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REVIEW

Clinical Burden of Angiographic Vasospasm and Its Complications After Aneurysmal Subarachnoid Hemorrhage: A Systematic Review

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ABSTRACT

Introduction: Angiographic vasospasm (VSP), the narrowing of intracranial arteries, is a complication of aneurysmal subarachnoid hemorrhage (aSAH) and often results in delayed cerebral ischemia (DCI) and cerebral infarction. The objective of this systematic review was to summarize the clinical burden of angiographic VSP and its related complications (DCI and cerebral infarction) after aSAH.

Methods: Systematic searches of MEDLINE, Embase, and the Cochrane Library were conducted (in January 2021) in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to identify studies reporting clinical outcomes of angiographic VSP and its related complications after aSAH. Study outcomes included measures of functional status (modified Rankin Scale [mRS], Glasgow Outcome Scale [GOS], extended Glasgow Outcome Scale [GOS-E], modified Barthel Index, or the modified National Institutes of Health Stroke Scale), cognitive status (Montreal Cognitive Assessment or the Mini Mental State Exam), clinical events (rebleeding), and mortality. Study selection, data extraction, and qualitative analyses were conducted.

Results: Of 5704 abstracts reviewed, 110 studies were selected: 20 comparative and 39 regression-based studies were included in the qualitative synthesis, 51 descriptive studies were excluded. Most studies (51) were observational and conducted in a single country (53). The occurrence of angiographic VSP and its related complications after aSAH resulted in significantly poorer functional outcomes in three of nine comparative and 11 of 13 regression-based studies, measured by the mRS, and in five of six comparative and eight of nine regression-based studies, measured by the GOS and GOS-E. Angiographic VSP and its related complications were significantly associated with poor cognitive status in all five regression-based studies. Numerically or significantly higher mortality rates in patients with versus those without angiographic VSP and its related complications were reported in five of ten comparative studies and in eight of nine regression-based studies. Six studies looked at specific VSP populations (e.g., by severity or timing of VSP).

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Conclusion: Patients with angiographic VSP and its related complications often had poor functional, neurological, and cognitive outcomes and reduced odds of survival both in hospital and at follow-up. We estimate that angiographic VSP and its related complications, DCI and cerebral infarction, lead to an approximately threefold higher odds of poor functional and cognitive outcomes, and about a twofold increase in the odds of death.

PLAIN LANGUAGE SUMMARY

Aneurysmal subarachnoid hemorrhage is a medical emergency in which an aneurysm, a weakened outpouching of a cerebral blood vessel, ruptures causing bleeding in the subarachnoid space. Components from the bleeding can trigger a process leading to the constriction of cerebral arteries, called angiographic vasospasm. Angiographic vasospasm is a frequent occurrence after aneurysmal subarachnoid hemorrhage and can also result in delayed cerebral ischemia and cerebral infarction, which can severely impact patients' health. This study summarizes the published literature to describe the clinical burden that patients may experience due to angiographic vasospasm, delayed cerebral ischemia, and cerebral infarction after aneurysmal subarachnoid hemorrhage. The evidence from these studies emphasizes numerous clinical consequences that patients may experience. These patients may suffer from diminished neurological and intellectual activity, leading to disability and a loss of functional independence in everyday activities. Angiographic vasospasm and its related complications also reduce the chances of survival, both in the hospital and at follow-up. The considerable clinical burden associated with angiographic vasospasm, delayed cerebral ischemia, and cerebral infarction highlights the importance of their prevention.

Keywords: Aneurysmal subarachnoid hemorrhage; Angiographic vasospasm; Cerebral infarction; Clinical burden; Delayed cerebral ischemia; Systematic review

Key Summary Points

Why carry out this study?

This may be the first study to systematically review the clinical burden caused by angiographic vasospasm (VSP) and its related complications (delayed cerebral ischemia [DCI] and cerebral infarction) after aneurysmal subarachnoid hemorrhage (aSAH).

What was learned from this study?

Patients with aSAH experience considerable clinical burden associated with angiographic VSP, DCI, and cerebral infarction.

Angiographic VSP, DCI, and cerebral infarction after aSAH were associated with poor functional outcomes in terms of disability or dependence in daily activities.

Angiographic VSP, DCI, and cerebral infarction after aSAH were predictive of later impaired cognitive abilities.

Patients with angiographic VSP, DCI, and cerebral infarction after aSAH also experienced reduced odds of survival both in hospital and at follow-up.

INTRODUCTION

Aneurysmal subarachnoid hemorrhage (aSAH) is caused by rupture of an aneurysm and leads to life-threatening bleeding in the subarachnoid space [1, 2]. Up to 70% of patients with aSAH experience angiographic vasospasm (VSP) [3], defined as the angiographic finding of narrowed cerebral arteries [4]. Angiographic VSP usually begins around day 3, peaks in intensity between days 8 and 11, and resolves within 21 days [5]. It

is a serious complication of aSAH that can lead to VSP-related complications such as delayed cerebral ischemia (DCI, also known as DIND [delayed ischemic neurological deficit] and defined as a decline in consciousness of $\geq$ 2 points on the Glasgow Coma Scale [GCS] or the occurrence of a new focal neurological deficit, lasting for $>$ 1 h, after exclusion of other potential causes of clinical deterioration [4]) and cerebral infarction (defined radiologically as the presence of a new hypodensity on computed tomography [CT] scan located in a vascular distribution [6]). It has been postulated that in addition to angiographic VSP, other factors, including cortical spreading depression, microthrombosis, microcirculatory constriction, and capillary transit time heterogeneity may contribute to DCI and delayed cerebral infarction [7, 8].

Clinical deterioration due to DCI occurs in 20–50% of patients with aSAH and begins 4–-14 days after securing the aneurysm [5]. Angiographic VSP after aSAH is also a strong predictor of cerebral infarction, with the incidence of cerebral infarction increasing with increasing severity of angiographic VSP as measured by angiography, rising to $>$ 50% in patients with severe angiographic VSP following aSAH [9]. In addition, approximately 80–90% of patients with cerebral infarction have evidence of angiographic VSP [6, 10, 11]. Both DCI and cerebral infarction are predictors of poor long-term clinical outcomes [3, 4].

This study completes our endeavors to elucidate the burden of angiographic VSP and its related complications after aSAH. Previously [12], we identified a substantial direct and indirect economic burden and poorer health-related quality of life that was long-lasting in aSAH patients who developed angiographic VSP and its related complications, compared with those who did not. Here we report an up-to-date understanding of the clinical burden of angiographic VSP and its related complications after aSAH based on a systematic review of relevant literature that reported comparative or regression-based analyses of aSAH patients.

METHODS

Search Strategy

Systematic searches were conducted in indexed literature databases to identify pertinent peer-reviewed studies that were relevant to the research question: *What is the clinical burden of patients who had experienced VSP and its related complications after aSAH?*

The search strategies, study selection, and data extraction used here are similar to those published in our systematic review of the economic and humanistic burden of angiographic VSP and its related complications after aSAH [12]. A systematic search of MEDLINE, Embase, and the Cochrane Library was conducted on 8 January 2021, in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) 2020 guidelines [13]. Searches were developed on separate search terms for the disease ("subarachnoid hemorrhage" or "vasospasm") and outcomes of interest. Initially, no restrictions on time or language were applied. Conference abstracts, editorials, and narrative reviews were excluded.

