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Quantifying the Impact of Delayed Cerebral Ischemia-Related Cerebral Infarction on Clinical Outcomes Following Aneurysmal Subarachnoid Hemorrhage

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Tables 1 to 5 are available in the Supplementary Files section.

Quantifying the Impact of Delayed Cerebral Ischemia-Related Cerebral Infarction on Clinical Outcomes Following Aneurysmal Subarachnoid Hemorrhage

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DETAILS PAGE

1. Compliance with Instructions to Authors

The authors confirm that this manuscript complies with all requirements specified in the current Instructions for Authors of Neurocritical Care, including those pertaining to manuscript structure, word count, references, figures and tables, ethical disclosures, and reporting standards.

2. Individual Author Contributions

Author contributions are described according to the CRediT (Contributor Roles Taxonomy) framework. All authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship adopted by Neurocritical Care.

IPM: Conceptualization; Methodology; Investigation; Data curation; Formal analysis; Visualization; Writing — original draft; Writing — review and editing.

NVOS, BGS, RT, EB, CR, ECRR, CBR: Investigation; Data curation; Writing — review and editing.

GSS, FST: Methodology; Supervision; Resources; Writing — review and editing.

PK: Conceptualization; Methodology; Formal analysis; Supervision; Project administration; Resources; Writing — review and editing.

3. Authorship Requirements and Final Approval

All listed authors meet the four ICMJE criteria for authorship adopted by Neurocritical Care: substantial contributions to the conception and design of the work, the acquisition of data, or the analysis and interpretation of data; drafting the work or revising it critically for important intellectual content; final approval of the version to be published; and agreement to be accountable for all aspects of the work. All authors have read and approved the final version of the manuscript submitted to Neurocritical Care.

4. Originality and Exclusivity of Submission

The authors confirm that this manuscript has not been published elsewhere, in whole or in part, and is not currently under consideration by any other journal.

5. Adherence to Ethical Guidelines, IRB Approval, and Informed Consent

This study was approved by the institutional review board or research ethics committee at each participating center and was conducted in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments. Approval was granted by the Research Ethics Committee of the Instituto Estadual do Cérebro Paulo Niemeyer, Rio de Janeiro, Brazil (CAAE 90533025.6.0000.8110; opinion no. 7.772.570) and by the Research Ethics Committee of the Universidade Federal de São Paulo / Hospital São Paulo, São Paulo, Brazil (CAAE 26768619.8.0000.5505; opinion no. 3.903.436). Informed consent was obtained from patients or their legally authorized representatives when required by local regulations; where the ethics committee waived the requirement for informed consent, this is stated.

6. Disclosure of Potential Conflicts of Interest

The authors declare that they have no competing interests, financial or non-financial, related to this work.

7. Reporting Checklist

This study is reported in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement for cohort studies. The completed STROBE checklist is included at the end of this manuscript. The mediation analysis is additionally reported in accordance with the AGReMA (A Guideline for Reporting Mediation Analyses) statement, and the completed AGReMA short-form checklist is also included at the end of this manuscript.

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9. Disclosure of AI-Assisted Technologies

The authors declare that generative artificial intelligence (Claude, Anthropic) was used to assist with the formatting and layout of the manuscript and its tables and the conversion of in-text citations in the same pattern. No data were generated, analyzed or interpreted using AI-assisted technologies; all statistical analyses were performed by the authors in R, and all results, interpretations and conclusions are the authors' own. The authors reviewed and take full responsibility for the entire content of the manuscript.

Abstract

Background: Aneurysmal subarachnoid hemorrhage (aSAH) is associated with high mortality and long-term disability. Although delayed cerebral ischemia (DCI) is strongly associated with poor outcome, its contribution to in-hospital mortality and its role in mediating the effect of initial severity on functional outcome remain uncertain. We aimed to quantify DCI-attributable in-hospital mortality and its mediating role between poor admission grade and unfavorable functional outcome.

Methods: We conducted a prospective multicenter cohort of consecutive patients with aSAH admitted to 4 specialized centers in Brazil and Belgium between 2016 and 2023. DCI-related infarction was defined according to Vergouwen et al. The attributable fraction (AF) for in-hospital mortality was estimated by regression standardization from a multivariable logistic model. Causal mediation analysis assessed how much DCI mediated the effect of poor admission grade (World Federation of Neurosurgical Societies [WFNS] grade ≥4) on unfavorable outcome (modified Rankin Scale [mRS] score, 4–6).

Results: Among 1789 patients (median age, 55 years; 73% female), 439 (25%) developed DCI-related infarction and 441 (25%) died in-hospital. Vasospasm, seizures, hypertension, and higher WFNS grade were independently associated with DCI. After adjustment, the AF of in-hospital mortality attributable to DCI was 12.1% (95% CI, 7.0–17.2%; P<0.001). Unfavorable outcome occurred in 71% of patients with DCI versus 35% without DCI (P<0.001). Poor admission grade increased the absolute probability of unfavorable outcome by 35.7 percentage points, of which 2.6 were mediated through DCI (7.3% mediated; 95% CI, 3.6–12.6%).

