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RESEARCH ARTICLE

Peripheral blood-derived expression of IL-6, IL-1β, and TNF-α in patients with ruptured intracranial aneurysms

Reza Aditya Digambiro[1*], Dewi Hastuty[2], Florinda Ilona[3], Julian Chendrasari[3]

[1]Department of Anatomical Pathology, Faculty of Medicine, Universitas Trisakti, Jakarta, Indonesia
[2]Department of Neurology, Faculty of Medicine, Universitas Trisakti, Jakarta, Indonesia
[3]Department of Anatomical Pathology, Faculty of Medicine, Universitas Trisakti, Jakarta, Indonesia
[*]Correspondence: Reza Aditya Digambiro; Address: Jl. Kyai Tapa No.1, RT.5/RW.9, Tomang, Kec. Grogol Petamburan, Kota Jakarta Barat, Daerah Khusus Ibukota Jakarta 11440; Email address: drdigambiro@trisakti.ac.id

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ABSTRACT

Ruptured intracranial aneurysms (IAs) are a devastating cause of subarachnoid hemorrhage (SAH), often driven by complex inflammatory mechanisms. Pro-inflammatory cytokines such as IL-6, IL-1β, and TNF-α have been implicated in vascular wall degeneration leading to rupture. A cross-sectional study was conducted on 30 patients with radiologically confirmed ruptured IAs in Satya Negara Hospital and Mitra Keluarga Hospital. Blood samples were collected within 72 hours post-ictus. Expression of IL-6, IL-1β, and TNF-α mRNA was quantified using real-time PCR at Hopkins Clinic and Lab, with GAPDH and β-actin as reference genes. CT values were analyzed and correlated with clinical severity based on Hunt & Hess grading. Mean CT values were IL-6: 32.56 ± 1.15, IL-1β: 31.47 ± 1.23, and TNF-α: 30.69 ± 1.15. Strong inverse correlations were observed between CT values and Hunt & Hess scores: IL-6 ($r = -0.891$), IL-1β ($r = -0.930$), and TNF-α ($r = -0.919$), all with $p < 0.0001$. Expression of IL-6, IL-1β, and TNF-α is associated with greater severity within ruptured IA cases, correlating with clinical severity. These cytokines may serve as biomarkers and therapeutic targets in aneurysmal SAH.

1. Introduction

Intracranial aneurysms (IAs) are frequently clinically silent yet pose a persistent risk: rupture precipitates subarachnoid haemorrhage (SAH) with high morbidity and mortality (Simon & Grote, 2021). Despite improvements in neurovascular imaging and therapeutic strategies, the molecular determinants that govern aneurysm instability and rupture remain incompletely characterised. While mechanical forces and genetic predisposition have received considerable attention, mounting evidence implicates inflammation as a central driver of vessel wall weakening and aneurysm progression (Hu *et al.*, 2020).

Lateral view cerebral angiography demonstrates robust opacification of the right internal carotid artery (ICA) extending into its intracranial branches. A saccular aneurysm (green arrow) is identified at the bifurcation of the right middle cerebral artery (MCA), located precisely at the transition from the M1 segment to the superior and inferior M2 divisions (Figure 1). The aneurysm appears to be of small to medium size, with a broad neck and a dome projecting superiorly and posteriorly, involving both daughter branches. Distal flow into the right MCA and anterior cerebral artery (ACA) remains preserved, with no evidence of vasospasm or distal occlusion.

Pro-inflammatory cytokines—notably IL-6,

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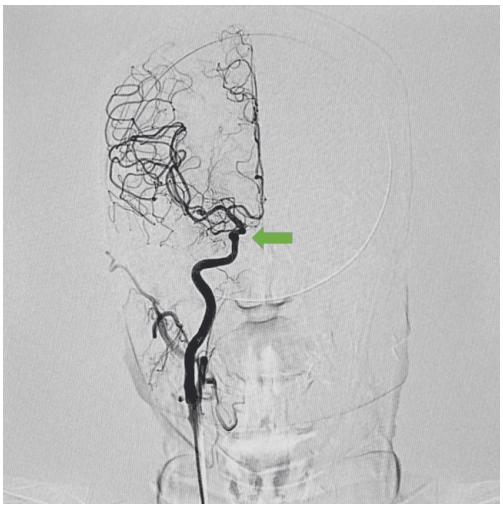

Figure 1. Digital subtraction angiography (DSA) of the brain – right ICA injection, lateral projection.

