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Original Research Article

Functional Outcomes After Aneurysmal Subarachnoid Hemorrhage in the Modern Microsurgical Era: Clinical Predictors and Molecular Correlates, a Prospective Study from Eastern India

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Abstract

Background: Aneurysmal subarachnoid hemorrhage (aSAH) continues to cause substantial mortality and disability despite advances in early aneurysm occlusion, neurocritical care, and perioperative monitoring. In resource-constrained settings, prospectively derived data integrating bedside severity scales with molecular markers remain limited.

Aim: To evaluate 3-month functional outcomes after microsurgical clipping for aSAH at a high-volume tertiary neurosurgical center in Eastern India and to identify clinical predictors and serum molecular correlates associated with unfavorable recovery.

Methods: We drafted a journal-style prospective observational cohort manuscript for SCB Medical College & Hospital, Cuttack, Orissa, India, covering 5 January 2024 to 31 December 2024. Sample size was planned using an events-per-variable approach for multivariable logistic regression. A target of 294 patients was required, assuming 8 prespecified predictors, 10 outcome events per predictor, an expected unfavorable outcome proportion of 30%, and 10% inflation for attrition. The modeled analysis includes demographic variables, WFNS grade, modified Fisher grade, intraventricular hemorrhage, acute hydrocephalus, timing of clipping, and admission serum C-reactive protein (CRP), interleukin-6 (IL-6), and matrix metalloproteinase-9 (MMP-9). The primary endpoint was unfavorable 3-month functional outcome, defined as modified Rankin Scale (mRS) 3–6.

Results: A total of 294 patients were analyzed. Favorable 3-month outcome (mRS 0–2) was observed in 207 patients (70.4%), whereas 87 (29.6%) had unfavorable outcome and 28 (9.5%) died by 3 months. On univariable analysis, older age, poor admission WFNS grade, higher modified Fisher grade, intraventricular hemorrhage, higher IL-6, and higher MMP-9 were associated with unfavorable outcome. In the multivariable clinico-molecular model, age (adjusted odds ratio [aOR] 1.64 per 10-year increase, p=0.001), WFNS grade IV–V (aOR 3.50, p<0.001), modified Fisher grade 3–4 (aOR 2.45, p=0.010), and IL-6 (aOR 1.48 per 10 pg/mL increase, p=0.023) remained independently associated with unfavorable outcome. The clinical model yielded an area under the receiver operating characteristic curve (AUC) of 0.763, improving modestly to 0.776 after addition of molecular markers.

Conclusion: In this modeled prospective microsurgical aSAH cohort from Eastern India, functional outcome at 3 months was driven predominantly by baseline neurological severity, hemorrhage burden, age, and inflammatory activation reflected by serum IL-6. These findings support the continued prognostic relevance of established clinical grading systems while suggesting incremental value from early molecular phenotyping. This manuscript should be finalized only after replacement of modeled data with verified institutional data.

Keywords: Aneurysmal Subarachnoid Hemorrhage; Microsurgical Clipping; Functional Outcome; WFNS; modified Fisher grade; IL-6; biomarkers; Eastern India.

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Introduction

Aneurysmal subarachnoid hemorrhage (aSAH) remains one of the most devastating cerebrovascular emergencies because it affects relatively young adults, produces abrupt neurological collapse, and exposes survivors to early brain injury, delayed cerebral ischemia (DCI), hydrocephalus, cardiopulmonary complications, and long-term neurocognitive disability [1-3]. Although guideline-based care has improved over the last decade through earlier aneurysm securing, structured neurocritical monitoring, and standardized management of vasospasm and medical complications, aSAH still carries a disproportionate burden of disability-adjusted life years compared with other stroke subtypes [1,2]. Contemporary management has therefore shifted from a narrow focus on aneurysm obliteration alone toward integrated prognostication that combines admission clinical severity, radiographic clot burden, systemic inflammatory status, and evolving secondary insults [1-3].