Conclusions: DCI accounted for an estimated 12% of in-hospital mortality but mediated only a small fraction of the effect of poor admission grade on unfavorable functional outcome. Although DCI is potentially preventable and treatable, these estimates should be interpreted

cautiously given the observational design. Prospective interventional studies are needed to determine whether preventing or mitigating DCI improves survival and functional outcomes.

Keywords: subarachnoid hemorrhage; delayed cerebral ischemia; critical care; intracranial aneurysm; vasospasm

Introduction

Aneurysmal subarachnoid hemorrhage (aSAH) remains a major cause of premature death and long-term disability despite advances in neurocritical care and aneurysm treatment [1,2], with a higher burden in low- and middle-income countries [3,4]. Prognosis is strongly influenced by initial neurological severity, blood burden, early brain injury, rebleeding, and delayed cerebral ischemia (DCI) [5–8]. Clinical grading systems such as the World Federation of Neurosurgical Societies (WFNS) scale are widely used to stratify severity and predict outcome, but individual prognosis remains difficult because outcomes reflect multiple independent baseline and in-hospital factors [9–12].

DCI occurs in approximately 30% of patients who survive the initial hemorrhage, and is strongly associated with poor functional outcome and mortality [13]. Although historically attributed primarily to angiographic vasospasm, DCI is now understood as a multifactorial process involving disturbances in cerebral perfusion, cortical spreading depolarizations, microthrombosis and neuroinflammation [14]. Cerebral infarction attributable to DCI is a particularly robust endpoint for retrospective research and has consistently been associated with worse functional outcomes and higher mortality across observational cohorts [15,16].

However, the magnitude of DCI's independent contribution to mortality remains uncertain. Observational associations alone do not establish how much mortality is attributable to DCI or the extent to which DCI mediates the effect of initial clinical severity on functional outcome [17]. In this multicenter observational cohort, we aimed to estimate the fraction of in-hospital mortality attributable to DCI and the proportion of the effect of poor admission grade on unfavorable functional outcome mediated through DCI. We also explored factors associated with DCI development.

Methods

Study Design and Participants

We conducted a prospective multicenter study of consecutive adult patients admitted with SAH between 2016 and 2023 to four specialized neurointensive care units in Brazil and Belgium. The study was approved by the research ethics committee at each participating center and conducted in accordance with the Declaration of Helsinki. Approval was granted by the Research Ethics Committee of the Instituto Estadual do Cérebro Paulo Niemeyer (CAAE 90533025.6.0000.8110; opinion no. 7.772.570) and by the Research Ethics Committee of the Universidade Federal de São Paulo / Hospital São Paulo (CAAE 26768619.8.0000.5505; opinion no. 3.903.436). Informed consent was obtained from patients or their legally authorized representatives when required by local regulations; a waiver of informed consent was granted for patients who could not be contacted.

Patients were eligible if ≥18 years, had SAH confirmed by head computed tomography (CT) or magnetic resonance image (MRI), and aneurysmal etiology confirmed by CT angiography (CTA), MR angiography (MRA), or digital subtraction angiography (DSA). Patients admitted in brain death, with an expected survival < 24 hours, or with nonaneurysmal SAH were excluded. Data were collected prospectively, and follow-up was performed during outpatient visits or by telephone.

Clinical Management and DCI Monitoring

Clinical management was determined by the treating neurocritical care team at each center according to local protocols and guideline-based practice. Ruptured aneurysms were secured by surgical clipping or endovascular treatment as early as feasible. Oral nimodipine was administered consistently, and acute hydrocephalus was treated with external ventricular drain when indicated [2]. DCI surveillance included transcranial doppler (TCD), DSA, and CT perfusion, particularly in patients with limited neurological examination [14,18]. Treatment of suspected DCI was individualized and could include induced hypertension with

norepinephrine, milrinone, intra-arterial vasodilators, and balloon angioplasty in refractory cases [18,19].

Baseline and Clinical Variables

Baseline variables included age, sex, race, vascular risk factors, smoking, alcohol and illicit substance use, and preadmission medications. Clinical and radiological severity were assessed using the WFNS (Figure 1), Hunt-Hess grade, modified Fisher (mFisher) score, and VASOGRADE scales [9,10,20,21]. Aneurysm location was categorized according to the PHASES framework (Population, Hypertension, Age, Size of aneurysm, Earlier aSAH from another aneurysm, Site of the aneurysm) [22]. We also recorded time from symptom onset to hospital admission and aneurysm treatment, treatment modality, ICU and hospital length of stay, and relevant in-hospital complications.

Primary outcomes were in-hospital mortality and unfavorable functional outcome, defined as a modified Rankin Scale (mRS) score of 4–6 at 3–6 months.

DCI and DCI-Related Infarction Definition

Clinical DCI and DCI-related cerebral infarction were defined according to Vergouwen et al. [15]. Clinical DCI was defined as new focal neurological impairment or a decrease of ≥2 points on the Glasgow Coma Scale lasting at least 1 hour and not attributable to another cause. DCI-related cerebral infarction was defined as a new cerebral infarction identified within 6 weeks after aSAH, absent on imaging 24-48 hours after aneurysm treatment, and not attributable to procedural or other causes [15]. Because of its greater objectivity and lower interobserver variability, DCI-related cerebral infarction was used as the primary DCI variable in the analysis [15].