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors. For full details of the search strategy, see Electronic Supplementary Material (ESM) Tables S1 and S2.

Study Selection

Publications identified through the searches were screened against the Population, Intervention, Comparators, Outcomes, and Study (PICOS) design eligibility criteria (Table 1). Following the removal of duplicate references, two reviewers independently reviewed the final list of abstracts against these criteria, with consensus reached by mutual agreement or by a third reviewer when discrepancies arose. Due to the high volume of literature identified, further inclusion criteria were systematically applied after abstract screening was completed to increase the sensitivity of the search. Only studies published after 2010, with a sample

Table 1 The Population, Intervention, Comparators, Outcomes, and Study (PICOS) design eligibility criteria

PICOS design criteria	Description
Population	Patients (any age) with VSP or its related complications following aSAH after clipping surgery or coiling
Interventions/ Comparators	Any treatment received in the ICU and post-ICU setting
Outcomes	Including—but not limited to—measures of: mortality, clinical events, cognitive status, functional status
Study design	Clinical trials (RCTs, NRS)
	Observational studies (any study design): real-world studies, hospital databases, or chart reviews
	Excluded: commentaries, expert reviews, case reports
Other considerations	Minimum sample size: ≥ 2 individuals
Exclusion criteria	Studies not meeting the inclusion criteria outlined above

aSAH aneurysmal subarachnoid hemorrhage, *ICU* intensive care unit, *NRS* non-randomized study, *RCT* randomized controlled trial, *VSP* vasospasm

size > 30, that mentioned VSP, DCI, or cerebral infarction in the title or abstract were included. Additionally, studies that examined only the diagnosis or epidemiology of VSP were excluded. Cross-checking of eligible data from our previous systematic review [12] was also undertaken.

After full-text screening, using the double review process described above, the included clinical studies were systematically categorized into three groups: comparative studies (i.e., analyzed clinical outcomes for patients with VSP/DCI vs. those without), regression-based studies (i.e., reported findings based on a regression-type of analysis that estimated the probability of a clinical outcome using VSP/DCI severity as a predictor), and descriptive studies (i.e., reported clinical findings for patients with VSP/DCI without a reference or control group).

Data Extraction

For the comparative and regression-based studies, data on the objective, study characteristics, patient characteristics, medication and outcomes of each study were extracted by a single reviewer using a predetermined extraction sheet. Study outcomes included measures of functional status, cognitive status, clinical events, and mortality (ESM Table S3). Full validation of the extracted data was conducted by a second reviewer against clean copies of the references.

Clinical burden related to functional outcomes was measured using the modified Rankin Scale (mRS), which is the preferred primary clinical outcome measure in acute stroke research [14], the Glasgow Outcome Scale (GOS) [15] or the extended GOS (GOS-E) [16].

Other measures of functional status included the modified Barthel Index [17] and the modified National Institutes of Health Stroke Scale (mNIHSS) [18].

Clinical burden related to cognitive outcomes was assessed using the Montreal Cognitive Assessment (MoCA) [19] or the Mini-Mental State Exam (MMSE) [20].

Clinical burden related to clinical events (rebleeding) and mortality were also assessed.

Synthesis of Results

The high degree of heterogeneity observed in the included studies prevented meta-analyses of the study outcomes. Therefore, the results are presented qualitatively by identifying trends in the outcomes across the studies considering differences in study and patient characteristics, and grouped according to the methodological approach used in the study (i.e., comparative or regression-based).

The definition of angiographic VSP and multivariate adjustments used in the studies were considered in the data synthesis.

VSP can be diagnosed by angiography (angiographic VSP), transcranial Doppler (TCD) (defined as mean flow velocity in any vessel > 120 cm/s) or as DCI (i.e., a decline in consciousness of ≥ 2 points on the GSC or the occurrence of a new focal neurological deficit, lasting for > 1 h, after exclusion of other potential causes of clinical deterioration) [3, 4].

Diagnosis of VSP in each study was coded to reflect ≥ 1 of the following four categories: angiographic VSP (diagnosed by digital subtraction angiography [DSA], computed tomography angiography [CTA], or magnetic resonance angiography [MRA]), DCI (clinical VSP), and others, such as TCD VSP or combined diagnosis (VSP with DCI or VSP with cerebral infarction). The term "cerebral VSP" refers to VSP determined using a combination of angiographic, TCD, and/or clinical diagnosis, or when the method used to diagnose VSP was not reported.

For regression-based studies reporting multivariate analyses, four variables were extracted: age, premorbid history of hypertension, neurological status at admission measured by the World Federation of Neurosurgical Societies (WFNS) grade, and Fisher grade at admission.

RESULTS

Included Studies

Searches in MEDLINE (4005 hits), Embase (4391 hits), and Cochrane (1468 hits) identified 5704 abstracts for review after duplicates were removed. From these, 366 records were selected for full-text review and 264 articles were excluded, leaving 102 studies meeting the inclusion criteria. An additional eight eligible studies reporting clinical outcomes were identified from our previous systematic review [12]. Therefore, the final number of studies analyzed was 110 (Fig. 1).

Data on the clinical burden of angiographic VSP and its related complications after aSAH were identified from 20 comparative studies [21–40] and 39 regression-based studies [41–79] (study characteristics are presented in ESM Table S4). The remaining 51 studies were purely descriptive and are not included (study listing available on request).

Most of the studies were observational (19 of 20 comparative studies, 32 of 39 regression-based studies), the majority of which were conducted retrospectively (15 of 19 comparative studies, 27 of 32 regression-based studies). Only four comparative studies and five regression-based studies were based on prospective designs. Eight studies were based on clinical trials, including seven post hoc analyses of data (5 from the CONSCIOUS-1 trial) [35, 41, 45, 56, 60, 61, 67] and a small (n = 66) randomized controlled trial (RCT) study from India [68] (ESM Table S4).

Most studies (20 of 20 comparative studies, 33 of 39 regression-based studies) were conducted in a single country (ESM Table S4). Two countries together comprised half of the included studies: Germany (13 studies) [22, 27, 30, 33, 36, 43, 48, 49, 53, 54, 63, 65, 78] and the USA (14 studies) [23, 24, 32, 37, 38, 44, 47, 50, 51, 55, 58, 64, 74, 76]. Six studies were based on data from multiple countries: Aldakkan et al. 2017 [41] and five post hoc analyses of the CONSCIOUS-1 trial [45, 56, 60, 61, 67].

Among the studies, 17 of 20 comparative studies and 28 of 39 regression-based studies were conducted in single centers (ESM Table S4). Seven regression-based studies collected data from a large number (i.e., > 30) of centers, including five post hoc analyses of the CONSCIOUS-1 trial [45, 56, 60, 61, 67] and two studies based in Japan [62, 73].

Patient numbers varied widely across the studies, ranging from 34 patients [22] to 1647 patients [29] for the comparative studies and from 40 patients [46] to 17,343 patients [62] for the regression-based studies (ESM Table S4).