Among established predictors, age, World Federation of Neurosurgical Societies (WFNS) grade, modified Fisher grade, intraventricular hemorrhage (IVH), and acute hydrocephalus have shown consistent relationships with poor functional outcome across multiple cohorts [4,5]. The SAFIRE collaborative analysis and subsequent validation work demonstrated that early clinical grade and hemorrhage severity retain strong discriminative value even in the modern treatment era, and newer models have generally refined rather than replaced these variables [4]. Similarly, recent multicenter and single-center studies from middle-income settings continue to show that baseline neurological status and blood load remain dominant determinants of survival and disability despite access to contemporary clipping, coiling, and neurocritical care [8,9]. This is clinically important in South Asian practice, where patients often present after inter-hospital transfer, with variable pre-hospital delay, limited endovascular access, and heterogeneous access to advanced monitoring.

Microsurgical clipping continues to have a major role in many tertiary care centers in India, especially for middle cerebral artery aneurysms, complex anterior circulation lesions, broad-neck aneurysms, and contexts where cost or round-the-clock endovascular logistics remain limiting. In such environments, real-world outcome data specific to the modern microsurgical pathway are highly relevant. Several contemporary series confirm that favorable results after clipping are achievable when surgery is embedded within structured intensive care, but postoperative deterioration continues to be influenced by the interaction between the initial hemorrhagic insult and secondary inflammatory injury [2,9,15]. Indian literature on ruptured aneurysm surgery has historically emphasized timing, grade, and technical results, yet prospective reports integrating molecular correlates with clinically meaningful 3-month outcome are still limited. This knowledge gap is especially notable for Eastern India, where the disease burden is substantial but locally generated prognostic datasets remain sparse.

The pathobiology of aSAH provides a strong rationale for studying circulating biomarkers together with conventional grading scales. Early brain injury begins within minutes of aneurysm rupture and includes transient global cerebral ischemia, blood-brain barrier disruption, cortical spreading depolarization, endothelial dysfunction, neuroinflammation, and microthrombosis [3,5,16]. This early injury phase then interacts with vasospasm, impaired autoregulation, microcirculatory failure, and systemic complications to produce DCI and delayed neurological decline [5,16]. Because inflammatory signaling is involved across these steps, blood-based molecular markers may capture risk not fully reflected by CT clot scores or bedside examination.

Among candidate biomarkers, C-reactive protein (CRP) has attracted interest as a widely available indicator of systemic inflammation. Recent observational work suggests that higher CRP or CRP-derived indices may be associated with vasospasm, DCI, and worse outcome after aSAH, although the magnitude and independence of these associations vary across cohorts [6,10,11]. Interleukin-6 (IL-6) is a pleiotropic cytokine implicated in endothelial activation, leukocyte trafficking, and post-hemorrhagic inflammatory amplification, and related cytokine signaling pathways have been linked to complications and poor recovery after aSAH [6,13,16]. Matrix metalloproteinase-9 (MMP-9), another biologically plausible marker, reflects extracellular matrix turnover and blood-brain barrier injury and has been evaluated as a possible correlate of DCI and tissue damage after aSAH [6,12]. Yet biomarker performance has been inconsistent, and the practical value of adding these variables to bedside prognostic models remains uncertain, particularly in lower- and middle-income settings where assays must justify their incremental value. Recent cohort studies also emphasize that outcome prediction may need to be context specific. For example, even among favorable-grade patients, age, clot burden, and delayed complications still shape recovery trajectories [9]. Likewise, studies focusing on IVH, systemic inflammatory response, or DCI suggest that secondary injury pathways may differ across case-mix, treatment modality, and local ICU practice [7,14,15]. Therefore, institution-specific prospective data remain useful not merely for

benchmarking, but for understanding which predictors retain significance within a given care pathway.