Statistical Analysis

Analyses were performed in R (R Foundation for Statistical Computing, Vienna, Austria). Continuous variables are presented as median (interquartile range [IQR]) and categorical

variables as number (percentage). Group comparisons used the Pearson χ^2 or Fisher exact test for categorical variables and the Wilcoxon rank-sum or Kruskal-Wallis test for continuous variables, as appropriate. All tests were two-sided, with $P<0.05$ considered statistically significant.

The adjusted attributable fraction of in-hospital mortality associated with DCI was estimated using a model-based adjusted attributable fraction derived from multivariable logistic regression and regression standardization [23]. The observed probability of death was compared with the counterfactual probability obtained by setting DCI to absent for all patients while retaining measured covariates [23,24]. This approach allows adjustment for multiple confounders and improves on crude attributable fraction estimates [25]. Estimates were obtained using the AF package in R with sandwich-based standard errors and 95% confidence intervals. Covariates were selected a priori based on clinical relevance and the prespecified causal framework [23,24].

Causal mediation analysis was performed within the potential-outcomes framework to assess the extent to which DCI mediated the effect of poor admission grade (WFNS grade ≥4) on unfavorable functional outcome [26,27]. The total effect was decomposed into the average direct and indirect effects, and the proportion mediated was estimated [26,28]. Estimates and 95% CIs were obtained from 1,000 nonparametric bootstrap resamples [27]. A prespecified directed acyclic graph was used to identify the adjustment set and mitigate confounding bias (Figure 2) [29].

Factors associated with DCI were assessed using multivariable logistic regression. Candidate variables were selected based on clinical plausibility, and model reduction was guided by statistical contribution, parsimony, and the Akaike information criterion [30,31]. Associations are reported as odds ratios (ORs) with 95% CIs, and the events-per-variable ratio was assessed to limit overfitting [32].

Generative artificial intelligence (Claude, Anthropic) was used to assist with the formatting and layout of the manuscript and its tables and the conversion of in-text citations in the same pattern. No data were generated, analyzed or interpreted using AI-assisted technologies; all statistical analyses were performed by the authors in R, and all results, interpretations and conclusions are the authors' own.

Results

Study population and baseline characteristics

Of 1,800 patients with aSAH screened across four centers, 11 (0.6%) were excluded for incomplete baseline or outcome data, leaving 1,789 for analysis. Median age was 55 years (IQR, 46–63), 73% were female, 59% had hypertension, and 39% had a history of smoking. At admission, 31% were classified as WFNS 4–5 and 41% as mFisher 4. Communicating artery aneurysms accounted for 44% of cases and middle cerebral artery aneurysms for 19%. Aneurysm treatment consisted of surgical clipping in 57%, endovascular coiling in 29%, and no aneurysm occlusion in 14%. Median time from ictus to aneurysm occlusion was 6 days. In-hospital mortality was 25%, and 44% of 1,671 patients with 3- to 6-month follow-up had an unfavorable outcome (mRS 4–6).

Associations with DCI, Mortality, and Functional outcome

DCI-related cerebral infarction occurred in 439 patients (25%). Patients with DCI were more frequently female (77% vs 72%; P=0.027), had a higher prevalence of hypertension (63% vs 57%; P=0.031), and had a higher admission WFNS and mFisher grades (both P<0.001). Age did not differ significantly between groups. DCI was associated with higher rates of vasospasm (61% vs 34%), new postoperative neurological deficit (44% vs 17%), seizures, hydrocephalus, herniation, and rebleeding, as well as longer hospitalization (median, 20 vs 16 days). In-

hospital mortality was 39% among patients with DCI vs 20% among those without DCI, and unfavorable functional outcome occurred in 71% vs 35%, respectively (all P≤0.003).

Patients who died during hospitalization were older (median, 59 vs 54 years) and had greater neurological and radiological severity at admission (WFNS grade 5, 41% vs 8.5%; mFisher ≥4, 65% vs 33%; both P<0.001). DCI and most in-hospital complications were more frequent among nonsurvivors. Vasospasm rates did not differ between survivors and nonsurvivors (39% vs 41%; P=0.6). Similar differences in admission severity and in-hospital complications were observed according to functional outcome.

Attributable Fraction and Causal Mediation Analysis

After adjustment for age, sex, diabetes, hypertension, WFNS, mFisher, hydrocephalus, rebleeding, and seizures, the estimated attributable fraction of in-hospital mortality associated with DCI was 12.1% (95% CI, 7.0–17.2%; P<0.001; Table 4, Figure 4).

Poor admission neurological grade (WFNS grade ≥4) was associated with a 35.7 percentage-point increase in the absolute probability of unfavorable functional outcome (total effect; 95% CI, 30.7–41.4) (Table 4). The average direct effect was 33.1 percentage points (95% CI, 27.9–38.3), and the average causal mediation effect through DCI was 2.6 percentage points (95% CI, 1.3–4.5; P<0.001), corresponding to a proportion mediated of 7.3% (95% CI, 3.6–12.6%).