IL-1β, and TNF-α—have been repeatedly implicated in aneurysm formation, progression, and rupture (Duan *et al.*, 2023). Secreted largely by macrophages and other immune cells, these mediators alter endothelial permeability, modulate vascular tone, and promote degradative remodelling of the arterial wall. Clinical and experimental data suggest characteristic patterns: IL-6 concentrations are often higher in cerebrospinal fluid (CSF) than in serum after aneurysmal SAH, consistent with a central nervous system–predominant inflammatory response and correlating with clinical severity and delayed cerebral ischemia (Kaminska *et al.*, 2021, 2022; Vlachogiannis *et al.*, 2019; Simon & Grote, 2021). IL-1β functions as an upstream pro-inflammatory signal that is associated with rupture status in nuanced ways (Rahmanian *et al.*, 2022), while TNF-α contributes to both the initiation and amplification of vascular injury (Hu *et al.*, 2020).

Together, IL-6, IL-1β, and TNF-α form a cytokine axis intimately linked to neurovascular inflammation. Elevations in these cytokines have been correlated with aneurysm size in unruptured lesions, suggesting progressive inflammatory priming prior to rupture (Kaminska *et al.*, 2022). Ruptured aneurysms display a markedly amplified cytokine profile, consistent with loss of homeostatic control and an exacerbated inflammatory state (Giotta Lucifero *et al.*, 2022). Genetic and signalling contexts further modulate this inflammatory milieu: polymorphisms such as IL-6 -572G>C associate with aneurysm susceptibility in certain populations (Lucifero *et al.*, 2022), and NF-κB signalling has emerged as a central regulator of aneurysm-related inflammatory transcriptional programs (Khan *et al.*, 2023).

Most prior work has emphasised CSF analyses or animal models, leaving insufficient characterisation of peripheral inflammatory gene expression following aneurysm rupture. This study therefore examines peripheral blood expression of IL-6, IL-1β, and TNF-σ by quantitative PCR in patients with ruptured IAs, aiming to define systemic inflammatory signatures that may reflect, amplify, or precede neurovascular catastrophe.

2. Materials and Methods

2.1. Study design and ethical approval

This descriptive observational study used a cross-sectional design to evaluate peripheral blood gene expression of three pro-inflammatory cytokines—interleukin-6 (IL-6), interleukin-1β (IL-1β), and tumour necrosis factor-α (TNF-α)—in patients with ruptured intracranial aneurysms (IAs). The focus was on early systemic inflammatory activity assessed by quantitative real-time PCR (qPCR).

Ethical approval was granted by the Hopkins Clinic and Lab Ethical Committee (approval number HC/XII/3/2023). Written informed consent was obtained from all participants or their legal representatives. All procedures adhered to the Declaration of Helsinki and Good Clinical Practice.

2.2. Participants and sample size

Adult patients (≥18 years) admitted to Satya Negara Hospital and Mitra Keluarga Hospital with radiologically confirmed ruptured IAs were eligible. Rupture was confirmed by non-contrast head computed tomography (CT), which demonstrated subarachnoid haemorrhage (SAH), and by cerebral digital subtraction angiography (DSA), which identified the aneurysm and its location. Eligible patients were those from whom peripheral blood could be obtained within 72 hours of clinical onset. Exclusion criteria were prior autoimmune or chronic inflammatory disease, active systemic infection (by clinical or laboratory criteria), recent head trauma, or haemorrhage related to arteriovenous malformation. Informed consent was obtained from conscious, competent patients or from next of kin when patients were incapacitated.

A purposive sample of 30 patients was recruited based on feasibility and on prior qPCR studies of cytokine expression in neurovascular conditions. This sample size was intended to support descriptive analyses and exploratory correlations with clinical severity scores (Hunt & Hess and Fisher grades).

2.3. Sample collection and qPCR assay

Peripheral venous blood (3–5 mL) was collected into EDTA tubes and processed promptly. Total RNA was extracted from peripheral blood leukocytes using

Table 1. Primer sequences used for qPCR

Target Gene	Forward Primer Sequence (5′ → 3′)	Reverse Primer Sequence (5′ → 3′)
IL-6	ACTCACCTCTTCAGAACGAATTG	CCATCTTTGGAAGGTTCAGGTTG
IL-1β	ATGATGGCTTATTACAGTGGCAA	GTCGGAGATTCGTAGCTGGA
TNF-α	CCTCTCTCTAATCAGCCCTCTG	GAGGACCTGGGAGTAGATGAG
GAPDH	GAAGGTGAAGGTCGGAGT	GAAGATGGTGATGGGATTTC

a commercial spin-column kit (Qiagen RNeasy®), following the manufacturer's instructions to preserve RNA integrity. Extracted RNA was reverse transcribed to complementary DNA (cDNA) using validated reverse transcriptase reagents optimised for qPCR.