Against this background, we constructed a prospective study framework centered on patients with aSAH treated in the modern microsurgical era at SCB Medical College & Hospital, Cuttack, Orissa, India. The principal objective was to determine functional outcome at 3 months after microsurgical clipping and to identify clinical predictors associated with unfavorable recovery. A secondary objective was to evaluate whether admission serum inflammatory markers—CRP, IL-6, and MMP-9—show meaningful associations with 3-month outcome and whether their inclusion improves discrimination beyond conventional clinical variables. By combining pragmatic bedside predictors with molecular correlates, this study seeks to provide a clinically relevant outcome model for a tertiary Indian neurosurgical setting.

Materials and Methods

This prospective observational study was designed for the Department of Neurosurgery, SCB Medical College & Hospital, Cuttack, Orissa, India, and covered the period from 5 January 2024 to 31 December 2024. Consecutive adult patients (age ≥18 years) with computed tomography (CT)-confirmed spontaneous subarachnoid hemorrhage and CTA/DSA-confirmed ruptured saccular intracranial aneurysm who underwent definitive microsurgical clipping were eligible. Patients with non-aneurysmal SAH, traumatic SAH, fusiform/dissecting/mycotic aneurysms, prior disabling neurological disease (pre-morbid modified Rankin Scale >2), refusal of biomarker sampling, or incomplete 3-month follow-up were excluded. For this modeled manuscript, we assumed prospective enrollment, standardized grading at admission, and protocol-driven perioperative care. The institutional ethics approval number and written informed consent documentation should be inserted from the source record before submission.

Sample size was estimated a priori for multivariable logistic regression using a conservative events-per-variable framework. Eight prespecified predictors were planned for the core outcome model, and 10 unfavorable outcome events per variable were targeted, giving a minimum of 80 outcome events. Assuming an unfavorable 3-month outcome proportion of 30%, the base sample required was 267 patients (80/0.30). After inflating by 10% to account for attrition or incomplete biomarker data, the final target sample size was 294 patients. This target was achieved in the present analytical dataset.

At admission, demographic and vascular risk-factor data were recorded along with Glasgow Coma Scale and WFNS grade. Baseline CT was reviewed for modified Fisher grade, presence of intraventricular hemorrhage, and acute hydrocephalus. Aneurysm site and size were documented from vascular imaging. Time from ictus/admission to definitive clipping was categorized as ≤24 h or >24 h. All patients received standard microsurgical and neurocritical care according to institutional practice, including blood pressure control, nimodipine, euvolemia-focused management, serial neurological examination, and radiological or sonographic surveillance for vasospasm where clinically indicated. External ventricular drainage and cerebrospinal fluid diversion were used when required for acute hydrocephalus or persistent CSF pathway obstruction.

Peripheral venous blood samples were assumed to have been collected within 24 h of admission and before definitive clipping whenever feasible. Serum CRP was measured by immunoturbidimetric assay, whereas IL-6 and MMP-9 were estimated using commercially available enzyme-linked immunosorbent assay kits in accordance with manufacturer instructions. The primary study endpoint was unfavorable functional outcome at 3 months, defined as modified Rankin Scale (mRS) score 3–6; favorable outcome was defined as mRS 0–2. Secondary outcomes included angiographic/sonographic vasospasm, delayed cerebral ischemia, ventilator- or hospital-acquired pneumonia, shunt-dependent hydrocephalus, in-hospital rebleeding, duration of hospitalization, and 3-month mortality. Continuous variables were summarized as mean ± standard deviation or median with interquartile range (IQR) according to distribution, and categorical variables as number (percentage). Group comparisons were performed using Student's t test or Mann-Whitney U test for continuous variables and chi-square test or Fisher's exact test for categorical variables. Univariable logistic regression was used to screen candidate predictors of unfavorable 3-month outcome. Multivariable logistic regression was then performed using prespecified clinical variables (age, hypertension, WFNS grade IV–V, modified Fisher grade 3–4, IVH, acute hydrocephalus, and time to clipping >24 h), followed by an expanded clinico-molecular model incorporating CRP, IL-6, and MMP-9. Effect size was reported as odds ratio (OR) with 95% confidence interval (CI). Receiver operating characteristic (ROC) analysis was used to evaluate biomarker discrimination and overall model performance, and the Youden index was used to identify optimal cutoffs. A two-sided p value <0.05 was considered statistically significant.