Factors Associated With DCI

In multivariable logistic regression, DCI was associated with vasospasm (OR, 2.51 [95% CI, 1.96–3.21]; P<0.001), increasing WFNS grade (OR per point, 1.33; 95% CI, 1.22–1.45; P<0.001), seizures (OR, 1.49; 95% CI, 1.10–2.01; P=0.010), and arterial hypertension (OR, 1.42; 95% CI, 1.11–1.83; P=0.006). The mFisher scale was not independently associated with DCI in either model (P=0.44 and P=0.47). The reduced model had a lower Akaike information than the full model (1783.3 versus 1793.3), with effect estimates for retained covariates.

Between-Center Differences

Patients enrolled at the Belgian center (n = 257) differed from those enrolled at the three Brazilian centers (n = 1,532) in baseline characteristics and processes of care (Supplementary Table S2). Poor admission grade (WFNS 4–5) occurred in 42% of patients at the Belgium center and 29% at the Brazilian centers, while mFisher grade 3–4 occurred in 89% and 68%, respectively. Median time from ictus to aneurysm occlusion was 1 day [IQR 0–2] at the Belgium center and ranged from 4 to 9 days across the Brazilian centers. Intracranial-pressure monitoring was used in 52% versus 21%, DCI-related cerebral infarction occurred in 39% versus 22% (P<0.001), and withdrawal of life-sustaining therapy occurred in 13% versus 6.2%, with rates of 12%, 2.5% and 0.4% across the three Brazilian centers.

In-hospital mortality was 28% at the Belgian center and 24% across the Brazilian centers, while unfavorable functional outcome (mRS 4–5) at 3 to 6 months occurred in 49% at the Belgian center and approximately 44% across the Brazilian centers. Across individual centers, unfavorable outcome at 3–6 months occurred in 49% at the Belgian center and approximately 44% across the Brazilian centers. Across individual centers, unfavorable outcome ranged from 36% to 53%, with both extremes observed at Brazilian centers. Median hospital length of stay was 18 days at the Belgian center and ranged from 13 to 20 days across the Brazilian centers. All comparisons were unadjusted and intended to characterize between-center heterogeneity [4].

Discussion

In this prospective, multicenter, multinational cohort of 1,789 patients with aSAH, we used causal-inference methods to estimate the contribution of DCI to mortality and functional outcome. Three main findings emerged. First, DCI was associated with an adjusted attributable fraction of 12.1% for in-hospital mortality. Second, DCI mediated only a small proportion (7.3%) of the effect of poor admission grade on unfavorable functional outcome. Third, vasospasm, seizures, hypertension, and higher WFNS grade were independently associated with DCI. Notably, crude mortality and functional outcomes were relatively similar between

290 the Belgian center and the Brazilian centers overall, whereas substantially greater variability in
291 functional outcome was observed across individual Brazilian centers
292 Cohort studies have consistently linked DCI to mortality and disability after aSAH [7,13,33,34], but
293 most have reported relative measures of association rather than the proportion of outcome
294 burden potentially attributable to DCI. In our cohort, crude in-hospital mortality was nearly
295 twice as high among patients with DCI-related infarction (39% vs 20%), whereas the adjusted
296 attributable fraction was 12.1%. Under the assumptions of the causal model, this corresponds
297 to approximately one in eight in-hospital deaths being attributable to DCI. This distinction is
298 clinically relevant: relative associations describe prognostic differences between patients with
299 and without DCI, whereas attributable fractions provide an estimate of the population-level
300 burden potentially amenable to prevention. Similar discrepancies between crude associations
301 and attributable mortality have been described in critical-care epidemiology, where adjustment
302 for baseline severity and competing events substantially reduces crude estimates [29,35,36].
303 The mediation analysis provides a complementary perspective on functional outcome. Poor
304 admission grade increased the absolute probability of unfavorable outcome by 35.7 percentage
305 points, but only 2.6 percentage points–7.3% of the total effect– were mediated through DCI.
306 Thus, most of the association between initial neurological severity and subsequent disability
307 appears to operate through pathways other than DCI. This is consistent with the central role of
308 early brain injury and primary hemorrhage severity in determining outcome after aSAH [7,37]. At
309 the same time, the mediated component remains clinically relevant because, unlike admission
310 severity, DCI represents a potentially preventable and treatable complication.
311 Vasospasm was the strongest factor associated with DCI but was not itself associated with in-
312 hospital mortality in the unadjusted analysis. This finding is consistent with the growing
313 distinction between angiographic vasospasm and clinically meaningful ischemic injury after
314 aSAH. [16,34]. Trials of vasospasm-directed therapy have demonstrated that reducing arterial

narrowing does not necessarily translate into improved functional outcome, reinforcing cerebral infarction and clinical DCI as more relevant endpoints [6,16,19].

The lack of an independent association between the mFisher and DCI differs from previous studies showing an association between blood burden and DCI risk [10,11,38]. This finding should be interpreted cautiously, as adjustment for downstream variables and the inherent subjectivity of semiquantitative blood-burden assessment may have attenuated the association. It should therefore not be interpreted as evidence against the prognostic value of radiographic blood burden.

