcts and brain volume measurements could be used as outcome markers in pharmaceutical trials.

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Keywords

Subarachnoid hemorrhage, MRI, brain injury, cerebral infarction, volume measurements, radiology

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Introduction

Case-fatality rates after aneurysmal subarachnoid hemorrhage (aSAH) have decreased over the past decades. Today, approximately one-third of patients die within three months after the event.¹ Of the patients who survive, many have long-term functional and cognitive impairments.^{2,3}

Common determinants of poor functional outcome are the impact of the acute hemorrhage, also known as early brain injury (EBI),^{4,5} bleeding related acute ischemia,^{6,7} and complications such as rebleeding of the aneurysm, procedure-related complications,^{8,9} delayed

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cerebral ischemia (DCI),^{10–13} and hydrocephalus.¹⁴ It remains unclear, however, how these events lead to MRI changes in the chronic phase after aSAH, and how the MRI changes relate to adverse functional outcome.

Previous MRI research has focused on the assessment of focal brain injury or brain volume changes occurring after aSAH. As well, the relation between brain injury and clinical- or neuropsychological outcome has been investigated. In the present review, we grouped the results of studies performed in this area with the purpose to provide insight for future research. The following aims were formulated: (1) to analyze the proportion of aSAH patients with cerebral infarction or brain volume changes in the chronic phase; (2) to investigate baseline determinants predictive of MRI-detected damage; and (3) to assess if MRI-detected damage is predictive of patient outcome.

Methods

Search strategy

A literature search was conducted using the PUBMED, EMBASE, and Web of Science databases and included articles published between 1 January 2000 and 4 October 2017. The search variables were: (magnetic resonance OR MRI) AND (subarachnoid hemorrhage OR SAH) OR (DCI OR DCI OR DIND). Eligible articles were identified according to PICO criteria. Patient population (P): (1) ≥ 10 patients included with aSAH, defined as the presence of subarachnoid blood shown by CT or lumbar puncture and the presence of an aneurysm on CT angiography, magnetic resonance angiography, or digital subtraction angiography; (2) MRI scans performed >21 days after aSAH. Intervention (I): imaging sequences were either T1-weighted imaging, T2-weighted imaging, proton density-weighted imaging (PD), and/or fluid-attenuated inversion recovery (FLAIR). Comparator (C): N/A. Outcomes (O): MRI brain damage, either infarcts or brain volume change, >21 days after aSAH. Exclusion criteria were (1) article not reporting original data; (2) article written in another language than English, French, German, or Dutch; (3) conference abstract; (4) cause of the hemorrhage unknown or other than aneurysmal in $>5\%$ of patients; (5) animal study. Two authors (J.D.V. and L.v.d.K.) screened on title and abstract. In case of disagreement, a consensus reading was performed. Subsequent full text screening was conducted by B.S., and exclusion was performed in consensus with J.D.V. If more than one article used the same or overlapping patient population and the same outcome measures, only the report with the largest patient population was included. If an article reported

on MRI findings but the timing of imaging was unclear, the corresponding author was contacted for additional information. In case of no response, the article was excluded. The reference lists of included articles were hand-searched for additional eligible articles. A flow-chart of the screening process can be found in Figure 1. The review methodology was published in the PROSPERO database (CRD42016040095). The PRISMA 2009 checklist for transparent reporting of systematic reviews and meta-analyses was applied.

Quality assessment, risk of bias assessment, and level of evidence assessment

Quality assessment was conducted based on a previously published scoring system^{15,16} adapted to fit the studies within the scope of this review (Supplemental Table 1). Two authors (B.S. and J.D.V.) conducted the assessment independently, and disagreement was resolved by consensus. A high-quality article was pre-defined as a score between 12 and 18. A score below 12 was considered to reflect a low-quality article.