Studies also varied considerably in the period of data coverage and length of data collection. For the comparative studies, data were collected from as early as 2002 [34, 37] to 2017 [26], with data collection periods ranging from < 1 year [26] to 9 years [29, 33, 34, 39]. Regression-based studies tended to examine data from earlier time periods and have a wider data collection period. The earliest regression-based studies collected data as early as August 1996 to June 2013 [44] and from April 1996 to April 2014 [70]

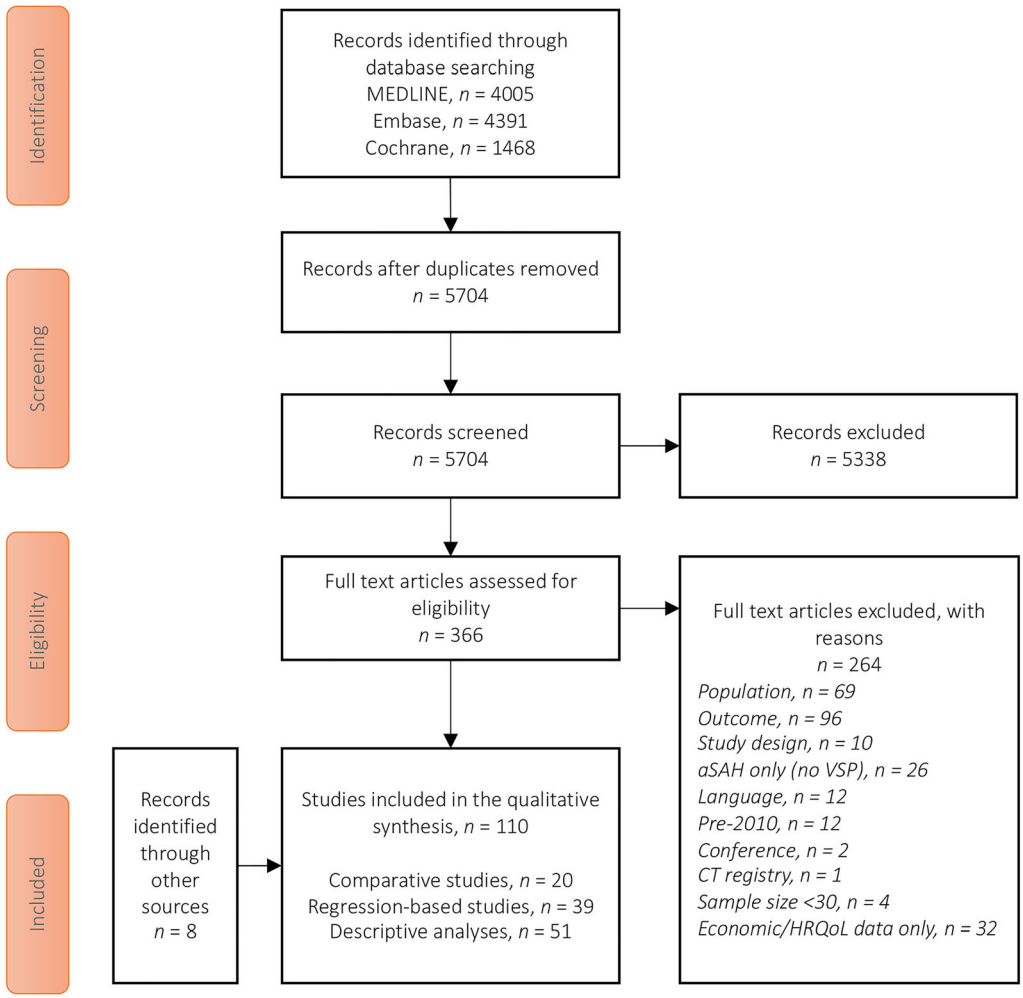

Fig. 1 The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) diagram showing the study selection process. *aSAH* Aneurysmal subarachnoid hemorrhage, *CT* clinical trial, *HRQoL* health-related quality of life,

while the most recent study reported data from January 2013 to July 2019 [58]. Data collection periods for regression-based studies ranged from 1 year [54] to 21 years [59].

VSP diagnosis varied across the studies, with most studies relying on angiographic criteria (15 of 20 comparative studies, 32 of 39 regression-based studies) and the use of multiple (i.e., at least two) diagnostic criteria more common than a single-criteria approach (ESM Table S5).

Of the 39 regression-based studies, 32 reported adjusting for a number of different factors to predict clinical outcomes for angiographic VSP patients, with age the most commonly employed adjustment factor, followed by WFNS grade (ESM Table S6).

Patient Characteristics

Patient populations were broadly comparable between the studies. However, a few studies included a highly selective patient population, such as those who were in need of an external ventricular drain [22], had received specific anesthetics [23], or had undergone specific treatments, such as anticonvulsants [32]. Patient characteristics of age, hypertension, Fisher grade, and WFNS grade were selected to

describe the patient population at baseline (ESM Tables S7–S11).

Age was a commonly reported patient characteristic, available in 19 of 20 comparative studies and 36 of 39 regression-based studies (ESM Table S7). Among the comparative studies, most reported mean or median patient ages in the age range of 50–59 years, with the average age of patients ranging from a mean of 43 ± 11 years in the new symptomatic subgroup of Tekle et al. [38] to a mean of 65 (range 46–87) years in Uozumi et al. [39]. Likewise, among the regression-based studies, reported mean or median patient ages were predominantly in the age range 50–59 years with some exceptions due to specific subpopulations investigated. The youngest patients (mean 44.2 ± 13 years) were reported in the control arm of a small RCT of propofol in Indian aSAH patients [68]. The oldest (mean 81 ± 5 years) were from a study that examined aSAH in advanced age (i.e., ≥ 75 years) [62].

Pre-existing hypertension was a less commonly reported patient characteristic, only available in nine of 20 comparative studies and 15 of 39 regression-based studies (ESM Table S8). There was heterogeneity in terms of the proportion of the study population with pre-existing hypertension, ranging from 29% (in the severe VSP subgroup of Mortimer et al. [35]) to 64% (in the new symptomatic VSP subgroup of Tekle et al. [38]) in comparative studies and from 18% [66] to 77% [76] in regression-based studies.

Most studies included a patient population with relatively high disease severity at baseline using the Fisher scale or the modified Fisher scale (ESM Tables S9, S10). Among the comparative studies, most patients had a Fisher grade of ≥ 3. Likewise, in regression-based studies most patients had a Fisher grade of ≥ 3, with the exception of two studies with 60% aSAH patients with Fisher grade 2 [42, 77] and a small RCT of propofol in Indian aSAH patients, which enrolled approximately 60% of patients with Fisher grade 1–2 [68].

In contrast, studies varied widely in terms of the WFNS grades of patients recruited (ESM Table S11). Some studies recruited patients with low-severity aSAH (i.e., WFNS 1–2) mostly [76, 79] or exclusively [41, 46], while other studies investigated patients from the entire range of WFNS grades (i.e., WFNS 1–5) [25, 26, 30, 33, 34, 36, 52, 70, 71, 76, 77].