Target genes (IL-6, IL-1β, TNF-α) were amplified using gene-specific primers alongside two reference genes (GAPDH and β-actin) for normalisation. Amplification was performed on a real-time PCR platform with either SYBR Green or TaqMan probe chemistry, depending on reagent availability. The thermal profile included an initial denaturation step followed by 40 cycles of denaturation, annealing, and extension; protocols were optimised for the primer sets used. qPCR assays were performed in triplicate for each gene. No-template controls and standard laboratory quality-control procedures were included. Primer sequences are provided in Table 1. Assay design and reporting conformed to the Minimum Information for Publication of Quantitative Real-Time PCR Experiments (MIQE) guidelines.

Cycle threshold (CT) values were recorded automatically by the qPCR instrument software. For each sample, ΔCT values were calculated relative to the geometric mean of the two housekeeping genes. ΔCT values were used as the primary quantitative measure of gene expression (inversely related to mRNA abundance).

2.4. Statistical analysis

Primary outcomes were CT (and ΔCT) values for IL-6, IL-1β, and TNF-α, treated as continuous variables. Secondary clinical variables (Hunt & Hess and Fisher grades) were extracted from medical records and treated as ordinal variables. Hunt & Hess scores were stratified as mild (grades 1–2), moderate (grade 3), and severe (grades 4–5) for subgroup analyses. Normality was assessed with the Shapiro–Wilk test. Normally distributed variables are reported as mean ± standard deviation; non-normally distributed variables as median and interquartile range. Correlations between cytokine expression and clinical severity were evaluated using Pearson's correlation for parametric data and Spearman's rank correlation for nonparametric data. Group comparisons across Hunt & Hess strata were performed and visualized using amplification curves and boxplots. Statistical analyses were conducted using standard statistical software, with two-tailed tests and a significance threshold of $p < 0.05$.

3. Results

A total of 30 patients with radiologically confirmed ruptured intracranial aneurysms were included. The mean age was 52.4 ± 11.7 years; sex distribution was 16 males and 14 females. Most patients presented within 72 hours of ictus and underwent DSA during the same admission. Median Hunt & Hess score was 3 (range 1–5) and median Fisher score was 3 (range 1–4) (Table 2).

Table 2. Demographic and clinical characteristics of patients

Variable	Value (n = 30)
Age (mean ± SD)	52.4 ± 11.7 years
Sex	16 males / 14 females
Hunt & Hess Score	Median: 3 (Range: 1–5)
Fisher Score	Median: 3 (Range: 1–4)

Gene expression profiling by real-time qPCR was completed for all 30 samples. CT values for IL-6, IL-1β, and TNF-α were approximately normally distributed. Mean CT values were: IL-6 32.56 ± 1.15, IL-1β 31.47 ± 1.23, and TNF-α 30.69 ± 1.15 (Table 3).

Table 3. Mean CT values (± SD)

Cytokine	Mean CT ± SD
IL-6	32.56 ± 1.15
IL-1β	31.47 ± 1.23
TNF-α	30.69 ± 1.15

Pearson correlation analysis revealed strong, significant negative correlations between CT values and Hunt & Hess scores for all three cytokines: IL-6 showed $r = -0.891$ ($p = 4.0 \times 10^{-11}$), IL-1β showed $r = -0.930$ ($p = 9.8 \times 10^{-14}$), and TNF-α showed $r = -0.919$ ($p = 8.1 \times 10^{-13}$). These findings indicate that higher

Table 4. Correlation between cytokine CT values and Hunt & Hess scor

Cytokine	Correlation (r)	p-value	Interpretation
IL-6	-0.891	4.0×10^{-11}	Strong negative, highly significant
IL-1β	-0.930	9.8×10^{-14}	Very strong negative
TNF-α	-0.919	8.1×10^{-13}	Very strong negative