Risk of bias assessment was performed by two authors (B.S. and J.D.V.) to evaluate external validity, internal validity, and overall risk of study bias (Supplemental Table 2).¹⁷

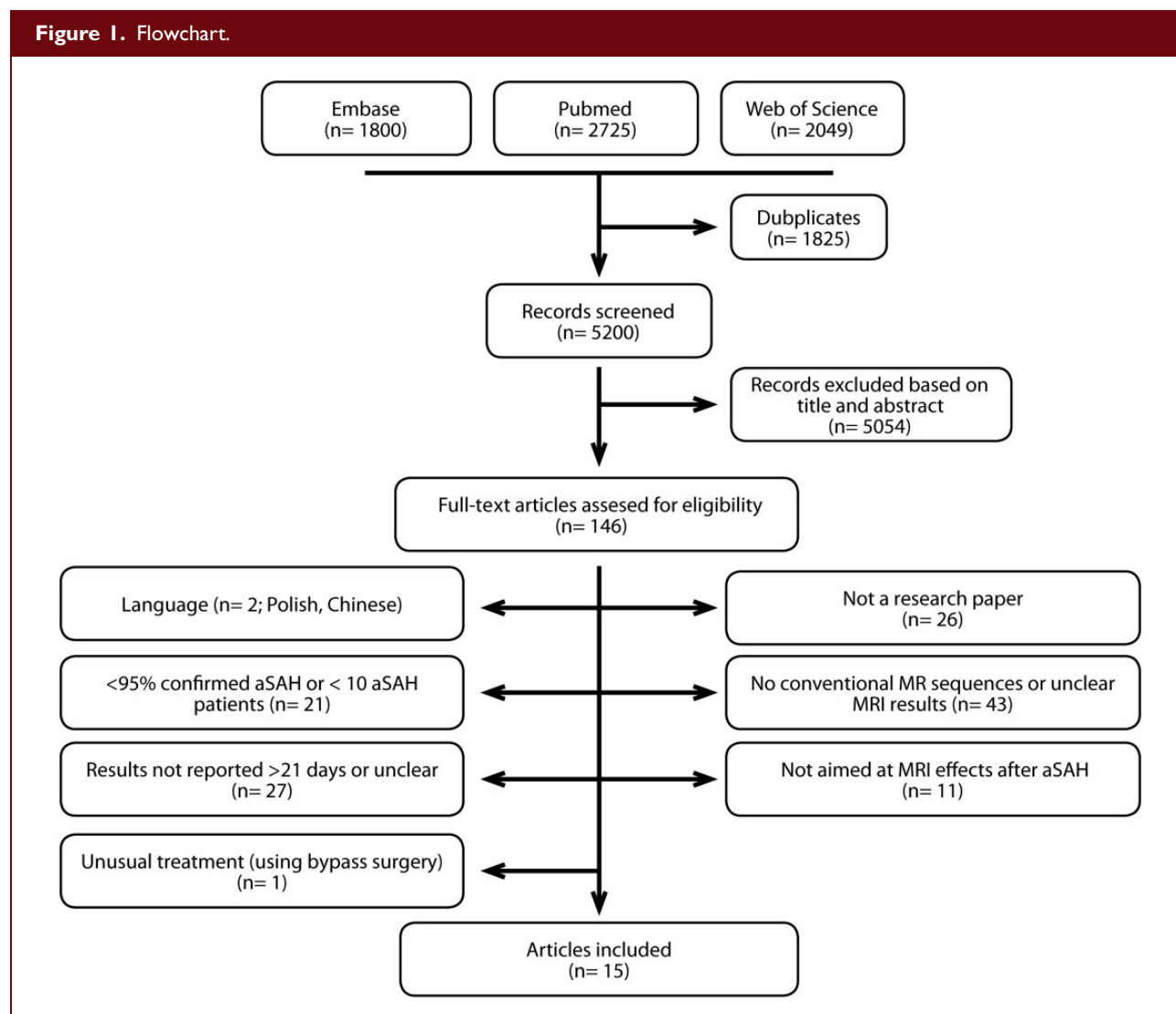
The level of evidence (strong, moderate, weak, low, or inconsistent) for a certain finding was determined based on study quality and number of studies supporting the finding (Supplemental Figure 1).

Data extraction and analyses

The following baseline characteristics were extracted: number of patients who received MR imaging, age, sex, clinical condition at admission, i.e. Hunt and Hess scale (H&H)¹⁸ or World Federation of Neurosurgical Societies SAH grading system (WFNS),¹⁹ amount of blood on admission CT, i.e. Hijdra scale²⁰ or Fisher grade,²¹ type of aneurysm treatment, the timing of the MRI, MRI sequences, and field strength.