Clinical Burden

Angiographic VSP-Related Complications: DCI and Cerebral Infarction

As this systematic review aimed to describe and quantify the clinical burden of angiographic VSP and its related complications (i.e., DCI and new cerebral infarction) after aSAH, it was considered necessary to assess the correlations between angiographic VSP, DCI and new cerebral infarction. While causality in the classical sense cannot be derived from such correlations, they at least are complications whose burden is directly related to angiographic VSP.

A statistically significant relationship between angiographic VSP and DCI was reported in two comparative studies [30, 40] and three regression-based studies [41, 44, 53], and between TCD-defined VSP and DCI in one comparative study [25] (ESM Table S12).

Angiographic VSP and cerebral infarction were investigated directly as separate outcomes in five studies. Two comparative studies [31, 37] suggested that cerebral infarction was higher in patients with angiographic VSP. Three regression-based studies [44, 59, 71] found an association between angiographic VSP and cerebral infarction, but suggested that other factors also contribute to whether angiographic VSP leads to cerebral infarction (ESM Table S13).

Functional Status: Modified Rankin Scale

Three [26, 29, 39] of nine comparative studies and 11 [48, 49, 52–54, 60, 63, 65, 71, 73, 74] of 13 regression-based studies found that patients with angiographic VSP or VSP-related complications have significantly poorer functional outcomes, as measured by the mRS, both at discharge and follow-up, than patients without angiographic VSP or VSP-related complications. In six studies [33, 38, 44, 59, 66, 76] that looked at specific VSP populations (e.g., by severity or timing of angiographic VSP, TCD-defined VSP or cerebral VSP), the outcomes were mixed.

In comparative studies, patients with angiographic VSP or DCI-related infarction had significantly poorer mRS functioning at 3 [29, 39] or 6 months [26] post aSAH than patients without angiographic VSP or DCI-related infarction. In contrast, patients with versus those without angiographic VSP or DCI had similar mRS functional outcomes at discharge in three studies [23, 25, 31], and at 3 months [27] or 18 months [21] in one study each. Similar functional outcomes at 3 months were also reported in one study between patients with severe angiographic VSP and those with mild or no angiographic VSP [35] (ESM Table S14).

Two comparative studies assessed the mRS of specific VSP populations (e.g., by severity of cerebral VSP or TCD-defined VSP). One of these identified significantly better functional outcomes (mRS score 0–2) at 6 months in patients with cerebral VSP lasting > 14 days compared with matched-pair patients with cerebral VSP lasting ≤ 14 days [33]. The second study, in which all patients had TCD-defined VSP, found no significant difference in the proportion of patients with poor functional outcome (mRS 3–6) at discharge who developed a new episode of TCD-defined VSP in a previously asymptomatic artery or not [38] (ESM Table S14).

In studies that employed a regression-based approach, five [48, 53, 63, 65, 74] of six studies found an association between angiographic VSP or DCI and unfavorable functional outcome on the mRS using univariate analysis (Fig. 2). Patients who had angiographic VSP or DCI were significantly more likely to exhibit neurological dysfunction after 6 months [48, 53]. Early angiographic VSP (i.e., angiographic VSP within 72 h post aSAH) independently predicted unfavorable outcome at discharge and at the 6 months' follow-up [63]. Increasing severity of angiographic VSP (i.e., angiographic VSP vessel narrowing > 33% and > 66%) was significantly

Study	Population	Time point	Adjustment	OR (95% CI)
AlMatter (2018) [43]	Cerebral VSP	At discharge	Univariate	1.37 (1, 2)
Jabbarli (2016) [63]	Early aVSP	At discharge	Univariate	2.39 (1.3, 4.4)
Pegoli (2015) [74]	Cerebral VSP	Month 5.5	Univariate	2.04 (1.25, 3.33)
Pegoli (2015) [74]	DCI	Month 5.5	Univariate	2.7 (1.67, 5)
Brawanski (2019) [48]	DCI	Month 6	Univariate	2.66 (1.7, 4.3)
Darkwah Oppong (2018) [53]	aVSP	Month 6	Univariate	1.52 (1.2, 1.9)
Jabbarli (2016) [63]	Early aVSP	Month 6	Univariate	2.63 (1.43, 5)
Konczalla (2016) [65]	aVSP (vessel narrowing >33%)	Month 6	Univariate	2.94 (1.67, 5)
Konczalla (2016) [65]	aVSP (vessel narrowing >66%)	Month 6	Univariate	3.45 (1.67, 10)
AlMatter (2018) [43]	Cerebral VSP	At discharge	Multivariate	1.45 (0.83, 2.5)
Dinc (2019) [54]	Cerebral VSP	At discharge	Multivariate	6.3 (2, 19.3)
Jabbarli (2016) [63]	Early aVSP	At discharge	Multivariate	2.93 (1.3, 6.5)
CONSCIOUS-1 [60]	Severe aVSP	Month 3	Multivariate	10.01 (4, 27)
Ozono (2020) [73]	Severe aVSP, age <65 years	Month 3	Multivariate	16.47 (6.5, 41.7)
Ozono (2020) [73]	Severe aVSP, age ≥65 years	Month 3	Multivariate	10.13 (4.3, 23.9)
Brawanski (2017) [49]	Severe aVSP, age <70 years	Month 6	Multivariate	1.01 (1, 1)
Brawanski (2017) [49]	Severe aVSP, age 70-79 years	Month 6	Multivariate	10.4 (1.2, 93.5)
Brawanski (2019) [48]	DCI	Month 6	Multivariate	2.29 (1.3, 4)
Konczalla (2016) [65]	Absence of mild and/or severe aVSP	Month 6	Multivariate	3.4 (1.6, 7)
Cinotti (2019) [52]	aVSP	Month 12	Multivariate	2.6 (1.1, 6.7)
Mortimer (2015) [71]	aVSP-related infarction	Month 16	Multivariate	19 (1.7, 216.4)

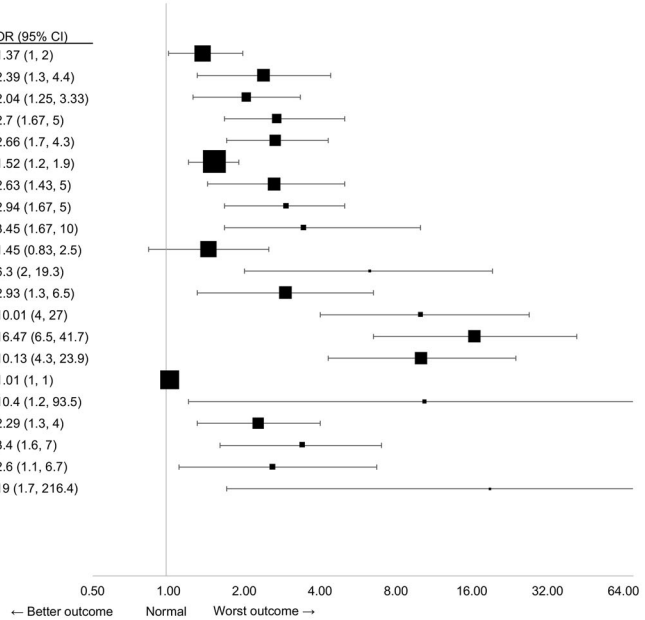

Fig. 2 Clinical burden, as measured by functional outcome (mRS scores, OR), from regression-based studies. The size of the square corresponds to the number of patients assessed. The OR of AlMatter et al. [43], Jabbarli et al. [63], Konczalla et al. [65], and Pegoli et al. [74] have been transformed so that the results point in the same direction as the other studies, meaning that OR < 1 indicates the "better outcome", OR = 1 indicates the "same outcome", and OR > 1 indicates the "worst outcome". The transformation equation is as follows: if OR = (a/b)/(c/d), ORt = 1/OR = 1/((a/b)/(c/d)) = (c/d)/(a/b), with ORt = transformed ORs. *aVSP* Angiographic vasospasm, *CI* confidence interval, *DCI* delayed cerebral ischemia, *mRS* modified Rankin scale, *OR* odds ratio, *VSP* vasospasm