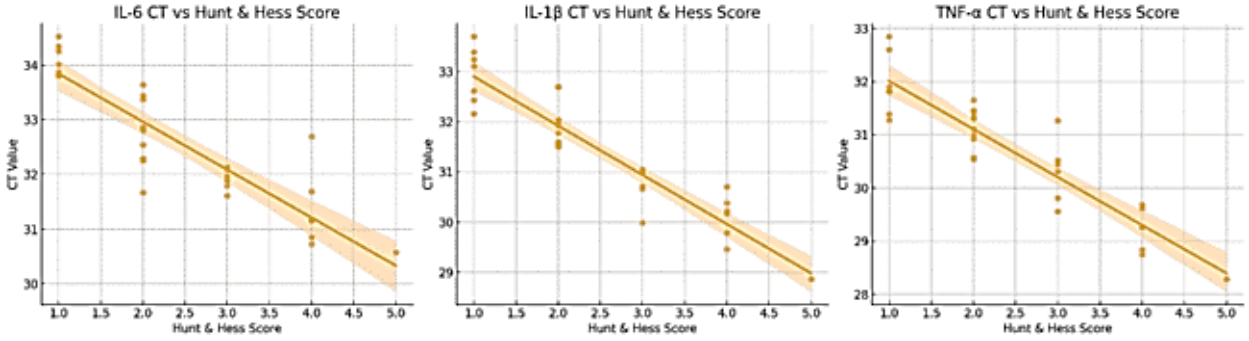

Figure 2. Scatter plots showing the inverse linear relationship between Hunt & Hess score and qPCR CT values for IL-6, IL-1β, and TNF-α (n = 30). Each plot displays individual data points, a fitted linear regression line, and 95% confidence intervals. Lower CT indicates higher mRNA expression; correlations (Pearson's r) are IL-6: r = =0.891 (p = 4.0×10-11), IL-1β: r = -0.930 (p = 9.8×10-14), and TNF-α: r = -0.919 (p = 8.1×10-13). The negative slopes indicate increased cytokine expression with greater clinical severity.

Table 5. Median CT values by SAH severity

SAH Severity	n	Median CT IL-6	Median CT IL-1β	Median CT TNF-α
Mild (Hunt & Hess 1–2)	17	33.45	32.16	31.39
Moderate (Hunt & Hess 3)	6	31.93	30.86	30.38
Severe (Hunt & Hess 4–5)	7	31.16	30.17	29.26

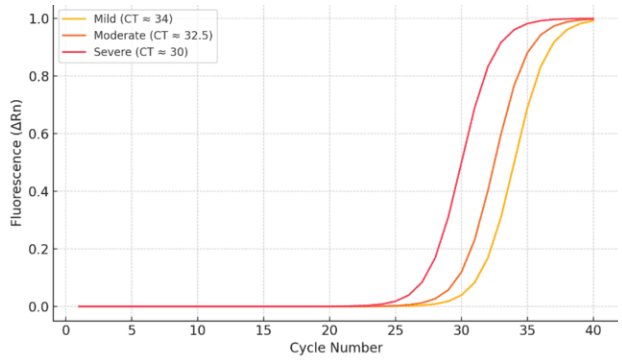

Figure 3. qPCR Amplification Curve for IL-6 Expression Across SAH Severity Levels.

clinical severity is associated with greater cytokine expression (lower CT) (Table 4, Figure 2).

Patients were stratified by Hunt & Hess into mild (1–2, n = 17), moderate (3, n = 6), and severe (4–5, n = 7) groups. Median CT values declined with increasing severity for all cytokines, consistent with escalating transcriptional activity (Table 5).

qPCR amplification curves demonstrated efficient, sigmoid kinetics with clear leftward shifts in threshold crossing as clinical severity increased. In severe cases, TNF-α amplification occurred around cycle 28, reflecting pronounced upregulation (Figures 3–5, Figure 6).

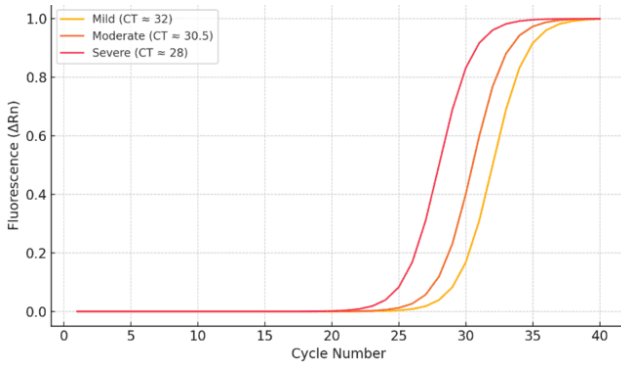

Figure 4. qPCR amplification curves for TNF-α stratified by SAH severity (mild, moderate, severe; n = 30). Curves show typical sigmoid kinetics with a clear leftward shift as severity increases: severe cases cross threshold earliest (approx. CT ≈ 28), moderate around CT ≈ 30–31, and mild around CT ≈ 32, indicating progressively higher TNF-α expression with greater clinical burden.