To address the first aim, data on the number of patients with a cerebral infarct were extracted, and the proportion (with 95% CI) of patients with an infarct was calculated. Additionally, the number of infarcts per patient and infarct size was extracted. As well, brain volume measurement results were extracted. Due to the heterogeneity of the used measurements, it was chosen to focus on the cerebrospinal fluid/intracranial volume ratio (CSF/ICV) or measures related to it, and on the ventricular-to-intracranial-width ratio (VIWr). The incorporated measures related to the CSF/ICV were brain parenchymal volume (BPV), lateral ventricle volume, and peripheral CSF volume.

Figure 1. Flowchart.



To address the second aim, data on determinants and their relation to cerebral infarct or brain volume changes were extracted. The parameters investigated were: age, the clinical condition on admission, and the amount of extravasated blood on admission CT. For brain volume changes, two additional determinants could be investigated: preoperative- or symptomatic hydrocephalus, and DCI.

To address the third aim, data describing the relation between brain damage and neuropsychological or clinical outcome were extracted.

Statistical analyses were performed using SPSS Statistics (SPSS, Inc., Chicago, IL, version 22).

Results

The search strategy yielded 5200 unduplicated articles of which 15 were included (Figure 1). Of these 15

articles, two had an overlapping patient population, but different outcome measures.^{22,23} The articles totaled 996 aSAH patients with a median number of 55 per study (range 20–138). Four articles included control subjects with a median number of 30 subjects (range 25–30).^{22–25} For each study, study characteristics are presented in Supplemental Table 3. Seven out of the fifteen articles fulfilled the criteria for high-quality studies.^{22–24,26–29} Levels of evidence of the findings described below are presented in Table 1.

Proportion of aSAH patients with cerebral infarction or brain volume changes

Cerebral infarction. Twelve studies, with a median number of 50 patients per study (range 20–138), reported on the presence of cerebral infarcts.^{24–28,30–36} Of 791 patients, 372 showed a cerebral infarct.

Table 1. Level of evidence

Statement	Level of evidence
Brain damage – Cerebral infarct	
25–81% of patients showed an cerebral infarct on MRI in the chronic phase after aSAH	Strong
Brain damage – Volume measurements	
There was a significant difference in brain volume measurements between patients and controls	Strong
Determinants of volume changes	
Patient age was significantly correlated with a higher CSF/ICV and VIWr	Moderate
DCI was found to be related to smaller brain parenchymal volumes and lateral ventricle enlargement	Low
Brain damage and clinical or neuropsychological outcome – Cerebral infarct	
The presence of infarcts or infarct volumes was significantly correlated with clinical and neuropsychological outcome	Moderate
Brain damage and neuropsychological or clinical outcome – Volume measurements	
Brain parenchymal volume measurements and VIWr were related to clinical and neuropsychological outcome	Strong

The percentage of patients with an infarct ranged between 25 and 81 percent between studies (see Supplemental Table 3). The included studies varied in patient disease severity between WFNS I or II at admission or H&H grade 1 up to 4.^{31,36}

One study reported on the number of infarcts detected in the patients who demonstrated infarcts: 152 infarcts in 84 patients.³¹ Six studies reported on the size of the infarcts.^{25,26,28,29,32,35} Three studies used a volume measurement (ml or cm³) and found a mean volume of 8.6–43.4 ml in a total of 108 patients.^{25,28,35} The other three studies reported the mean diameter of the deficit, which ranged from 19 mm to 57 mm in a total of 102 patients.^{26,29,32} These results are shown in Table 2.