associated with an increasing likelihood of unfavorable outcome (mRS > 2) at 6 months post aSAH [65]. Patients without cerebral VSP or DCI after aSAH had significantly better odds of good functional outcome (mRS 0 or 1) after a mean follow-up of 5.5 months [74].

One single-center, retrospective cohort study of 693 aSAH patients (only $n = 177$ [25.5%]) identified with cerebral VSP found that cerebral VSP was not significantly associated with worse mRS outcome at discharge using univariate analysis [43].

Eleven studies adjusted for the effects of confounding variables that affect outcome potentially independent of angiographic VSP and DCI (Fig. 2). Of these, nine studies [48, 49, 52, 54, 60, 63, 65, 71, 73] found angiographic VSP, severe angiographic VSP (defined as permanent deficit and/or appearance of low-density area on CT [73] or vessel diameter > 66% [49]), cerebral VSP, or DCI was a significant predictor of poor outcome at discharge [54, 63] or 3 months [60, 73], 6 months [48, 49, 65], or 1 year or later [52, 71] using multivariate regression analysis.

Two studies found no significant association between cerebral VSP or DCI and poor outcome using multivariate regression analysis. A single-center, retrospective cohort study of 693 aSAH patients (only $n = 177$ [25.5%] identified with cerebral VSP) found no association between cerebral VSP and worse mRS outcome at discharge [43]. One retrospective observational cohort study of 237 aSAH patients found DCI was not significantly predictive of poor outcome at 3 months [75].

Four regression-based studies looked at specific VSP populations. A prospective, longitudinal cohort study of 1286 aSAH patients found that ultra-early angiographic VSP (defined as angiographic VSP within the first 48 h of aSAH) was not significantly associated with poor functional outcome at 3 months using multivariate regression analysis [44]. A single-center retrospective study of 80 patients with angiographic VSP reported a significant ($p = 0.01$) association between cerebral infarction and poor outcome (mRS 3–6) at 3 months [59]. Another retrospective case series, which assessed functional mRS outcomes at 1 month and ≥ 12 months post aSAH in 88 aSAH patients with DCI, found no significant association between patients with severe versus mild-to-moderate cerebral VSP using univariate analysis [66]. Finally, a retrospective cohort study of 159 aSAH patients who underwent endovascular treatment for angiographic VSP (including intra-arterial vasodilator infusion and/or balloon angioplasty) found no significant association between angiographic VSP and mRS at discharge after adjusting for confounding factors [76].

Functional Status: Glasgow Outcome Scale Score and Extended Glasgow Outcome Scale Score

Five [22, 28, 30, 36, 40] of six comparative studies and eight [45–47, 57, 61, 69, 77, 78] of nine regression-based studies found that patients with angiographic VSP, TCD-defined VSP, cerebral VSP, or VSP-related DCI post aSAH had poorer neurological outcomes, measured by the GOS and GOS-E, both at discharge and at follow-up, compared with those without angiographic VSP, TCD-defined VSP, cerebral VSP, or VSP-related DCI.

Among the comparative studies (ESM Tables S15, S16), one small (< 55 patients) prospective study found that patients with VSP-related DCI, compared to those without, had significantly higher odds of poor neurological status (GOS < 4) at discharge (OR 5.4, 95% CI 1.2–24; $p = 0.03$), which persisted 3-months after aSAH (odds ratio [OR] 10, 95% confidence interval [CI] 2.0–49; $p < 0.01$) [22], and another reported that aSAH patients with angiographic VSP had significantly worse neurological outcomes on the GOS-E scale at 6 months ($p = 0.01$ vs. those without angiographic VSP) [40]. Retrospective studies found that aSAH patients with cerebral VSP had significantly poorer neurological outcomes at discharge, as assessed by the GOS ($p < 0.001$ vs. no cerebral VSP) ($n = 224$) [28], and that severe TCD-defined VSP predicted poorer neurological outcomes (GOS 1–3) at 3, 6, and 12-months post aSAH compared with mild or moderate TCD-defined VSP (all $p < 0.01$) ($n = 142$) [36]. Similarly, aSAH patients with angiographic VSP had poorer GOS-E scores at discharge ($p = 0.01$ vs. no

angiographic VSP) but not at 3–6 months follow-up, whereas patients with DCI had poorer GOS-E scores at both discharge and at 3–-6 months of follow-up ($p < 0.001$ and $p = 0.002$ vs, no DCI, respectively) ($n = 138$) [30].

Conversely, a post hoc analysis of prospectively acquired clinical trial data found no significant differences in discharge GOS or 90-day GOS (favorable outcome dichotomized as GOS 4–5) between patients with mild or no cerebral angiographic VSP ($n = 63$) and patients with severe angiographic VSP ($n = 17$) [35] (ESM Table S15).

Multivariate regression-based studies (Fig. 3) found that cerebral VSP predicted poor neurological outcome at discharge (GOS 1–2) in a small prospective study of 40 patients with aSAH [46], while the presence of DCI increased the odds by > 2-fold for an unfavorable neurological outcome (GOS 1–3) at 3 months post aSAH in a retrospective analysis of 270 patients with aSAH [57]. Likewise, a retrospective analysis of short-term outcomes after aSAH found that the presence of DCI increased the odds by > 4-fold for an unfavorable outcome (GOS 2, 3) at discharge and by > 7-fold when the evaluation of morbidity included death (GOS 1–3), even after controlling for confounding factors [77]. In a retrospective review of 374 patients with aSAH, cerebral infarction, but not cerebral VSP, was independently predictive of poor GOS at discharge [47]. Post hoc analyses of data from the CONSCIOUS-1 (Clazosentan to Overcome Neurological iSChemia and Infarction OccUrring after Subarachnoid hemorrhage) trial found that both moderate and severe, but not mild angiographic VSP, predicted poor GOS-E at 3 months [61], with a > 3-fold increase in the odds of poor neurological outcomes identified for moderate or severe angiographic VSP compared with mild or no angiographic VSP [45]. Similarly, a single-center retrospective study of 176 patients identified DCI as a significant predictor of unfavorable outcomes (GOS 1–3) at 1 year after aSAH ($p = 0.01$) using proportional odds logistic regression analysis [78]. A retrospective analysis found that aSAH patients ($n = 112$) with cerebral infarction due to angiographic VSP were significantly ($p < 0.0001$) more likely to experience a poor outcome (GOS 1–3) at discharge than a good outcome using univariate analysis [69].

