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Review Article

Predictors of Delayed Cerebral Ischaemia After Aneurysmal Subarachnoid Haemorrhage

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Abstract

Background: Delayed cerebral ischaemia (DCI) remains a leading preventable cause of poor outcome after aneurysmal subarachnoid haemorrhage.

Objective: To synthesise the literature on clinical, radiographic and biomarker predictors of DCI, and on monitoring and prevention strategies.

Methods: Narrative review of consensus statements, grading-scale studies, biomarker cohorts, monitoring-accuracy studies and randomised trials.

Findings: Clinical grade (Hunt-Hess, WFNS) and radiographic clot burden (modified Fisher scale) are the strongest bedside predictors, combined in the VASOGRADE. Age, thick haemorrhage and poor neurological status predict DCI. Interleukin-6 and natriuretic peptides show the most consistent biomarker associations. Doppler and continuous EEG add monitoring value. Nimodipine remains the only intervention with proven benefit; other agents reduce vasospasm without improving function.

Conclusions: DCI risk stratification should combine clinical grade, radiographic burden, and biomarker and multimodal monitoring data to target surveillance and guide the still-limited preventive armamentarium.

Keywords: Delayed cerebral ischaemia; Subarachnoid haemorrhage; Vasospasm; Cerebral aneurysm; Neurocritical care

Abstract

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Keywords: delayed cerebral ischaemia; subarachnoid haemorrhage; vasospasm; cerebral aneurysm; neurocritical care

Introduction

Aneurysmal subarachnoid haemorrhage (aSAH) carries substantial early mortality, but a large share of the disability among survivors accrues not from the initial bleed but from a secondary, delayed injury classically attributed to angiographic vasospasm of the large cerebral arteries. Because clinical deterioration, radiographic infarction and angiographic narrowing do not always coincide, a multidisciplinary consensus group proposed the term delayed cerebral ischaemia (DCI) and standardised its definition as either a new cerebral infarction on CT/MRI not attributable to a procedural complication, or clinical deterioration (a new focal deficit or a sustained fall in Glasgow Coma Scale of two or more points lasting over an hour) after exclusion of other causes [1]. This definitional clarity has enabled more consistent comparison across observational cohorts and trials, and underlies a large body of work identifying predictors of DCI amenable to risk stratification, monitoring and, in some cases, prevention [2].

This narrative review synthesises that literature across four domains: clinical and radiographic predictors available at presentation; circulating biomarkers; monitoring modalities used during the at-risk window (typically days 3-14 after haemorrhage); and the evidence base for pharmacological and endovascular prevention and management, closing with the prognostic implications of DCI for functional outcome.

Pathophysiology of Delayed Cerebral Ischaemia

DCI was long equated with large-vessel vasospasm driven by subarachnoid blood breakdown products, but the consensus definition deliberately separates the clinical/radiographic syndrome from the angiographic finding because not all patients with angiographic vasospasm develop DCI, and DCI occurs in some patients without demonstrable macrovascular narrowing [1]. Contemporary understanding implicates a multifactorial cascade: early brain injury and blood-induced cortical spreading depolarisations, microcirculatory dysfunction and microthrombosis, impaired cerebral autoregulation, and a systemic and intrathecal neuroinflammatory response involving cytokines such as interleukin-6, superimposed on large-vessel arterial narrowing [3]. This multifactorial model explains why predictors drawn from clinical grade, radiographic clot burden, inflammatory and cardiac biomarkers, and neurophysiological or perfusion monitoring each carry partially independent predictive information rather than simply proxying for

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angiographic spasm [2].

Clinical and Radiographic Predictors

The two oldest and still most widely used clinical grading instruments — the Hunt and Hess scale, originally developed to stratify surgical risk [4], and the World Federation of Neurological Surgeons (WFNS) scale, which standardises grading around the Glasgow Coma Scale [5] — both correlate with DCI risk, worse grades predicting higher incidence. Radiographically, the original Fisher CT grading system linked the volume and distribution of subarachnoid blood to vasospasm risk [6], and was subsequently revised as the modified Fisher scale to account for concomitant intraventricular haemorrhage; in a cohort of 1355 patients the modified scale remained an independent predictor of symptomatic vasospasm after adjustment (adjusted OR 1.28 per grade), whereas the original Fisher scale did not [7]. Because clinical grade and radiographic burden capture complementary information, the VASOGRADE was developed and validated as a simple three-tier scale combining WFNS grade and modified Fisher score, stratifying patients into green (low), yellow (intermediate) and red (high) risk for DCI [8].