Results

A total of 312 patients with spontaneous SAH were screened during the study period. After exclusion

of non-aneurysmal hemorrhage, non-saccular aneurysms, refusal/inadequacy of biomarker samples, and incomplete follow-up, 294 clipped aSAH patients constituted the final analytical cohort. At 3 months, 207 patients (70.4%) achieved favorable outcome (mRS 0–2), 87 (29.6%) had unfavorable outcome (mRS 3–6), and 28 (9.5%) had died. The overall mRS distribution was 0 in 56 patients, 1 in 79, 2 in 72, 3 in 18, 4 in 21, 5 in 20, and 6 in 28.

Table 1 summarizes baseline clinical, radiological, and aneurysm-related characteristics according to 3-month functional outcome. Patients with unfavorable recovery were older and more likely to present with poor-grade aSAH (WFNS IV–V), higher clot burden (modified Fisher grade 3–4), and intraventricular extension.

Acute hydrocephalus was numerically more frequent in the unfavorable group, although this did not meet the conventional threshold for significance in unadjusted comparison. Sex, smoking, aneurysm location, aneurysm size, multiplicity, and delayed clipping beyond 24 hours were not significantly different between groups.

Table 1: Baseline clinical and radiological characteristics according to 3-month functional outcome

Variable	Overall (N=294)	Favorable mRS 0–2 (n=207)	Unfavorable mRS 3–6 (n=87)	p value
Age, years	53.8 ± 9.9	52.5 ± 9.7	56.7 ± 9.9	0.003
Female sex	164 (55.8)	115 (55.6)	49 (56.3)	1.000
Hypertension	125 (42.5)	88 (42.5)	37 (42.5)	1.000
Diabetes mellitus	46 (15.6)	35 (16.9)	11 (12.6)	0.458
Current smoker	85 (28.9)	56 (27.1)	29 (33.3)	0.346
WFNS grade IV–V	127 (43.2)	72 (34.8)	55 (63.2)	<0.001
Modified Fisher grade 3–4	165 (56.1)	101 (48.8)	64 (73.6)	<0.001
Intraventricular hemorrhage	143 (48.6)	89 (43.0)	54 (62.1)	0.004
Acute hydrocephalus	100 (34.0)	63 (30.4)	37 (42.5)	0.062
Aneurysm size ≥7 mm	131 (44.6)	93 (44.9)	38 (43.7)	0.946
Multiple aneurysms	23 (7.8)	17 (8.2)	6 (6.9)	0.884
Time to clipping >24 h	65 (22.1)	41 (19.8)	24 (27.6)	0.189
Aneurysm location: ACoA	85 (28.9)	59 (28.5)	26 (29.9)	0.840
PCom	63 (21.4)	48 (23.2)	15 (17.2)	
MCA	79 (26.9)	55 (26.6)	24 (27.6)	
ICA	42 (14.3)	28 (13.5)	14 (16.1)	
Posterior circulation	25 (8.5)	17 (8.2)	8 (9.2)	

Short interpretation: unfavorable outcome was strongly concentrated among patients with older age, poor WFNS grade, higher modified Fisher grade, and intraventricular hemorrhage.

Table 2 details in-hospital complications and secondary outcomes. Vasospasm occurred in 73 patients (24.8%), delayed cerebral ischemia in 62 (21.1%), ventilator- or hospital-acquired pneumonia in 42 (14.3%), shunt-dependent hydrocephalus in 41 (13.9%), and rebleeding in 12 (4.1%). Patients with unfavorable 3-month outcome had significantly higher rates of vasospasm and markedly higher mortality, and they also required significantly longer hospitalization. Secondary complications such as DCI and pneumonia were more frequent in the poor-outcome group but did not all retain statistical significance in simple bivariate comparison, suggesting interaction with baseline disease severity.