An important finding was the substantial heterogeneity across centers. Crude mortality and functional outcomes were relatively similar between the Belgian center and the Brazilian centers overall, whereas functional outcome varied considerably across the individual Brazilian centers. This within-country variation may reflect differences in referral pathways, treatment delays, resource availability, access to specialized neurocritical care and rehabilitation, and broader socioeconomic inequalities that are not captured by country-level income classification alone. This contrasts with prior cross-continental aSAH data comparing Brazil and the United States, in which marked between-country differences in treatment timing, treatment modality, rehabilitation access, and outcomes were observed. Together, these findings suggest that disparities after aSAH may operate both between and within health systems.

These comparisons should, however, be interpreted cautiously. The Belgian cohort was substantially smaller than the Brazilian cohort and was derived from a single center, limiting both statistical precision and the ability to generalize its findings to Belgium or other high-income settings. Accordingly, the present data are better suited to describing center-level heterogeneity than to supporting formal conclusions regarding differences between high- and middle-income health systems.

Differences in DCI detection and end-of-life practices may have contributed to between-center heterogeneity. DCI–related infarction depends on repeat imaging and may therefore be more frequently detected in centers with more intensive surveillance [18]. Withdrawal of life-sustaining therapy also varied substantially across centers (0.4%–13%), potentially influencing crude mortality comparisons. Referral and transfer patterns may further contribute to these differences. These differences reinforce that center-level processes of care should be considered when interpreting multinational aSAH cohorts [4].

This study has several strengths, including its prospective, multicenter, multinational design, large sample size, standardized definition of DCI-related cerebral infarction, and assessment of both mortality and longer-term functional outcome. Methodologically, the use of regression standardization and causal mediation analysis within a prespecified causal framework allowed us to move beyond conventional measures of association and estimate the potential contribution of DCI to clinically relevant outcomes [17,23,24]. A further strength is the assessment of functional outcome in addition to mortality. Among patients with DCI-related cerebral infarction, 71% had an unfavorable functional outcome at follow-up, underscoring that the burden of DCI extends beyond survival. This is consistent with contemporary stroke research emphasizing disability and quality of life as meaningful outcomes alongside mortality [39,40]. Accordingly, evaluating DCI solely through mortality may underestimate its overall impact after aSAH.

Several limitations should also be acknowledged. First, attributable-fraction and mediation analysis rely on causal assumptions, including absence of unmeasured confounding, correct model specification, and consistency, which cannot be fully verified in an observational study. The mediation analysis may also be affected by exposure-induced mediator–outcome confounding, and the estimated proportion mediated is sensitive to model specification and effect scale [28] Second, DCI is a time-varying exposure that can only be observed among patients

surviving the relevant at-risk period, while discharge represents a competing event that was not formally modeled [29]. Third, management, neuromonitoring, and imaging practices were not standardized across centers, potentially affecting ascertainment of DCI-related infarction and outcomes. The Belgian cohort was derived from a single center and represented a relatively small proportion of the overall sample, limiting formal comparisons between countries or health-system income levels. Finally, functional outcomes were assessed within a 3- to 6-month window and partly by telephone, which may have introduced measurement variability [15,18].

Conclusions

In this prospective multinational cohort, causal-inference methods estimated that DCI contributed to a meaningful proportion of in-hospital mortality after aSAH while mediating a small proportion of the effect of poor admission grade on unfavorable functional outcome. Because DCI represents a potentially preventable and treatable complication, these findings help quantify its potential therapeutic relevance and support evaluating both survival and functional outcomes in future prospective studies.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Figure Captions

Figure 1. World Federation of Neurosurgical Societies (WFNS) grading scale.

Figure 2. Directed acyclic graph specifying the assumed causal structure linking poor admission grade, delayed cerebral ischemia (DCI)-related cerebral infarction, and unfavorable functional outcome after aneurysmal subarachnoid hemorrhage. Node shading follows the DAGitty convention: the exposure (poor admission grade) and the outcome (unfavorable functional outcome) are shown in green; the mediator (DCI-related cerebral infarction) in amber; ancestors of both exposure and outcome in red; and ancestors of the outcome only in blue. Arrows denote assumed directed causal effects. mRS, modified Rankin Scale.

Figure 3. Study population flow diagram. Analytic subset sizes differ because of variable-specific missing data and availability of follow-up. DCI, delayed cerebral ischemia; mRS, modified Rankin Scale.

Figure 4. (A) Population attributable fraction of delayed cerebral ischemia (DCI) for in-hospital mortality, comparing observed mortality with the counterfactual mortality estimated when DCI is eliminated. (B) Decomposition of the effect of poor admission grade on unfavorable functional outcome into the direct effect and the effect mediated through DCI. CI, confidence interval; pp, percentage points.

Reporting Checklist

STROBE Statement—checklist of items that should be included in reports of cohort studies. Page numbers refer to the pages of this manuscript file.