Finally, in a univariate analysis of a retrospectively collected series of 460 aSAH patients, cerebral VSP was significantly related to poor outcome at 30 days (OR not reported; $p = 0.024$), but this association was not significant by multivariate logistic regression analysis (Fig. 3) [70].

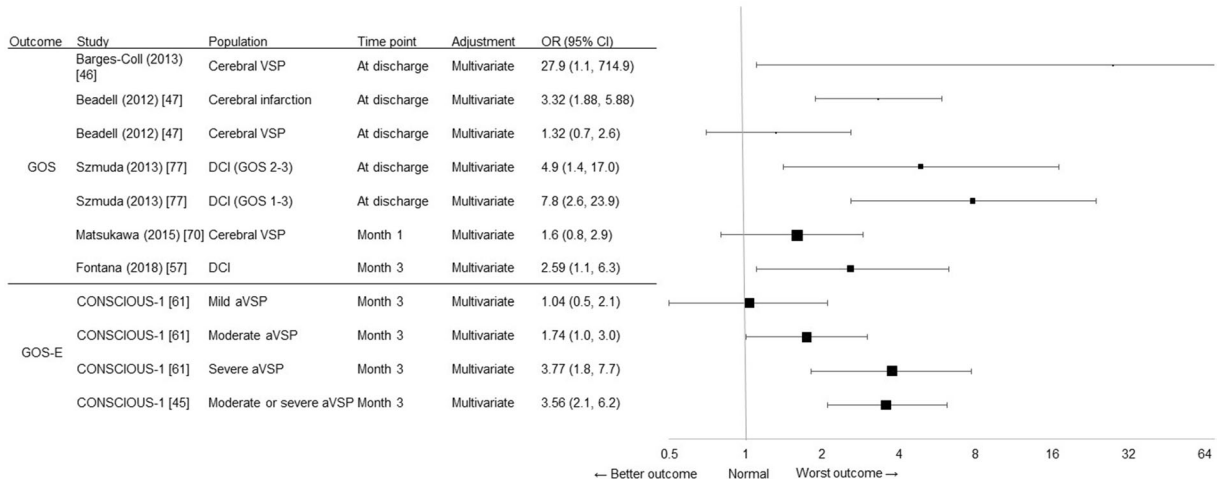

Fig. 3 Clinical burden, as measured by functional outcome (OR) reported in regression-based studies based on GOS scores and GOS-E scores. The size of the square corresponds to the number of patients assessed. *GOS* Glasgow Outcome Scale, *GOS-E* extended Glasgow Outcome Scale

Functional Status: Other Measures

Two studies reported less commonly used measures of neurological functioning. In a retrospective analysis of 299 aSAH patients with stress-induced cardiomyopathy, cerebral VSP was significantly associated with poorer functional outcomes measured using the modified Barthel Index at both 3 and 12 months (p value not stated) [64]. In contrast, a retrospective analysis of 74 aSAH patients found similar neurological functioning measured using the mNIHSS at 3 months regardless of the occurrence or not of TCD-defined VSP (median mNIHSS 7.5 [range 1–25.5] vs. 6 [range 2–10], respectively, for patients with vs. those without TCD-defined VSP; p value not reported) [27].

Cognitive Impairment

All five regression-based studies [42, 58, 67, 68, 79] found that angiographic VSP, TCD-defined VSP, and DCI were significantly associated with poor cognitive status measured using the MoCA or the MMSE (ESM Table S17).

DCI ($p = 0.022$), but not cerebral VSP, was significantly predictive of cognitive impairment (MoCA < 22) at discharge in a retrospective review of aSAH patient records from 2013 to 2019 [58]. A prospective observational study found that cerebral infarction due to DCI (MoCA < 26) accounted for 38% of the variance in cognitive outcomes at 3 months [79]. A prospective observational study of 82 aSAH patients reported that the number of days with DCI was a significant risk factor for cognitive dysfunction (MoCA < 21) at 1 year, even after accounting for confounding factors [42].

In a post hoc analysis of CONSCIOUS-1, significantly lower mean MMSE scores were identified at 12 weeks after aSAH in patients with severe angiographic VSP versus those with no angiographic VSP (18 vs. 28, respectively; Kruskal–Wallis, $p < 0.0001$), with no apparent differences between patients with moderate, mild, or no angiographic VSP [67]. Cerebral infarction due to DCI accounted for 31% of the variance in cognitive outcomes (MMSE < 27) at 3 months by a multiple regression analysis [79]. Finally, the occurrence of TCD-defined VSP predicted cognitive impairment at discharge by multivariate analysis in a small ($n = 66$) RCT study from India that employed a Hindi-language modification of the MMSE [68].

Mortality

Five [25–27, 34, 37] of ten comparative studies and eight [50, 55, 57, 63, 64, 72, 73, 78] of nine regression-based studies found numerically or significantly higher mortality rates in patients with than in patients without angiographic VSP or its related complications. In two studies [33, 59] that looked at specific VSP populations (e.g., by severity or timing of angiographic or cerebral VSP), the outcomes were mixed.

In comparisons of patients with versus those without angiographic VSP or its related complications (ESM Table S18), only one small retrospective study reported significantly higher in-hospital mortality rates in patients with DCI than in those without DCI ($p < 0.0001$; $n = 137$) [37]. In addition, a retrospective review of patient health records identified a marginally higher in-hospital mortality rate in aSAH patients who developed DCI than in those who didn't (16.5 vs. 13.7%, respectively, p-value not reported; $n = 463$) [34].

Four studies (including 2 retrospective studies [24, 31], 1 prospective study [22], and 1 post hoc analysis of a RCT [35]) found in-hospital mortality rates were not significantly different between patients with versus those without angiographic VSP [31, 35], DCI [22], or delayed infarction [24]. One outlying retrospective study identified lower in-hospital mortality in patients with versus those without DCI, albeit without statistical significance ($p = 0.357$) [21].

The evidence reporting mortality by VSP or DCI status at later time points was more consistent across three studies (ESM Table S18). In small prospective studies, mortality rates were twofold higher in patients with DCI than in patients without DCI at day 21 (p value not reported) [25] and significantly higher at 6 months in patients with angiographic VSP compared with those without ($p < 0.001$) [26]. In a small retrospective study, the rate of mortality at 3 months in patients with TCD-defined VSP was more than twice that of patients without TCD-defined VSP (p value not reported) [27].

One comparative study that assessed the mRS of a specific VSP population found that significantly more patients with cerebral VSP lasting ≤ 14 days died in hospital ($p < 0.0001$) or within 6 months ($p < 0.001$) than patients with cerebral VSP lasting > 14 days [33].