A comprehensive systematic review of clinical, laboratory and radiological predictors identified poor clinical condition on admission, greater amount of cisternal and intraventricular blood, and younger age as the principal independent predictors of DCI-related infarction, and used these to build a practical bedside risk chart [2]. A more recent, up-to-date systematic review reaffirmed clinical grade and radiographic clot burden as the most consistently reported predictors across the contemporary literature while highlighting substantial heterogeneity in how DCI itself is ascertained across studies [9]. Age, thick haemorrhage, obesity and pre-admission hypertension were confirmed as independent DCI risk factors even in a good-grade (WFNS I-III) population, a group sometimes assumed to be low risk [10]. Early perfusion CT obtained within hours of haemorrhage, particularly prolongation of mean transit time combined with clot volume, has emerged as an early radiographic surrogate for both DCI and six-month functional outcome, extending prediction beyond admission grading alone [11].

Table 1: Clinical and radiographic grading scales used to predict delayed cerebral ischaemia after aneurysmal subarachnoid haemorrhage [4,5,6,7,8].

Scale	Basis	Grades	DCI predictive value	Source
Hunt and Hess	Clinical exam (headache, meningism, consciousness, deficit)	I-V	Worse grade associated with higher DCI risk; originally designed for surgical risk	hunthess1968
WFNS	Glasgow Coma Scale + focal motor deficit	I-V	More objective than Hunt-Hess; incorporated into VASOGRADE	wfns1988
Original Fisher	CT blood distribution/thickness	1-4	Non-monotonic risk (peaks at Grade 3); not independently predictive after adjustment	fisher1980
Modified Fisher	CT blood thickness + intraventricular haemorrhage	0-4	Monotonic risk increase; independent predictor (adjusted OR 1.28/grade)	frontiera2006
VASOGRADE	WFNS grade + modified Fisher grade combined	Green/Yellow/Red	Validated 3-tier DCI risk stratification at presentation	vasograde2015

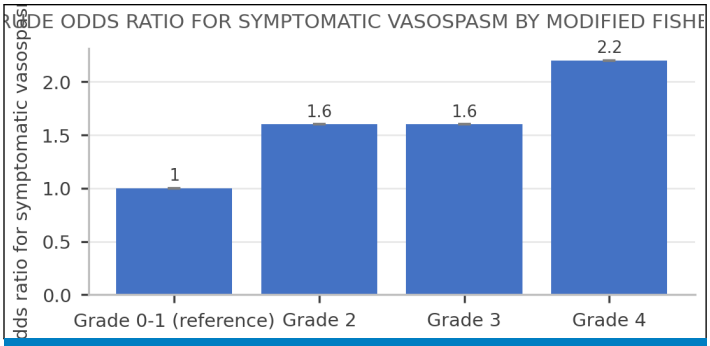

Figure 1: Crude odds ratio for symptomatic vasospasm by modified Fisher grade relative to Grade 0-1, in a cohort of 1355 patients: Grade 2, OR 1.6; Grade 3, OR 1.6; Grade 4, OR 2.2 [7].