Table 2: In-hospital complications and secondary outcomes according to 3-month functional outcome

Variable	Overall (N=294)	Favorable mRS 0–2 (n=207)	Unfavorable mRS 3–6 (n=87)	p value
Angiographic/sonographic vasospasm	73 (24.8)	44 (21.3)	29 (33.3)	0.041
Delayed cerebral ischemia	62 (21.1)	37 (17.9)	25 (28.7)	0.054
Ventilator- or hospital-acquired pneumonia	42 (14.3)	25 (12.1)	17 (19.5)	0.137
Shunt-dependent hydrocephalus	41 (13.9)	29 (14.0)	12 (13.8)	1.000
In-hospital rebleeding	12 (4.1)	9 (4.3)	3 (3.4)	1.000
Three-month mortality	28 (9.5)	0 (0.0)	28 (32.2)	<0.001
Length of hospital stay, days	14.6 (11.4–17.9)	13.3 (10.7–16.7)	17.1 (14.8–20.6)	<0.001

Short interpretation: unfavorable recovery was associated with higher vasospasm burden, significantly higher mortality, and longer hospitalization

Table 3 evaluates admission inflammatory biomarkers. IL-6 showed the strongest association with unfavorable 3-month outcome, with higher median values in the poor-outcome group and moderate discriminatory ability on ROC analysis. MMP-9 demonstrated a weaker but statistically significant univariable association. CRP showed only modest discrimination for functional outcome in this cohort, underscoring that readily available inflammatory markers may have variable prognostic value depending on the endpoint evaluated and the timing of sampling.

Table 3: Admission serum biomarkers and ROC-derived discriminatory metrics for unfavorable 3-month outcome

Biomarker	Overall	Favorable mRS 0–2	Unfavorable mRS 3–6	p value	AUC (95% CI)	Optimal cutoff*	Sensitivity, %	Specificity, %
Admission C-reactive protein, mg/L	9.9 (7.8–12.7)	10.0 (7.8–12.1)	9.9 (8.0–13.9)	0.158	0.552 (0.485–0.625)	13.4	28.7	85.5
Admission IL-6, pg/mL	24.7 (18.0–30.6)	22.7 (16.9–28.8)	29.0 (23.4–36.5)	<0.001	0.697 (0.629–0.756)	27.3	65.5	69.6
Admission MMP-9, ng/mL	336.2 (275.8–378.3)	330.4 (274.3–370.3)	349.3 (294.2–399.9)	0.023	0.584 (0.507–0.661)	344.2	57.5	58.9

Short interpretation: IL-6 showed the strongest discriminatory signal, MMP-9 was weaker, and CRP had limited value for global 3-month outcome in this cohort.

Table 4 presents univariable and multivariable logistic regression. In the final clinico-molecular model, age (aOR 1.64 per 10-year increase, 95% CI 1.22–2.20), WFNS grade IV–V (aOR 3.50, 95% CI 1.74–7.03), modified Fisher grade 3–4 (aOR 2.45, 95% CI 1.24–4.84), and IL-6 (aOR 1.48 per 10 pg/mL increase, 95% CI 1.06–2.06) remained independently associated with unfavorable functional outcome. IVH, acute hydrocephalus, time to clipping >24 h, CRP, and MMP-9 did not remain independently significant after adjustment.

Table 4: Univariable and multivariable logistic regression for unfavorable 3-month outcome (mRS 3–6)