Evidence from regression-based studies was generally consistent with the proposition that angiographic VSP and its related complications were associated with mortality (Fig. 4). A retrospective study of 531 patients found that in-hospital mortality increased twofold if angiographic VSP occurred within 72 h after aSAH using univariate analysis [63]. Three retrospective studies that investigated in-hospital mortality using multivariate analysis found that cerebral VSP reduced the odds of in-hospital survival by 75% [64], TCD-defined VSP increased the odds of in-hospital mortality by > 7-fold [55], and patients with DCI were 3.5-fold more likely to die in hospital [57]. A large retrospective study of 1124 patients identified severe angiographic VSP as a significant risk factor for mortality at 3 months in elderly patients aged ≥ 65 years, but not in patients aged < 65 years using multivariate analysis [73]. A smaller retrospective study of 114 aSAH patients identified cerebral VSP as an independent risk factor for mortality using multivariate analysis, although the degree of uncertainty (measured by the width of the 95% CI) was large (OR 46.093, 95% CI 4.149–512.105; $p = 0.002$) [72].

Conversely, one retrospective study of 198 aSAH patients [51] found no increased odds of in-hospital mortality in patients with TCD-defined VSP or DCI using multivariate analysis.

Two studies did not report effect sizes but only significant values. A large retrospective study ($n > 5000$) of the U.S. National Inpatient Sample database found that cerebral VSP significantly increased in-hospital mortality ($p < 0.0012$) using multivariable regression modeling [50]. A single-center retrospective study of 176 aSAH patients found that DCI was a significant predictor of mortality by day 30 ($p = 0.019$), but not at 1 year ($p = 0.177$), by proportional odds logistic regression analysis [78].

One single-center retrospective study in 80 aSAH patients with angiographic VSP, which investigated a specific VSP population, found that cerebral infarction and death at 3 months were significantly associated ($p = 0.003$) [59].

DISCUSSION

In this study we summarize the impact of angiographic VSP, DCI, and cerebral infarction

Study	Population	Time point	Adjustment	OR (95% CI)
Jabbarli (2016) [63]	Early aVSP	In hospital	Univariate	2.34 (1.3, 4.3)
Chou (2010) [51]	TCD-defined VSP	In hospital	Multivariate	1.32 (0.4, 4.1)
Chou (2010) [51]	DCI	In hospital	Multivariate	1.66 (0.5, 5.1)
Drazin (2015) [55]	TCD-defined VSP	In hospital	Multivariate	7.83 (1.4, 44.5)
Fontana (2018) [57]	DCI	In hospital	Multivariate	3.53 (1.2, 10.4)
Kilbourn (2013) [64]	Cerebral VSP	In hospital	Multivariate	4.00 (1.25, 10)
Orakdogen (2016) [72]	Cerebral VSP	In hospital	Multivariate	46.09 (4.14,512.10)
Ozono (2020) [73]	Severe aVSP, age <65 years	Month 3	Multivariate	2.02 (0.6, 6.8)
Ozono (2020) [73]	Severe aVSP, age ≥65 years	Month 3	Multivariate	2.17 (1, 4.7)

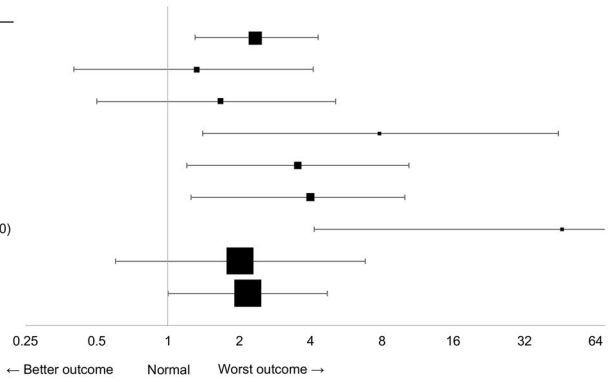

Fig. 4 Clinical outcome, with death (OR) as indicator, reported in regression-based studies. The size of the square corresponds to the number of patients assessed. The ORs of Kilbourn et al. [64] have been transformed so that the results point in the same direction as the other studies, meaning that OR < 1 indicates "best outcome", OR = 1 indicates "same outcome", and OR > 1 indicates "worst outcome". The transformation equation is as follows: if OR = (a/b)/(c/d), ORt = 1/OR = 1/((a/b)/(c/d)) = (c/d)/ (a/b), with ORt = transformed ORs. *TCD* Transcranial Doppler

post aSAH on functional outcomes (measured using the mRS, GOS, GOS-E, modified Barthel Index, and NIHSS), cognitive impairment (measured using the MoCA and MMSE) and mortality. We were unable to find other similar, comprehensive studies. Our analyses of 20 comparative and 39 regression-based studies found that the vast majority report a significant detrimental effect of angiographic VSP and its related complications, DCI and cerebral infarction, on outcomes of patients with aSAH (Fig. 5). Together with our previous publication [12], this study completes our synthesis of evidence across the overall (i.e., clinical, economic, and humanistic) burden of disease of angiographic VSP and its related complications after aSAH.

We were unable to conduct a meta-analysis due to the high degree of heterogeneity between studies. Nevertheless, eight of 15 comparative and 19 of 22 regression-based studies identified significantly poorer functional outcomes, as measured by the mRS, GOS, and GOS-E, in aSAH patients who experience angiographic VSP and its related complications than in those who do not. Most studies showed that these complications are associated with some functional impairment early on in the initial hospital stay, but that effects of angiographic VSP and its related complications become more apparent after 3 or 6 months [31, 35, 43]. One explanation may be that the clinical burden of the initial aSAH event overshadows the effect of angiographic VSP and its complications.

This analysis found that it was difficult to accurately estimate the effect size of angiographic VSP and its related complications on outcomes after aSAH. From the regression-based studies analyzed here, the median OR (interquartile range [IQR]) is 2.7 (2.2, 7.2) for functional outcome measured by the mRS, with the broad range arising from the often small population size of studies. However, if this