Brain volume changes. Six articles, with a median number of 65.5 patients per study (range 38–88), reported on brain volume changes.^{22–25,29,35} In four of the six

articles, patients were compared to age- and sex-matched controls.^{22–24,35}

Two articles reported on the CSF/ICV ratio,^{22,24} and in two other articles the CSF/ICV could be calculated.^{25,35} The results (Table 3) show that CSF/ICV ratios were significantly higher in patients compared to controls for two out of three studies,^{22,24} while there was no difference in the third.³⁵ The third studies' control group partly consisted of individuals who underwent endovascular intervention for a non-ruptured aneurysm.³⁵

Three articles reported the VIWr (Table 3).^{23,24,29} Two studies found a significant higher mean ratio in aSAH patients compared to controls.^{23,24} The third study reported results found in endovascular- and surgical-treated patients.²⁹

Baseline determinants predictive of MRI-detected damage

Determinants of cerebral infarction. Table 4 summarizes the results found on this topic. In short, 2 studies, with 38 and 88 patients, addressed this subject.^{25,29} Clinical condition at admission was found not to relate to presence of cerebral infarct or infarct volumes (descriptive analysis).²⁵

One study found no relation between the amount of extravasated blood on admission CT and the presence of cerebral infarcts or infarct volumes (descriptive analysis),²⁵ while the second study did find a significant association with a higher Fisher grade. More specifically, a higher Fisher grade was associated with an increased number of infarcts outside the territory of the parental artery of the aneurysm ($p = 0.001$).²⁹

Determinants of brain volume changes. Table 4 summarizes the results found on this topic. In short, three studies, with a median of 76 patients (range 38–77), reported on this subject.^{23–25} A significant correlation of age with brain volume changes was found in two studies (CSF/ICV: $r = 0.718$, $p < 0.001$; CSF/ICV: $r = 0.416$, $p < 0.001$; VIWr: $r = 0.366$, $p = 0.001$).^{23,24}

No relation between clinical grade at admission and brain volume changes was found in two studies (CSF/ICV: $p = 0.239$; BPV: B (95%CI); 3.2 (–5 – 12.1)).^{24,25} One study on the other hand, did find more brain atrophy in patients with higher H&H grade (VIWr: $p < 0.001$).²⁴

The amount of extravasated blood on admission CT was found to be associated with brain atrophy in one study (CSF/ICV: $p = 0.014$; VIWr: $p = 0.001$),²⁴ whereas another did not find a relation (BPV: B (95%CI); 0.38 (–0.71–1.46)).²⁵

One research group reported that patients with hydrocephalus on admission CT tended to have lower

Table 2. Size of the deficits in patients with a cerebral infarct

Study	No.	Mean volume of infarct (ml/cm ³)	SD	Mean diameter of infarct (mm)	SD
Bendel et al. ²⁸	15/67 ^a	17.6	35.8		
	33/71	20.9	46.5		
	7/67	27.6	26.3		
	11/71	43.4	69.7		
De Bresser et al. ^{35 35}	26/55	8.7 ^b	0.4–61.3 ^b		
De Bresser et al. ²⁵	16/38	8.6 ^b	1.1–80.9 ^b		
Koivisto et al. ²⁹	8/40 ^a			43	40
	21/47			36	31
	9/40			30	29
	8/47			52	30
Koivisto et al. ³²	6/19 ^c			19 ^d	13
	7/21			57	42
Soppi et al. ²⁶	21/62 ^e			39.3	27
	22/64			34.3	28

Note: In the articles it was not specified if, in case of multiple infarcts, a summation of the volumes or sizes was given or results of the largest infarct were given, unless stated otherwise.

No.: number of patients with an infarct / total MR population.

^aResults were presented based on vascular territory and treatment method (i.e. coiling or clipping), in descending order; infarcts in parental artery territory in coiled aSAH patients, infarcts in parental artery territory in clipped aSAH patients, infarct in vascular territories other than the parental territory in coiled aSAH patients, and infarcts in vascular territories other than the parental territory in clipped aSAH patients.

^bMedian and 10th–90th percentile.

^cPatients presented by treatment method; surgical and endovascular.

^dSize of infarction is size of largest deficit in case of multiple deficits.