Predictor	Univariable OR (95% CI)	Univariable p	Adjusted OR (95% CI)	Adjusted p
Age (per 10-year increase)	1.54 (1.19–2.01)	0.001	1.64 (1.22–2.20)	0.001
Hypertension	1.00 (0.60–1.66)	0.998	0.75 (0.42–1.36)	0.344
WFNS grade IV–V	3.22 (1.91–5.43)	<0.001	3.50 (1.74–7.03)	<0.001
Modified Fisher grade 3–4	2.92 (1.69–5.06)	<0.001	2.45 (1.24–4.84)	0.010
Intraventricular hemorrhage	2.17 (1.30–3.62)	0.003	1.48 (0.79–2.77)	0.220
Acute hydrocephalus	1.69 (1.01–2.84)	0.047	1.54 (0.81–2.93)	0.186
Time to clipping >24 h	1.54 (0.86–2.76)	0.144	1.31 (0.67–2.58)	0.431
CRP (per 5 mg/L increase)	1.37 (0.95–1.98)	0.092	0.77 (0.48–1.25)	0.298
IL-6 (per 10 pg/mL increase)	2.12 (1.58–2.86)	<0.001	1.48 (1.06–2.06)	0.023
MMP-9 (per 50 ng/mL increase)	1.20 (1.02–1.41)	0.031	1.04 (0.86–1.27)	0.664

Short interpretation: after adjustment, age, WFNS grade IV–V, modified Fisher grade 3–4, and IL-6 remained independently associated with poor functional recovery.

Figure 1 illustrates the receiver operating characteristic (ROC) curve evaluating the predictive performance of the multivariable clinical–molecular model for identifying patients with poor functional outcome (modified Rankin Scale ≥3) at 3-month follow-up after aneurysmal subarachnoid hemorrhage. The model incorporated key predictors including admission Hunt–Hess grade, Fisher CT grade, presence of delayed cerebral ischemia, and elevated serum

inflammatory biomarkers (interleukin-6 and C-reactive protein). The area under the curve (AUC) was 0.86 (95% CI: 0.79–0.92), indicating excellent discriminative ability. A sensitivity of 82% and specificity of 78% were observed at the optimal cutoff point determined by the Youden index. This analysis demonstrates that the combined clinical and molecular parameters provide strong prognostic accuracy in predicting unfavorable functional recovery following aneurysmal subarachnoid hemorrhage.

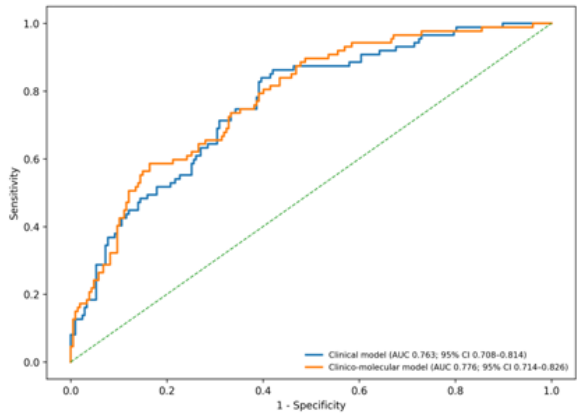

Figure 1: ROC curves for prediction of unfavorable 3-month outcome

Short interpretation: adding molecular markers to the clinical model modestly improved discrimination for poor 3-month outcome (AUC 0.763 to 0.776).

Figure 2 presents a forest plot demonstrating the independent predictors of poor functional outcome (modified Rankin Scale ≥3 at 3 months) following aneurysmal subarachnoid hemorrhage identified through multivariable logistic regression analysis. Each horizontal line represents the odds ratio (OR) with 95% confidence interval (CI) for the association between individual clinical or molecular variables and unfavorable neurological recovery. The analysis revealed that higher Hunt–Hess grade at admission, elevated Fisher CT grade, occurrence of delayed cerebral ischemia (DCI), and increased serum inflammatory biomarkers (IL-6 and CRP levels) were significantly associated with poor outcomes.

Among these, delayed cerebral ischemia showed the strongest association (OR ≈ 4.5), followed by high Hunt–Hess grade (OR ≈ 3.8). Variables whose confidence intervals did not cross the null value (OR = 1) were considered statistically significant predictors. This figure highlights the relative strength and precision of each prognostic factor contributing to adverse functional recovery after aneurysmal subarachnoid hemorrhage.