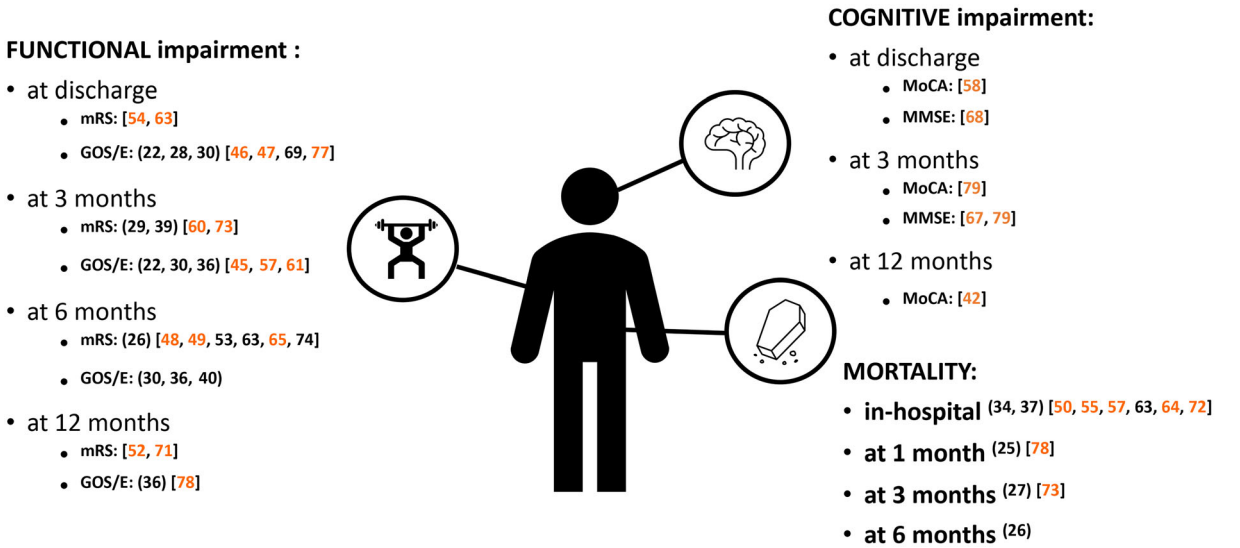

Fig. 5 Evidence showing the clinical impact of cerebral vasospasm and its related complications, delayed cerebral ischemia and cerebral infarction, on patients after aneurysmal subarachnoid hemorrhage, by outcome and time point. The figure only summarizes evidence reporting an association between cerebral vasospasm and its related complications with negative clinical outcomes. Functional evidence based on the Barthel Index and mNIHSS tools are not shown. References in parentheses indicate comparative studies, while references in square brackets indicate regression-based studies. Reference numbers highlighted in orange indicate outcomes based on multivariate evidence alone or combined with univariate evidence; reference numbers in black indicate outcomes based on univariate evidence alone. *GOS/E* Glasgow Outcome Scale/extended Glasgow Outcome Scale, *MMSE* Mini-Mental State Examination, *MoCA* Montreal Cognitive Assessment

median is used as a reference case, patients who experience angiographic VSP, DCI and cerebral infarction post aSAH have an approximately threefold higher odds of a poor functional outcome than those who do not. The regression-based evidence when the outcome measure is the GOS/GOS-E was virtually the same, with a reference case median OR (IQR) of 2.6 (1.5, 4.3).

Regarding the cognitive status of aSAH patients, despite the lower corpus of evidence, all five regression-based studies identified a significant association between angiographic VSP and its related complications and poor cognitive outcome measured using the MoCA or the MMSE. Notably, cognitive impairment was present at discharge, 3 months, and even at 1 year post aSAH in a prospective observational study of 82 aSAH patients [42]. This result is consistent with the findings of a prospective study that was published after our search was conducted [80], which reported significantly worse neuropsychological functioning in aSAH patients with DCI for up to 3 months after the hemorrhage compared with non-DCI patients. Similar to functional impairment, cognitive impairment appears to be irreversible. The effect size of cerebral infarction due to DCI on cognitive impairment is substantial, and, in one prospective observational study, accounted for 38% of the variance in cognitive outcomes (MoCA < 26) and 31% of the variance in cognitive outcomes (MMSE < 27) at 3 months [79]. The median OR (minimum, maximum) of 3 (1.3, 3.9) for cognitive abilities as per the MoCA score indicates a worst outcome in patients with angiographic VSP or VSP-related complications versus those without.

Most comparative and regression-based analyses found that patients with angiographic VSP or DCI had increased odds of in-hospital mortality [33, 37, 55, 57, 63] or reduced odds of in-hospital survival [64] that is present for up to 6 months [25–27, 33, 73]. This is consistent with the findings of a large retrospective study of the U.S. National Inpatient Sample database that reported a significant association between cerebral VSP and in-hospital mortality [50]. In terms of the effect size, the median OR (IQR) for mortality in aSAH patients with these complications was 2.3 (1.8, 5.9), meaning that these patients have an approximately twofold higher odds of dying compared with aSAH patients without such complications. We found one regression-based study that reported no significant differences in in-hospital mortality between patients with versus those without TCD-defined VSP [51]. However, the authors opined that the study was underpowered to detect such a difference. Similarly, four comparative studies [22, 24, 31, 35] did not identify increased mortality in patients with angiographic VSP and its related complications compared to those without such complications. However, in-hospital mortality in patients with angiographic VSP versus non-VSP patients was limited by the low number of deaths in these studies. For example, a post hoc analysis of an RCT reported that no patients with severe angiographic VSP ($n = 17$) and only two of 63 patients with none/mild angiographic VSP died in hospital [35].

Increasing severity of angiographic VSP, the presence of DCI or cerebral infarction, and older age may also adversely affect functional and cognitive outcomes and increase the likelihood of death. For example, the severity of VSP, but not the occurrence of VSP, per se, appears to be a significant factor driving cognitive dysfunction [67] and poorer functional outcomes [36, 45, 61, 65]. The sometimes not reported relationship of the occurrence of angiographic VSP to functional outcome and other outcomes may be because mild and moderate angiographic VSP are included and could lead to less DCI and cerebral infarction events than severe VSP [9]. Likely for similar reasons, DCI or cerebral infarction, but not angiographic VSP or cerebral VSP, were significantly predictive of cognitive impairment [58] and poor functional outcome [30, 47]. Finally, there may be an interaction between angiographic VSP and age. We found increased odds for mortality in elderly aSAH patients aged ≥ 65 years with severe angiographic VSP versus those with non-severe angiographic VSP, but not in patients aged < 65 years of age [73], while the occurrence of severe angiographic VSP was a significant predictor of an unfavorable functional outcome in aSAH patients aged 70–79 years, but not in those aged < 70 years [49].

Despite the majority of studies showing the clinical burden associated with angiographic VSP, DCI, and cerebral infarction, some studies report contradictory outcomes. A limitation of some studies may be their relatively small sample size, which may underpower a study to evaluate clinically important associations. A limitation specific to Abulhasan et al. [21] is that the mRS score used to assess the functional outcome was retrospectively calculated from medical records, which is less accurate than in-person assessment. The time point of measurement may also explain non-significant results. Indeed, for measurements taken in-hospital or at discharge, it is harder to disassociate clinical impairment due to the initial aSAH event versus the presence of complications, such as angiographic VSP, DCI, and cerebral infarction.

Strengths and Limitations

The strengths of this study are the comprehensive screening of the literature, resulting in 110 studies including 42,631 patients for analysis. The likelihood of having more heterogeneous results due to differences in the standard of care was limited by excluding studies published before 2010.

There are also a number of limitations. Most studies collected data in single centers, which may restrict the generalizability of the findings. Most studies were retrospective, and the data obtained from these are more likely to be inaccurate and biased by missing data and incomplete and unaudited variables and outcomes. Further limitations include the heterogeneity of the studies, and the different definitions of angiographic VSP, DCI and cerebral infarction. Indeed, clinical heterogeneity in the prevention and treatment of angiographic VSP across the studies could influence the mechanisms that lead to poor neurological outcomes in aSAH patients and skew the results. Almost all patients with aSAH develop some angiographic VSP, so heterogeneity in the severity and breadth of angiographic VSP between studies also could affect the results.

We also did not include the 51 descriptive studies because the association between VSP and a particular outcome was not reported.

CONCLUSION

This systematic review found that angiographic VSP and its related complications, DCI and cerebral infarction, were associated with worse clinical outcome, higher mortality, and poorer cognitive function in the majority of studies of patients with aSAH. We estimate that angiographic VSP and its related complications, DCI and cerebral infarction, lead to an approximately threefold higher odds of poor functional and cognitive outcomes, and about a twofold increase in the odds of death.

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Compliance with ethics guidelines. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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