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Immune-related Circulating Biomarkers in Intracerebral Hemorrhage: Implications for Nursing Management and Prognostic Assessment

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ABSTRACT

Intracerebral hemorrhage (ICH) remains one of the most severe stroke subtypes and requires continuous risk assessment across the acute, subacute, and rehabilitation-transition phases. This review summarizes established and emerging immune-related circulating biomarkers and discusses their relevance to nursing management and prognostic assessment. Markers with the highest current clinical readiness include peripheral blood cell counts and derived ratios, C-reactive protein (CRP), and procalcitonin (PCT), whereas cytokines, chemokines, broader immunometabolic mediators, and neuroinjury-inflammation cross-over markers remain mainly investigational. On the basis of the revised synthesis, we propose a stage-specific monitoring framework that emphasizes sampling at admission, approximately 24 hours, approximately 72 hours, and at clinically triggered reassessment points, together with interpretation of trajectories rather than isolated values. We further outline practice-oriented nursing scenarios in which biomarker trends may support escalation of neurologic observation, infection surveillance, airway care, glucose and nutrition management, structured handoff communication, and multidisciplinary coordination. Current evidence suggests that routinely available biomarkers may add value as adjunctive monitoring tools, but the literature remains limited by observational designs, heterogeneous assay platforms, inconsistent sampling windows, variable endpoints, incomplete confounder control, and uncertain action thresholds. At present, biomarkers should complement rather than replace imaging, neurological examination, and bedside nursing assessment. Future prospective studies should prioritize standardized sampling, trajectory-based analyses, integration into nursing workflows, and clinically interpretable multimodal models.

Keywords: Circulating biomarkers; Immunometabolism; Intracerebral hemorrhage; Neuroinflammation; Nursing management; Prognostic assessment

INTRODUCTION

Intracerebral hemorrhage (ICH) is a neurological emergency with high mortality, high disability, and marked early clinical instability. Even when the primary bleeding event is initially stabilized, subsequent deterioration may still occur because of cerebral edema, secondary brain injury, infection, metabolic stress, and systemic inflammatory responses.[1,2] For this reason, ICH management depends not only on early imaging

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and neurological scoring, but also on repeated bedside reassessment across the whole disease course.[3,4]

Nursing care is central to this process because nurses continuously connect pathophysiological change with practical action. In ICH, this includes neurologic observation, airway and line management, infection prevention, nutritional and metabolic support, structured handoff communication, and early identification of turning points that require escalation.[5–7] A major unanswered question is how circulating biomarker information can be translated into these routine nursing workflows rather than remaining an isolated laboratory signal.[5]

Conventional tools, such as cranial computed tomography (CT), hematoma volume assessment, Glasgow Coma Scale (GCS) or National Institutes of Health Stroke Scale (NIHSS) scoring, vital signs, and routine laboratory tests, remain indispensable, but they do not directly capture several dynamic processes that shape secondary injury, including inflammatory amplification, impaired resolution of inflammation, peripheral immune dysregulation, and persistent metabolic stress.[6,7] Immune-related circulating biomarkers are therefore attractive because they are accessible, repeatable, and potentially informative before overt clinical deterioration becomes obvious at the bedside.[8,9]

Most published reviews summarize inflammatory mechanisms or prognostic associations in general terms, whereas fewer studies explicitly prioritize biomarkers by clinical readiness, discuss standardized sampling windows, or explain how biomarker trajectories might alter nursing observation, handoffs, complication surveillance, and rehabilitation transition.[4,6] This translational gap is especially important in ICH, where many management decisions depend on trend recognition rather than one-time measurements.[9]

In this revised narrative review, we synthesize established and emerging immune-related circulating biomarkers in ICH, distinguish routine from investigational markers, summarize their monitoring and prognostic roles, and propose a practical framework for integrating biomarker trends into nursing management and stage-specific risk assessment.