^ePatients presented by treatment strategy; enteral and intravenous administration of nimodipine.

brain volumes (CSF/ICV: $p = 0.51$; VIWr: $p < 0.001$).²⁴ Another study reported that symptomatic hydrocephalus was not related to volume measurements (BPV: B (95% CI): -14 (-38 – 10); lateral ventricle volume: B (95% CI) 0.18 (-0.29 – 0.66)).²⁵

Lastly, it was reported that DCI is related to lower BPVs and lateral ventricle enlargement, which would result in a higher CSF/ICV (B (95% CI): -38 (-66 – -9); B (95% CI): 0.80 (0.26 – 1.35)).²⁵

Damage detected on MRI predictive of patient outcome

Clinical or neuropsychological outcome – Cerebral infarct. Table 5 shows all results on this topic. Two studies, with 32 and 88 patients, reported on the relation between presence of a cerebral infarct and clinical

outcome.^{29,34} An infarct ($p < 0.05$),³⁴ an infarct in the parental artery territory of the aneurysm ($p < 0.003$)²⁹ or in another vascular territory ($p = 0.003$)²⁹ was associated with worse clinical outcome. Logistic regression analysis proved an infarct in the parental artery territory of the ruptured aneurysm to be an independent predictor of poorer clinical outcome (OR 6.20; 95% CI 1.67–23.05; $p = 0.006$).²⁹

Two studies, with 88 and 138 patients, reported on the relation of infarct size and outcome.^{28,29} Size of infarcts in the parental artery territory ($p < 0.001$) or in another vascular territory ($p = 0.001$), was significantly associated with poorer clinical outcome.²⁹ A significant relation between infarct volume and deficits in several tests of visual reproduction, delayed story recall, performance intelligent quotient and verbal intelligence quotient was reported (most p -values < 0.01).²⁸

Table 3. Brain volume measurement outcomes

CSF/ICV ratio	No patients	CSF/ICV	No controls	CSF/ICV	p
Bendel et al. ²²	37	0.41 ± 0.036	30	0.38 ± 0.033	0.003
Bendel et al. ²⁴	76	0.36 ± 0.07	30	0.30 ± 0.063	0.001
De Bresser et al. ³⁵	55	0.21 ± 0.025	25	0.21 ± 0.029	0.681
De Besser et al. ²⁵	38	0.21 ± 0.034			
VIW ratio	No patients	Mean ± SD	No controls	Mean ± SD	p
Bendel et al. ²³	77	0.23 ± 0.06	30	0.20 ± 0.04	0.021
Bendel et al. ²⁴	76	0.23 ± 0.06	30	0.20 ± 0.038	0.020
Koivisto et al. ²⁹					
Endovascular patients	40	0.24 ± 0.07			
surgical patients	47	0.24 ± 0.08			

CSF/ICV; cerebrospinal fluid / intracranial volume; VIW: ventricular-to-intracranial width.

Clinical or neuropsychological outcome – Brain volume measurements. Table 5 shows all results on this topic. In short, four studies with a median of 65.5 patients (range 38–88) reported on correlations between brain volume measurements and clinical outcome.^{24,25,29,35}

The reported relations were as follows; a positive relation for BPV (at 6 ± 2 months OR 38.8, 95% CI 4.6–329.0; and at 18 months OR 91.2, 95% CI 2.5–3395.1),^{25,35} a positive relation for VIWr (GOS 2–4 vs. 5; 0.28 ± 0.06 vs. 0.23 ± 0.06, $p = 0.028$ and univariate analysis, $p = 0.04$),^{24,29} a positive relation for lateral ventricle volume (OR 7.4, 95% CI 1.6–33.5),³⁵ no relation for lateral ventricle volume (OR 1.1; 95% CI 0.2–5.1),³⁵ and no relation for peripheral CSF volume (OR 2.3, 95% CI, 0.6–8.0).³⁵ Sample size differences between the studies investigating the relation between lateral ventricle volume and outcome may have contributed to conflicting differences; the sample size was 55 in the study where a positive relation was found compared to 38 in the negative study.

Two studies, with 37 and 76 patients, reported on brain volume measures and neuropsychological outcome.^{22,24} In short, there was a positive relationship and a tendency towards a positive relationship between CSF/ICV and neurologic deficits (present vs. absent; 37.45 ± 6.13 vs. 32.66 ± 7.25, $p = 0.003$ and 42.0 ± 3.6 vs. 40.4 ± 3.5, non-significant).^{22,24} A higher VIWr was found in patients with any neuropsychological deficit (present vs absent; 0.25 ± 0.07 vs. 0.21 ± 0.05, $p = 0.028$), especially with a deficit in general intellectual functioning (present vs. absent; 0.30 ± 0.04 vs. 0.22 ± 0.06, $p < 0.001$).²⁴

Discussion

The following findings, summarized according to the aims of the review, were found: (1) 25–81% of aSAH patients show infarcts; there is a higher ratio of cerebrospinal fluid-to-intracranial volume in patients compared to controls; (2) there is a negative relation between age and DCI versus brain volume measurement outcomes; (3) lower BPV and the presence of infarcts or infarct volumes are associated with a worse outcome.