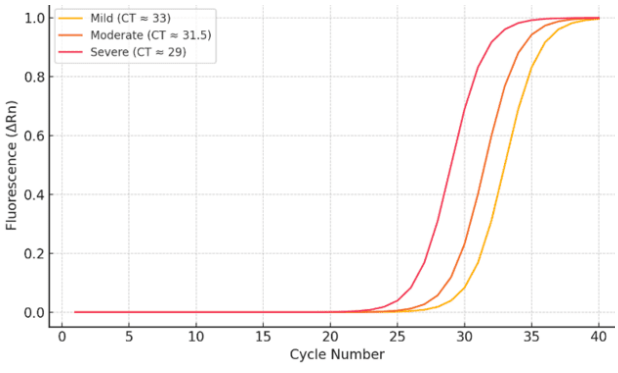

Figure 5. qPCR amplification curves for IL-1β stratified by SAH severity (mild, moderate, severe; n = 30). Curves display efficient sigmoid kinetics with a leftward shift corresponding to increasing severity: mild cases cross threshold at ≈ CT 33, moderate at ≈ CT 31–32, and severe at ≈ CT 29, indicating progressively higher IL-1β expression with greater clinical burden.

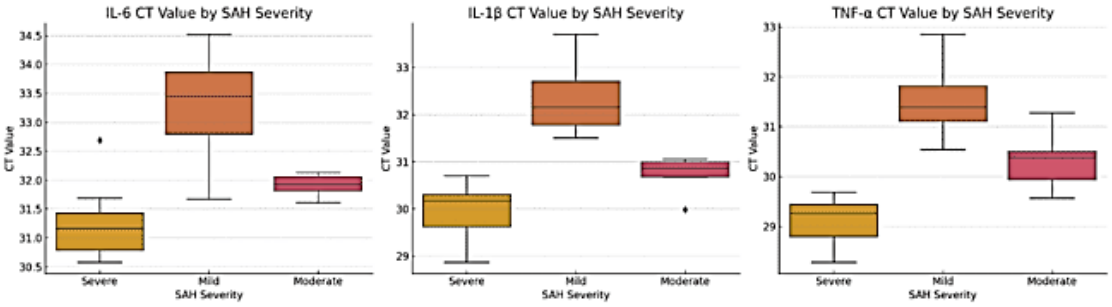

Figure 6. Boxplots of qPCR CT values for IL-6, IL-1β, and TNF-α by SAH severity (mild: Hunt & Hess 1–2; moderate: 3; severe: 4–5; n = 30). Lower CT indicates higher gene expression; all three cytokines show a stepwise decrease in median CT with increasing severity, consistent with greater systemic inflammatory activation in more severe SAH. Overall, ruptured intracranial aneurysms in this cohort were associated with peripheral upregulation of IL-6, IL-1β, and TNF-α, and higher expression levels correlated with greater clinical severity as measured by Hunt & Hess scores.

Amplification curves illustrate differences in IL-6 expression based on clinical severity of subarachnoid hemorrhage (SAH). Samples from patients with severe SAH (CT ≈ 30) show earlier amplification (leftward shift), indicating higher IL-6 expression. In contrast, mild cases (CT ≈ 34) exhibit delayed amplification, consistent with lower cytokine expression. The curve shapes reflect efficient, exponential amplification typical of qPCR, and highlight a gradational increase in IL-6 expression with increasing SAH severity.

4. Discussion

The pathogenesis of ruptured intracranial aneurysms (IAs) reflects a complex interaction of hemodynamic stress, vessel-wall remodelling, and inflammation-driven degeneration. Our findings reinforce the inflammatory paradigm: peripheral qPCR performed within 72 hours post-ictus showed a strong inverse relationship between CT values for IL-6, IL-1β, and TNF-α and clinical severity by Hunt & Hess—indicating higher systemic expression of these cytokines in more severe presentations.

Peripheral profiling offers a minimally invasive complement to CSF or aneurysm wall analyses, and accumulating data suggest peripheral markers can mirror intracranial inflammatory activity (Ishiguro *et al.*, 2024; Kaminska *et al.*, 2022). In this cohort, upregulation of IL-6, IL-1β, and TNF-α likely reflects both local intracranial inflammation and systemic amplification, supporting their roles as pathogenic mediators and potential biomarkers.