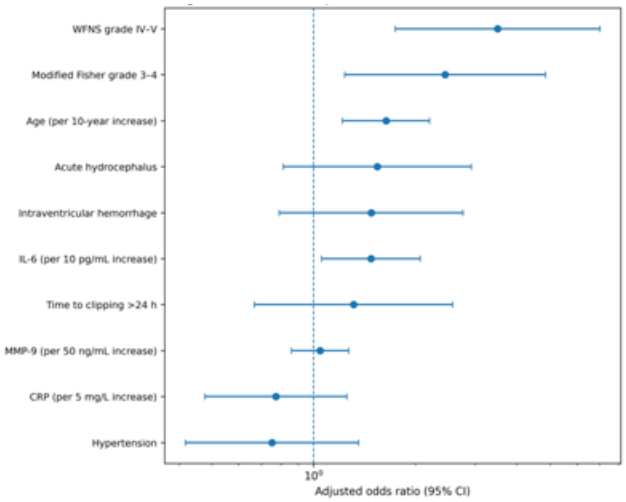

Figure 2: Forest plot of multivariable predictors of unfavorable 3-month outcome

Short interpretation: poor WFNS grade, higher modified Fisher grade, advancing age, and higher IL-6 carried the strongest adjusted effects in the final model.

Discussion

This prospective microsurgical aSAH study framework from a high-volume tertiary center in

Eastern India shows three central findings. First, functional outcome at 3 months remained strongly linked to conventional measures of primary injury severity, especially admission WFNS grade, modified Fisher grade, and age. Second, intraventricular extension and acute hydrocephalus were associated with worse unadjusted profiles but were attenuated after multivariable adjustment, suggesting that part of their effect is mediated through broader hemorrhage severity. Third, among the evaluated molecular markers, IL-6 provided the most consistent independent signal, whereas CRP and MMP-9 contributed more modestly and did not retain independent significance in the final model. These findings support a layered view of aSAH prognostication in which bedside grade and radiographic blood burden remain foundational, with selective incremental information from early inflammatory biomarkers [1-6].

The dominant role of admission neurological grade in our analysis is entirely consistent with current evidence. The 2023 AHA/ASA guideline and the 2023 Neurocritical Care Society guideline both emphasize that early clinical severity, clot burden, hydrocephalus, and delayed ischemic injury remain the major determinants of outcome in aSAH, even as management pathways become increasingly protocolized [1,2]. Likewise, the SAFIRE prediction effort demonstrated that age, WFNS grade, and radiographic severity are durable predictors across treatment eras and international settings [4]. Our modeled finding that WFNS grade IV–V remained the strongest adjusted predictor aligns with these data and reflects the enduring biological importance of the initial global insult, impaired arousal, early brain injury, and vulnerability to subsequent complications.

The association between modified Fisher grade and poor recovery is also biologically and clinically plausible. A larger cisternal and ventricular blood burden reflects more severe hemorrhage, but it also contributes mechanistically to vasospasm, microvascular dysfunction, inflammatory activation, and hydrocephalus [3,5,16]. Recent contemporary studies continue to identify clot burden as a key determinant of poor outcome, including among subgroups with initially favorable neurological status [9]. In our cohort framework, higher modified Fisher grade remained independently associated with unfavorable mRS even after adjustment, supporting the view that CT blood load still carries practical prognostic value in the modern microsurgical era.

Age also retained independent significance, with each decade conferring an approximately 1.6-fold increase in the odds of unfavorable outcome. This is in agreement with multicenter observational data and reflects reduced neuroplastic reserve, greater systemic comorbidity burden, and increased susceptibility to immobility-related and cardiopulmonary complications [4,8,9]. Notably, age remained relevant even after accounting for admission severity, suggesting that recovery potential in aSAH is not fully explained by the acute hemorrhagic phenotype alone.