The wide range (25–81%) in aSAH patients demonstrating brain infarcts (strong level of evidence) underscores the heterogeneity of patient populations in the included articles. Regarding brain volume changes, it was found that aSAH patients have a lower brain volume compared to controls (strong level of evidence).^{22–24} Unfortunately, due to the continuous nature of a volume measurement and the effect of age on such a measurement, a cut-off value for presence or absence of brain volume loss could not be established. Therefore, the proportion of aSAH patients with brain volume loss could not be calculated. However, in general, the decreased brain volume in aSAH patients as compared to controls does bring support for the EBI theory. Further support for the EBI theory is found in two of the studies included in this review. One study found brain atrophy independent of infarct presence,²² and a second study quantified global ventricular and sulcal enlargement.²⁴

Regarding the question whether there are determinants predictive of MRI-detected damage, our search

Table 4. Determinants of cerebral infarcts and brain volume measurements

Determinant – Cerebral infarcts			
	Study	Outcome (statistics)	
Age	–	–	
Clinical condition at admission	De Bresser et al. ²⁵	Not related to the presence of infarcts or infarct volumes (descriptive analysis)	
Amount of extravasated blood	De Bresser et al. ²⁵	Not related to the presence of infarcts or infarct volumes (statistics not given)	
	Koivisto et al. ²⁹	Higher Fisher grade is associated with increased number of infarcts outside the territory of the parental artery of the aneurysm ($p = 0.001$)	
Determinant – Brain volume measurement			
	Study	Measure	Outcome (statistics)
Age	Bendel et al. ²⁴	CSF/ICV	Significant correlation with a higher ratio ($r = 0.781$, $p < 0.001$)
	Bendel et al. ²⁴	VIWr	Significant correlation with a higher ratio ($r = 0.416$, $p < 0.001$)
	Bendel et al. ²³	VIWr	Significant correlation with a higher ratio ($r = 0.366$, $p = 0.001$)
Clinical condition at admission	Bendel et al. ²⁴	CSF/ICV	No relation at 12 months (H&H grade 1-2: 43.98 ± 7.54 vs. H&H grade 3–5: 37.15 ± 5.18 ; $p = 0.239$)
	De Bresser et al. ²⁵	BPV	No relation at 18 months (B, 95% CI: 3.2, –5–12.1)
	Bendel et al. ²⁴	VIWr	Higher H&H grade is related to higher ratio (H&H 1–2: 0.21 ± 0.06 vs. H&H 3–5: 0.29 ± 0.05 , $p < 0.001$)
Amount of extravasated blood	Bendel et al. ²⁴	CSF/ICV	Associated with a higher ratio (Fisher grade 0-2: 32.75 ± 7.75 vs. Fisher grade 3–4: 37.13 ± 6.10 , $p = 0.014$)
	Bendel et al. ²⁴	VIWr	Associated with a higher ratio (grade 0–2: 0.20 ± 0.06 vs. grade 3–4: 0.25 ± 0.06 , $p = 0.001$).
	De Bresser et al. ²⁵	BPV	No relation with Hijdra score (B, 95% CI: 0.38, –0.71–1.46)
Hydrocephalus	Bendel et al. ^{24a}	CSF/ICV	Tends to be related (hydrocephalus: 34.44 ± 7.57 vs. no hydrocephalus: 37.64 ± 5.35 , $p = 0.51$)
		VIWr	Significant correlation (hydrocephalus: 0.28 ± 0.06 vs. no hydrocephalus: 0.21 ± 0.06 , $p < 0.001$)
	De Bresser et al. ^{25b}	BPV	Not related (B, 95% CI: –14, –38–10)
			Lateral ventricle volume
DCI ^c	De Bresser et al. ²⁵	BPV	Related to smaller volumes (B, 95% CI: –38, –66– –9)
	De Bresser et al. ²⁵	Lateral ventricle enlargement	Related to lateral ventricle enlargement (B, 95% CI: 0.80, 0.26–1.35)

^aPreoperative hydrocephalus on admission CT.^bSymptomatic hydrocephalus defined as a decreased level of consciousness with increased bicaudate index that was larger than the upper 95th percentile for age.^cDefined as new focal deficits during admission or decreasing level of consciousness with new infarcts on CT.