Biomarker Predictors

Circulating and cerebrospinal fluid biomarkers have been

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extensively studied as adjuncts to clinical and radiographic risk stratification. Interleukin-6 (IL-6), a pro-inflammatory cytokine central to the neuroinflammatory hypothesis of DCI, is consistently elevated after aSAH; cerebrospinal fluid IL-6, more than serum IL-6, correlates with subsequent DCI and DCI-related infarction, reflecting compartmentalised intrathecal inflammation [3]. In a cohort study measuring CSF IL-6 during the first week after haemorrhage, elevated levels were among the most valuable early predictors of the subsequent clinical course, including DCI-related infarction [12]. Cardiac natriuretic peptides have an independent literature: brain natriuretic peptide (BNP) elevation correlates with transcranial-Doppler-defined vasospasm severity in early clinical studies [13], and in a later, larger cohort, BNP in the top quartile was independently associated with a four-fold increase in radiographic cerebral infarction, an association that was strongest in patients without angiographic vasospasm — suggesting BNP may flag vasospasm-independent mechanisms of ischaemia such as microcirculatory or neurocardiogenic dysfunction [14]. Together, inflammatory and cardiac biomarkers offer prognostic information that is only partially explained by clinical grade and radiographic burden, supporting a multimodal risk-prediction approach rather than reliance on any single biomarker.

Monitoring Strategies

Serial transcranial Doppler (TCD) ultrasonography remains the most widely deployed non-invasive bedside monitoring tool, using elevated middle cerebral artery mean flow velocity and the Lindegaard ratio (which corrects for hyperaemia by referencing extracranial internal carotid velocity) to flag developing vasospasm; a systematic review and meta-analysis found TCD velocity criteria predictive of DCI with reasonable pooled accuracy [15], and a more recent diagnostic-accuracy meta-analysis reported pooled sensitivity of approximately 76% and specificity of 77% for mean flow velocity, rising to roughly 82% and 88% respectively when the Lindegaard ratio was used [16]. Continuous electroencephalography (cEEG) offers a complementary, physiology-based monitoring approach: in a prospective multicentre diagnostic-accuracy study, quantitative cEEG features predicted DCI with high sensitivity, supporting its use to identify patients for closer surveillance or earlier intervention, particularly in poor-grade, sedated patients in whom serial examination is unreliable [17]. CT perfusion, discussed above as an early radiographic predictor, doubles as a monitoring tool when repeated during the at-risk window, with prolonged mean transit time serving as the most reproducible perfusion parameter for DCI detection [11]. No single modality is sufficient alone; contemporary neurocritical care increasingly combines clinical examination, TCD, and selective cEEG or perfusion imaging, informed by baseline VASOGRADE risk category [8].

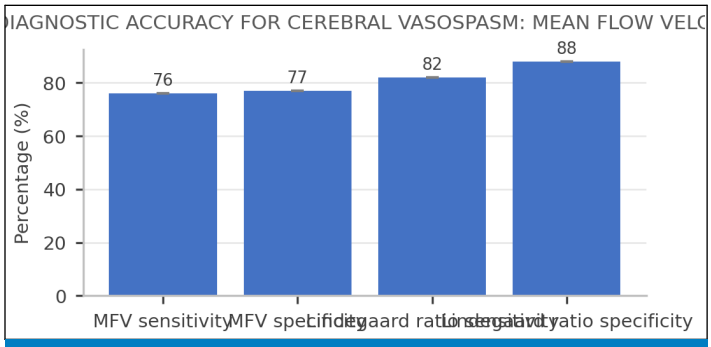

Figure 2: Pooled diagnostic accuracy of transcranial Doppler for cerebral vasospasm: mean flow velocity (MFV) sensitivity 76%/specificity 77% versus Lindegaard ratio sensitivity 82%/specificity 88% [16].

Prevention and Management Evidence

Oral nimodipine remains the only pharmacological intervention with robust trial evidence for improved functional outcome after aSAH: the British Aneurysm Nimodipine Trial randomised patients to nimodipine or placebo and demonstrated reduced cerebral infarction