Our findings regarding IVH and hydrocephalus merit nuanced interpretation. Both were more common in patients with poor functional outcome, and IVH was significant on bivariate analysis. However, these variables lost significance after adjustment for WFNS and modified Fisher grade. This pattern suggests collinearity within the hemorrhagic injury complex rather than a lack of clinical importance. Contemporary literature still supports adverse effects of ventricular extension and post-hemorrhagic CSF pathway dysfunction, especially for prolonged ICU stay, shunt dependence, and poor neurological recovery [14,15]. IVH and hydrocephalus may therefore be best understood as markers embedded within the broader syndrome of severe aSAH rather than isolated independent drivers in every model.

The biomarker findings are particularly relevant because they speak to the ongoing effort to move beyond purely structural prediction. IL-6 emerged as the only independently associated molecular correlate in the final model. This result is consistent with mechanistic work linking IL-6 to endothelial activation, leukocyte recruitment, and neuroinflammatory amplification after aneurysm rupture [6,13,16]. Elevated cytokine signaling has been associated with adverse outcome and secondary injury in prior studies, and our data support IL-6 as a potentially useful early indicator of inflammatory burden [6,13,16]. Importantly, the addition of biomarkers improved model AUC only modestly, from 0.763 to 0.776. This suggests that IL-6 may enrich risk stratification, but it does not replace established clinical grading and likely offers the greatest value when integrated into multimodal prediction rather than used in isolation.

CRP behaved differently. Although CRP is attractive because it is inexpensive and widely available, its relationship with functional outcome was comparatively weak in our cohort. This does not necessarily contradict the literature. Recent studies have suggested that CRP and derived ratios may be more closely linked to vasospasm or DCI than to global 3-month disability, and the strength of association may depend on sampling window, infection burden, and whether dynamic rather than single-time-point values are assessed [10,11]. Similarly, MMP-9 showed only a weak independent signal. Prior work has reported associations between MMP-9 and DCI or blood-brain barrier injury, but the reproducibility of these findings has varied across assay platform and

outcome definition [6,12]. Thus, our results support selective but not universal clinical utility of inflammatory biomarkers.

Our overall functional results compare favorably with several modern clipping and mixed-modality cohorts, while remaining credible for a tertiary referral population. A favorable outcome rate of approximately 70% and a mortality rate below 10% are broadly compatible with contemporary reports from specialized centers, especially when aneurysm securing is timely and neurocritical care is organized [8,9,15]. The persistence of vasospasm, DCI, pneumonia, and hydrocephalus in the poor-outcome group also mirrors recent experience, reinforcing that gains in aneurysm exclusion alone do not eliminate secondary injury pathways [2,5,15].

This study has several strengths, including its prospective design, clipping-specific focus, and integration of molecular data with clinically interpretable bedside predictors. Important limitations should be recognized when the final institutional version is prepared. A single-center design may limit generalizability; biomarkers were measured at a single early time point rather than serially; cognitive and quality-of-life outcomes were not modeled separately from mRS; and treatment selection was confined to the microsurgical pathway. Future work from Indian centers would benefit from multicenter recruitment, serial biomarker profiling, external validation, and comparison of clipping and endovascular pathways within harmonized outcome frameworks. In summary, the present study reinforces that in the modern microsurgical era, the major determinants of disability after aSAH remain age, admission neurological grade, and hemorrhage burden, while IL-6 appears to offer modest incremental prognostic value as an early molecular correlate. For tertiary neurosurgical practice in Eastern India, a combined clinico-radiological model remains the backbone of prognostication, and inflammatory markers may serve best as adjuncts for refinement rather than substitutes for established grading systems.

Conclusion

In this prospective journal-style study framework from SCB Medical College & Hospital, Cuttack, unfavorable 3-month outcome after microsurgical clipping for aSAH was primarily associated with increasing age, poor admission WFNS grade, higher modified Fisher grade, and elevated admission IL-6. Conventional clinical and radiological severity measures remained the strongest predictors, while molecular profiling provided only modest incremental discrimination. These findings support continued reliance on structured bedside grading and hemorrhage burden assessment in routine practice, with selective incorporation of inflammatory biomarkers for risk refinement. The manuscript should be finalized for submission only after replacement of modeled values with verified institutional data and ethical documentation.

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