CSF/ICV; cerebrospinal fluid/intracranial volume; VIWr: ventricular-to-intracranial width ratio; BPV: brain parenchymal volume; DCI: delayed cerebral ischemia.

Table 5. MRI damage predictive of patient outcome

Infarction and patient outcome		
	Study	Outcome (statistics)
Infarct presence	Pyysalo et al. ³⁴	Infarct presence was related to poorer clinical outcome ($p < 0.05$)
	Koivisto et al. ²⁹	Infarct presence within ($p < 0.003$) or outside the parental artery territory ($p = 0.003$) was associated with poorer clinical outcome. Infarct in the parental artery territory of the aneurysm was an independent predictor of poorer clinical outcome (OR 6.20; 95% CI 1.67–23.05; $p = 0.006$, logistic regression ^a)
Infarct volume	Bendel et al. ²⁸	Relation between infarct volumes and tests of visual reproduction, delayed story recall, performance intelligent quotient and verbal intelligence quotient (13 of 17 tests showed significant correlation, with most p -values < 0.01 .)
	Koivisto et al. ²⁹	Size of infarct within ($p < 0.001$) or outside the parental artery territory ($p = 0.001$) was associated with poorer clinical outcome
Brain volume measures and patient outcome		
Measure	Study	Outcome (statistics)
CSF/ICV	Bendel et al. ²⁴	A significant higher ratio was found in patients with a neurologic deficit (present: 37.45 ± 6.13 vs. absent: 32.66 ± 7.25 , $p = 0.003$)
	Bendel et al. ²²	In patients with at least one neuropsychological deficit, there was a trend towards a slightly higher ratio compared to patients without a deficit (present: 42.0 ± 3.6 vs. absent: 40.4 ± 3.5 , non-significant)
VIWr	Bendel et al. ²⁴	A higher ratio was found in patients with a lower GOS or patients with a neuropsychological deficit (GOS 2–4 vs. 5: 0.28 ± 0.06 vs. 0.23 ± 0.06 , $p = 0.028$ and deficit present vs. absent: 0.25 ± 0.07 vs. 0.21 ± 0.05 , $p = 0.028$). Especially with a deficit in general intellectual functioning (present vs. absent: 0.30 ± 0.04 vs. 0.22 ± 0.06 , $p < 0.001$)
	Koivisto et al. ²⁹	Relation between higher ratio and poorer clinical outcome (GOS) ($p = 0.04$)
BPV	De Bresser et al. ³⁵	Lower volume 6 months after ictus was associated with worse outcome (mRS) (OR 38.8, 95% CI 4.6–329.0)
	De Bresser et al. ²⁵	Lower BPV at 18 months after ictus was associated with worse outcome (mRS) (OR 91.2, 95% CI 2.5–3395.1)
Ventricle volume	De Bresser et al. ³⁵	Higher lateral ventricle volume 6 months after ictus was associated with worse clinical outcome (mRS) (OR 7.4, 95% CI, 1.6–33.5)
	De Bresser et al. ²⁵	No association was found between lateral ventricle volume at 18 months after ictus and outcome (mRS) (OR 1.1, 95% CI 0.2–5.1)
Peripheral CSF volume	De Bresser et al. ³⁵	Higher peripheral CSF volume 6 months after ictus was not associated with outcome (mRS) (OR, 2.3, 95% CI 0.6–8.0)

^aVariables used in the model: size of the ischemic lesion in the parental artery territory or in any other location; presence of an ischemic lesion in the parental artery territory or in any other location; deficit due to preoperative intracerebral hematoma and higher VIWr.