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(22% versus 33%) and improved three-month outcome, establishing it as standard of care [18]. Statins were subsequently investigated on the hypothesis that pleiotropic vascular effects might reduce vasospasm; a meta-analysis of six randomised trials and two cohort studies found a significant reduction in angiographic vasospasm but no significant benefit for delayed ischaemic neurological deficit, cerebral infarction or mortality [19], broadly consistent with an earlier meta-analysis reporting reduced vasospasm incidence without a clearly established mortality benefit [20]. Magnesium sulphate showed early promise, with a phase II trial suggesting reduced DCI and improved outcome [21], but the large phase III MASH-2 trial found intravenous magnesium did not improve clinical outcome after aSAH, and routine use was not recommended [22]. Endothelin-receptor antagonism with clazosentan has repeatedly reduced angiographic vasospasm and vasospasm-related morbidity — including in randomised trials in coiled patients [23] and in two Japanese phase III trials showing reduced vasospasm-related morbidity and all-cause mortality [24] — yet the international phase III REACT trial did not demonstrate a significant reduction in clinical deterioration due to DCI, underscoring a persistent disconnect between angiographic and functional efficacy for this drug class [25]. For medically refractory vasospasm, endovascular rescue therapy with intra-arterial vasodilators is used, and a meta-analysis found favourable angiographic and neurological response rates, though evidence quality remains limited by the predominance of observational data [26].

Table 2: Randomised trial and meta-analysis evidence for prevention and management of delayed cerebral ischaemia after aneurysmal subarachnoid haemorrhage [18,19,20,22,21,23,24,25,26].

Intervention	Study	Key result	Source
Oral nimodipine	British Aneurysm Nimodipine Trial	Reduced cerebral infarction (22% vs 33%) and improved 3-month outcome	pickard1989
Statins	Meta-analysis, 6 RCTs + 2 cohorts	Reduced vasospasm incidence; no significant DIND, infarction or mortality benefit	shen2017
Statins	Earlier meta-analysis	Reduced vasospasm incidence; mortality benefit not firmly established	sillberg2008
IV magnesium sulphate	MASH-2, phase 3 RCT	No improvement in clinical outcome; routine use not recommended	mees2012
IV magnesium sulphate	MASH pilot RCT	Suggested reduced DCI and improved outcome (not confirmed in phase 3)	vandenbergh2005
Clazosentan	RCT in endovascularly coiled patients	Reduced angiographic vasospasm	macdonald2012
Clazosentan	Two Japanese phase 3 RCTs	Reduced vasospasm-related morbidity and all-cause mortality	endo2022
Clazosentan	REACT, international phase 3 RCT	No significant reduction in clinical deterioration due to DCI	mayer2025
Intra-arterial vasodilators	Meta-analysis, refractory vasospasm	Favourable angiographic and neurological response; evidence mainly observational	venkatraman2018

Prognostic Implications

DCI is not merely a biomarker of illness severity but an independent driver of poor outcome, which is precisely why the consensus definition specifies cerebral infarction and functional outcome as primary trial endpoints rather than angiographic vasospasm alone [1]. Across the predictor literature, the same variables that flag DCI risk — poor clinical grade, thick radiographic clot burden, older age, and adverse biomarker profiles — also

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independently predict worse functional outcome, reinforcing the value of early risk stratification for triage, counselling and trial enrichment [2]. Biomarker studies illustrate this link directly: elevated BNP predicted radiographic infarction independent of angiographic vasospasm severity [14], and early S100B and neuron-specific enolase levels in poor-grade aSAH independently predicted clinical outcome, reinforcing that ischaemic and neuronal injury markers carry prognostic weight beyond initial clinical grade [27]. The persistence of heterogeneous DCI definitions across the contemporary literature, flagged in the most recent systematic review, remains an obstacle to precise, generalisable prognostic modelling and to comparing prevention strategies across trials [9].

Conclusion

Predicting DCI after aSAH is best approached as a multidomain problem: clinical grade and radiographic clot burden — captured jointly by the VASOGRADE — provide the foundation for baseline risk stratification, inflammatory and cardiac biomarkers add independent prognostic information, and TCD, continuous EEG and CT perfusion enable dynamic surveillance during the at-risk window. Despite this rich predictive literature, the prevention armamentarium remains comparatively narrow: nimodipine is the only therapy with unequivocal outcome benefit, while statins, magnesium and endothelin-receptor antagonists have consistently reduced angiographic vasospasm without translating reliably into functional gains. Future work should prioritise harmonised DCI definitions, prospective validation of combined clinical-radiographic-biomarker risk models, and trials targeting the vasospasm-independent mechanisms increasingly implicated in ischaemic injury after aSAH.

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