IL-6 demonstrated a marked association with clinical severity, consistent with its documented involvement in endothelial dysfunction, delayed cerebral ischemia, and prognosis after SAH (Simon & Grote, 2021; Vlachogiannis *et al.*, 2019). Experimental data linking STAT3-mediated IL-6 signalling to aneurysm progression further support IL-6's dual biomarker–effector role (Gao *et al.*, 2023; Jiang *et al.*, 2021; Xiao *et al.*, 2021; Zhang *et al.*, 2023).

IL-1β, an upstream driver of neuroinflammation, showed a very strong inverse correlation with Hunt & Hess (r = -0.930), echoing prior observations of elevated IL-1β in ruptured versus unruptured aneurysms and its contributions to endothelial disruption, leukocyte recruitment, and matrix degradation (Lucifero *et al.*, 2022; Li *et al.*, 2020; Rahmanian *et al.*, 2022).

TNF-α exhibited the most pronounced expression (lowest CT values), particularly in severe cases, aligning with its established roles in inducing MMPs, promoting vascular smooth muscle apoptosis, and facilitating inflammatory cell infiltration, mechanisms integral to aneurysm wall weakening and rupture (Croci *et al.*, 2022; Duan *et al.*, 2023; Fisher & Demel, 2019; Khan *et al.*, 2023; Yang *et al.*, 2022).

Collectively, these cytokines operate within an interconnected inflammatory axis. Their systemic elevation in severe cases supports the concept that rupture involves an inflammatory escalation reaching a critical threshold rather than solely a mechanical failure (Kaminska *et al.*, 2022). Upstream regulators such as NF-κB, identified in aneurysmal walls and perivascular infiltrates, likely drive this transcriptional program; experimental NF-κB inhibition reduces rupture rates and inflammation in animal models, consistent with our molecular observations (Khan *et al.*, 2022, 2023).

Genetic factors (e.g., IL-6 -572G>C promoter polymorphism) may modulate baseline cytokine expression and susceptibility to aneurysm formation in certain populations (Bennett *et al.*, 2021; Lucifero *et al.*, 2022; Wang *et al.*, 2022). Although we did not genotype participants, genetic variability could contribute to interindividual differences in peripheral expression and merits investigation in future studies.

Clinical implications are twofold. First, peripheral cytokine gene expression may serve as an adjunctive

biomarker for early risk stratification, complementing clinical scores (Hunt & Hess, Fisher) with biologically grounded measures of inflammatory burden. Second, these cytokines represent plausible therapeutic targets; preclinical interventions against IL-6 and TNF-α have shown benefit in reducing inflammation and wall degeneration (Gao *et al.*, 2023; Jiang *et al.*, 2021; Xiao *et al.*, 2021; Yang *et al.*, 2022). Translation will require careful evaluation of timing, route, and safety in acutely ill neurovascular patients.

This study provides a cross-sectional snapshot of peripheral gene expression within a 72-hour window; qPCR captures highly sensitive but temporally limited measures, and inflammatory kinetics may vary among individuals. Although we excluded overt systemic infection and chronic inflammatory disease, subclinical inflammation could confound results. Peripheral blood may not fully recapitulate intracranial microenvironmental signalling, and the sample size (n = 30) limits generalizability and multivariable adjustment. Finally, lack of genetic or protein-level confirmation (e.g., SNP analysis, ELISA) constrains mechanistic inference.

Peripheral upregulation of IL-6, IL-1β, and TNF-α is strongly associated with clinical severity following aneurysmal rupture, supporting an inflammation-driven model of aneurysm destabilisation. These markers warrant further validation as prognostic biomarkers and therapeutic targets in larger, longitudinal studies incorporating genotype and protein-level analyses to clarify temporal dynamics and causal relationships.

5. Conclusions

Systemic inflammation appears central to the pathogenesis of ruptured intracranial aneurysms. Peripheral expression of IL-6, IL-1β, and TNF-α correlated strongly with clinical severity, supporting their potential utility as biomarkers and as targets for therapeutic modulation. Future studies should incorporate genetic polymorphism analysis, longitudinal sampling to define cytokine kinetics, protein-level validation, and clinical outcome measures to enable precision-medicine strategies in aneurysmal SAH.

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Conflict of interest

The authors declare that they have no conflicts of interest regarding the publication of this paper.

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