CSF/ICV: cerebrospinal fluid/intracranial volume; VIWr: ventricular-to-intracranial width ratio; mRS: modified Rankin Scale; GOS: Glasgow outcome scale.

taught us that a patient's age is negatively related to brain volume (moderate level of evidence), and that DCI relates to smaller BPV and lateral ventricle enlargement (low level of evidence). The first, although yielding limited evidence, is not surprising. It is well

known that some quantity of brain volume loss is encountered with increasing age.³⁷ The second finding could be attributed to two things. One, in the study investigating this topic, the presence of new infarcts was included in their DCI definition.²⁵ Logically, this

would lead to a negative relation of DCI with brain volume due to volume loss within the infarcted area. Two, pronounced EBI, resulting in an increase of global parenchymal loss, may increase the likelihood of developing DCI. Besides the relation of age and DCI with MRI-detected damage, we were not able to identify any other positive or negative determinant. In fact, most investigated determinants produced conflicting results. This may be due to heterogeneity of the used research methods. Across studies, different tools or scoring systems were used for both determinants and outcome measures which made the results difficult to summarize and may have introduced inadequacies. For example, two scoring methods were used to assess the amount of extravasated blood, i.e. Fisher grade and Hijdra scale. Of these two, the Hijdra score is thought to be more precise since it takes into account specific anatomic locations and it is shown to have a better interobserver agreement than the Fisher scale.³⁸ The same accounts for the discrepancies in findings between CFS/ICV and VIWr. In general the laborious volume measurements are thought to be more precise than the simple planimetric measure of the VIWr.

Our assessment of the relationship between MRI-detected damage and patient outcome, resulted in the findings that BPV and VIWr are related to clinical- and neuropsychological outcome (strong level of evidence), and that the presence of infarcts or infarct volumes are significantly correlated with clinical or neuropsychological outcome (moderate level of evidence). This latter finding is not surprising, since neurologic deficits are expected when infarcts occur in critical brain areas. It is known that tests may be difficult to perform in aSAH patients due to test difficulty, poor clinical condition, or severe headache during mental exercise.³ Therefore, studies investigating these properties may be skewed towards patients with better clinical outcome due to selection bias. Furthermore, a simple clinical tool such as the GOS can underappreciate the neuropsychological impact due to the gross subdivision into categories. For instance, patients with GOS “5” (i.e. mild or no disability) might still have subtle cognitive deficits and a need to apply adaptive strategies in daily life.^{3,27,39}

A limitation of this review is that only cerebral infarcts and brain volume changes were investigated. Not only infarcts but also many different focal injury entities can occur, including white matter lesions, superficial siderosis, and leukoaraiosis. Taking these lesions into account might lead to stronger levels of evidence. However, the manner of data presentation in the included studies did not allow for a thorough evaluation of this.

Another limitation is that most studies showed skewness towards a good recovery for the included

patients. This is probably caused by the fact that patients had to endure scanning sessions and other follow-up investigations to be able to participate. Moreover, a few studies used data of MRI-sequences which were only obtained when the patient voluntarily stayed longer in the scanner, resulting in selection bias.^{22–24} As well, a few studies even stated a good clinical condition or functional recovery as a inclusion criterium.^{25,35} Thereby, it is likely that the general patient outcome in clinical practice, and thereby most likely the MRI results, is worse than the presented results.

Future directions

The findings of this review are relevant as they underscore that not only focal brain injury plays an important role in the course of the disease, but presumably EBI also attributes significantly to brain damage as was proven by brain volume loss irrespective of brain infarcts. The results regarding possible determinants of infarct development or brain volume loss, and the relation between brain damage and neuropsychological or clinical outcome, however, were scarce and heterogeneous of character. On the one hand, this shows the complexity of the effects of the disease with research focusing on different parameters, while on the other hand, it emphasizes the need to conduct research on a uniform basis to be able to draw solid conclusions.

Therefore, in future work the entity of EBI, its effect on volume changes and, in continuation, its effect on patient outcome should be investigated. Of equal importance is the question how to intervene in this process to constrain global neuronal loss. In addition, standardized research needs to be conducted to draw rigid conclusions regarding determinants of brain injury and/or brain volume measurement outcomes, and the relation with clinical- or neuropsychological outcome. Only when understanding the source of the damage and the subsequent effects on patient level, therapies can be targeted to prevent any additional damage and with that improve patient outcome.

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