Section/Topic	Item No	Recommendation	Page No
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1, 6
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	6–7
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	8
Objectives	3	State specific objectives, including any prespecified hypotheses	8
Methods			
Study design	4	Present key elements of study design early in the paper	8–9
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	9
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	9
		(b) For matched studies, give matching criteria and number of exposed and unexposed	Not applicable
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	9–10
Bias	9	Describe any efforts to address potential sources of bias	10–11, 18
Study size	10	Explain how the study size was arrived at	9, 12
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	11
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	11
		(b) Describe any methods used to examine subgroups and interactions	11, 13–14
		(c) Explain how missing data were addressed	25 (Figure 3 legend)
		(d) If applicable, explain how loss to follow-up was addressed	12, 18
		(e) Describe any sensitivity analyses	13
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	12, 25 (Figure 3)
		(b) Give reasons for non-participation at each stage	12
		(c) Consider use of a flow diagram	25 (Figure 3)
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	12–13 (Tables 1–3)
		(b) Indicate number of participants with missing data for each variable of interest	25 (Figure 3 legend)
		(c) Summarise follow-up time (eg, average and total amount)	12

Section/Topic	Item No	Recommendation	Page No
Outcome data	15*	Report numbers of outcome events or summary measures over time	12–13
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	13 (Tables 4–5)
		(b) Report category boundaries when continuous variables were categorized	13
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	13
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	13–14
Discussion			
Key results	18	Summarise key results with reference to study objectives	14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	18
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14–18
Generalisability	21	Discuss the generalisability (external validity) of the study results	17–18
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	5

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

AGReMA-SF (short form) checklist — reporting of the mediation analysis

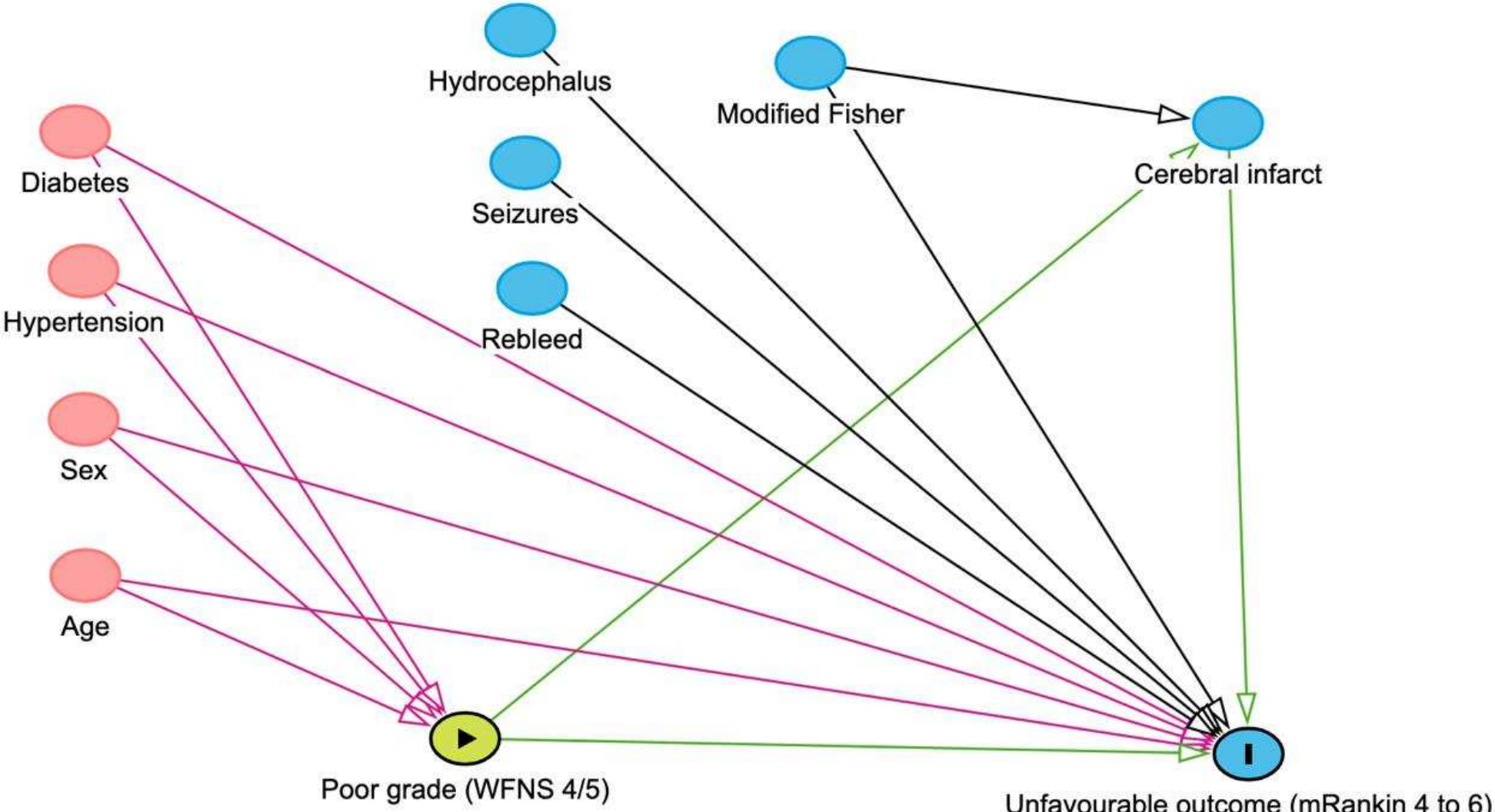
A Guideline for Reporting Mediation Analyses, short form, for studies in which the mediation analysis is a secondary focus. Page numbers refer to the pages of this manuscript file.

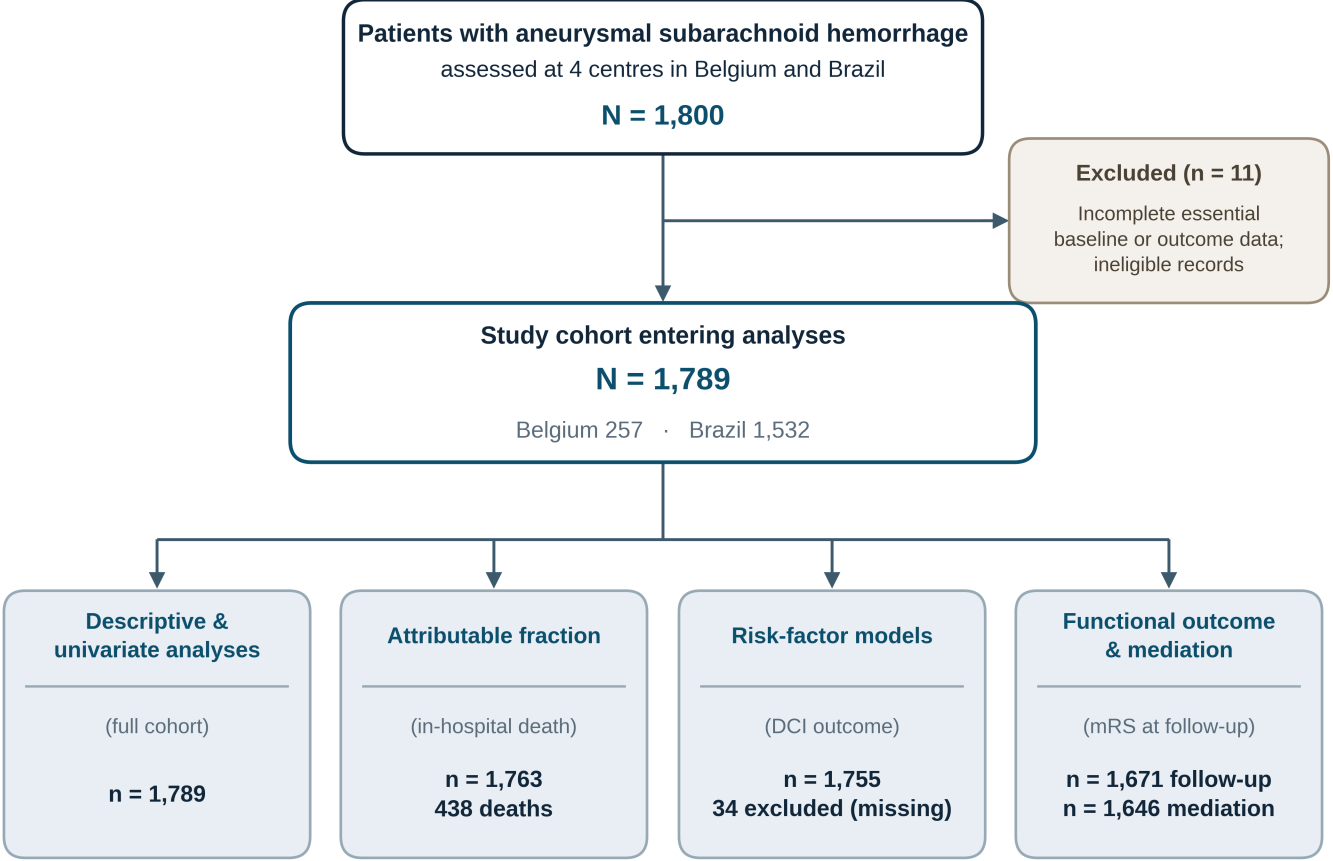
Section/Topic	Item No	Item Description	Reported on page No
Introduction			
Objectives	1	State the objectives of the study specific to the mechanisms of interest. The objectives should specify whether the study aims to test or estimate the mechanistic effects	6, 8
Methods			
Effects of interest	2	Specify the effects of interest	11
Causal assumptions	3	Specify assumptions about the causal model	11, 18, 25 (Figure 2)
Measurement	4	Clearly describe the interventions or exposures, mediators, outcomes, confounders, and moderators that were used in the analyses. Specify how and when they were measured, the measurement properties, and whether blinded assessment was used	9–11
Statistical methods	5	Describe the statistical methods used to estimate the causal relationships of interest. This description should specify analytical strategies used to reduce confounding, model building procedures, justification for the inclusion or exclusion of possible interaction terms, modelling assumptions, and methods used to handle missing data. Provide a reference to the statistical software and package used	10–11
Results			
Participants	6	Describe baseline characteristics of participants included in mediation analyses. Report the total sample size and number of participants lost during follow-up or with missing data	12–13 (Tables 1–3); 25 (Figure 3)
Outcomes and estimates	7	Report point estimates and uncertainty estimates for the exposure-mediator and mediator-outcome relationships. If inference concerning the causal relationship of interest is considered feasible given the causal assumptions, report the point estimate and uncertainty estimate	13 (Table 4, Figure 4)
Discussion			
Limitations	8	Discuss the limitations of the study including potential sources of bias	18
Interpretation	9	Interpret the estimated effects considering the study's magnitude and uncertainty, plausibility of the causal assumptions, limitations, generalizability of the findings, and results from relevant studies	14–18

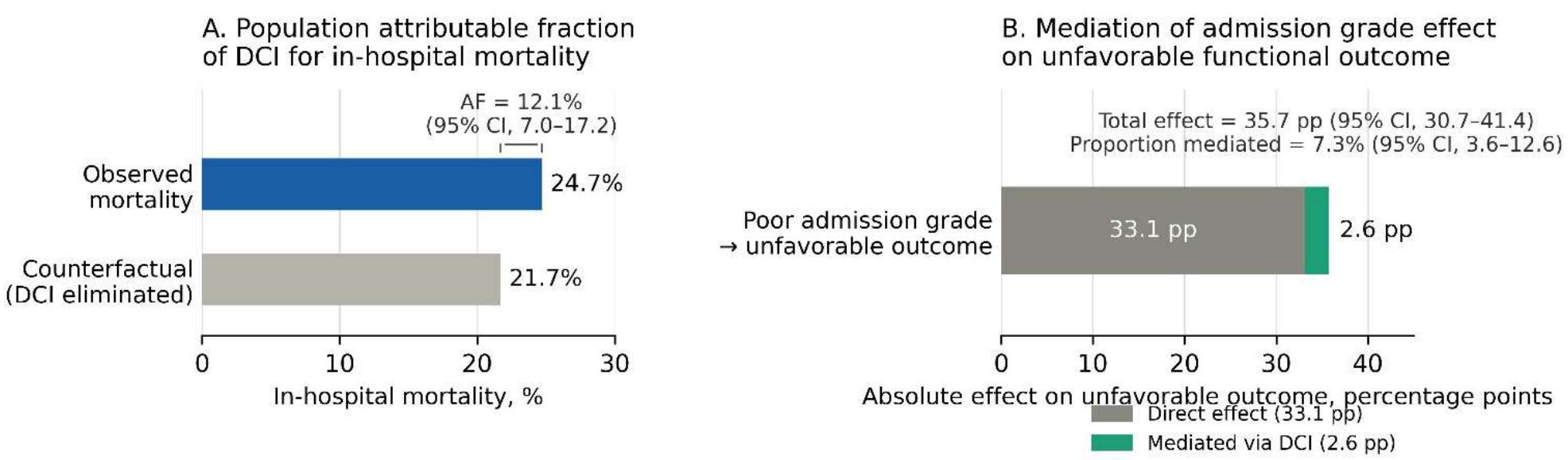
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AGReMA-SF is designed for articles that report mediation analyses of randomized trials or observational studies as a secondary focus of a paper. AGReMA-SF should be used in conjunction with CONSORT or STROBE for complete reporting. For more information, visit agrema-statement.org.

WFNS grade	Glasgow Coma Scale	Motor deficit
1	15	Absent
2	13-14	Absent
3	13-14	Present
4	7-12	Present or absent
5	3-6	Present or absent


Hydrocephalus
Modified Fisher
Diabetes
Seizures
Cerebral infarct
Hypertension
Rebleed
Sex
Age
Poor grade (WFNS 4/5)
Unfavourable outcome (mRankin 4 to 6)


Patients with aneurysmal subarachnoid hemorrhage
assessed at 4 centres in Belgium and Brazil
N = 1,800
Excluded (n = 11)
Incomplete essential baseline or outcome data; ineligible records
Study cohort entering analyses
N = 1,789
Belgium 257 · Brazil 1,532
Descriptive & univariate analyses
(full cohort)
n = 1,789
Attributable fraction
(in-hospital death)
n = 1,763
438 deaths
Risk-factor models
(DCI outcome)
n = 1,755
34 excluded (missing)
Functional outcome & mediation
(mRS at follow-up)
n = 1,671 follow-up
n = 1,646 mediation


A. Population attributable fraction of DCI for in-hospital mortality
AF = 12.1%
(95% CI, 7.0–17.2)
Observed mortality
24.7%
Counterfactual (DCI eliminated)
21.7%
0
10
20
30
In-hospital mortality, %
B. Mediation of admission grade effect on unfavorable functional outcome
Total effect = 35.7 pp (95% CI, 30.7–41.4)
Proportion mediated = 7.3% (95% CI, 3.6–12.6)
Poor admission grade → unfavorable outcome
33.1 pp
2.6 pp
0
10
20
30
40
Absolute effect on unfavorable outcome, percentage points
Direct effect (33.1 pp)
Mediated via DCI (2.6 pp)

Supplementary Files

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