Search Strategy and Scope of This Review

To improve transparency, the revised manuscript was organized through a structured narrative search of PubMed, Web of Science, Scopus, and Embase for English-language studies published between January 2010 and February 2026. Search terms combined controlled vocabulary and free-text keywords related to intracerebral hemorrhage, biomarkers, inflammation, immune response, neuroinflammation, immunometabolism, nursing management, complications, and prognosis. Priority was given to meta-analyses, guideline documents, multicenter cohorts, and clinically interpretable observational studies. Reference lists of key publications were also screened to identify additional relevant articles. Because this article remains a narrative review rather than a formal systematic review, the purpose of this strategy was to improve transparency, scope, and clinical interpretability rather than to generate a PRISMA-style study flow.

Pathophysiological Basis of Immune Imbalance, Immunometabolic Remodeling, and Neuroinflammation after ICH

Continuous Evolution from Primary to Secondary Brain Injury

Primary injury in ICH mainly results from mechanical compression of surrounding brain tissue by the hematoma, local perfusion impairment, and structural disruption.[11,12] Hematoma volume, location, expansion rate, and ventricular extension determine the severity of early neurological damage and provide the basis for initial clinical stratification.[3,4,11] However, extensive clinical and experimental evidence indicates that the subsequent disease course and final outcomes are not determined solely by primary injury; secondary brain injury exerts a major influence.[5–7,13]

Secondary brain injury is a dynamic process that evolves over hours to days or even longer and involves blood-brain barrier disruption, cerebral edema formation, oxidative stress amplification, cytotoxic injury, inflammatory escalation, and imbalance between tissue repair and inflammation resolution.[13–16] After blood components enter the brain parenchyma, erythrocyte breakdown products, heme, iron ions, and coagulation-related components can act as inflammatory stimuli, activate local innate immune cells, and aggravate tissue damage.[14–16] This helps explain why some patients with relatively moderate initial imaging injury still experience marked neurological deterioration or poor outcomes during follow-up.[5,13]

At a mechanistic level, it is useful to distinguish processes that are relatively well established from those

that remain more hypothesis-generating. The strongest evidence supports blood-brain barrier disruption, perihematomal edema, oxidative injury, innate immune activation, and recruitment of peripheral leukocytes as central components of secondary injury after ICH. By contrast, several broader immunometabolic signatures and inflammation-resolution pathways are promising but not yet sufficiently validated for routine clinical interpretation. Maintaining this distinction is important when translating biomarker findings into bedside decisions.

Neuroinflammation: A Core Regulatory Axis in Post-ICH Injury and Repair

Neuroinflammation after ICH exhibits clear temporal and biphasic features.[17,18] In the early stage, microglia and astrocytes rapidly sense tissue damage signals and become activated, releasing pro-inflammatory mediators, such as interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α), while producing chemokines that recruit neutrophils, monocytes, and other immune cells to the perihematomal region.[17–20] Neutrophils are especially important in the early amplification phase of inflammation, and their release of proteases, reactive oxygen species, and inflammatory mediators may further injure the blood-brain barrier and perihematomal tissue.[18–20]

Subsequently, monocytes/macrophages and different microglial phenotypes participate in necrotic tissue clearance, hematoma absorption, inflammatory regulation, and tissue repair.[17–19] During this phase, inflammation is not purely detrimental; it also supports clearance and repair. Therefore, post-ICH inflammatory regulation should not be framed simply as inflammation suppression, but rather as promotion of an appropriate balance between inflammatory activation and inflammation resolution.[18,19] Excessive or prolonged pro-inflammatory responses can aggravate secondary brain injury, whereas premature immune suppression or insufficient inflammatory responses may increase the risk of infection and impaired repair.[19,21,22]

Peripheral Immune Involvement and Remodeling of the Brain-peripheral Immune Axis

ICH is not a process confined to the central nervous system. Central injury can affect the peripheral immune system through neuroendocrine and autonomic pathways, inducing systemic inflammation and immune remodeling.[21,22] Common clinical manifestations include elevated white blood cell (WBC) counts, neutrophilia, lymphopenia, increased inflammatory proteins, and heightened susceptibility to infection in later stages.[21] These changes indicate an important role for the brain-peripheral immune axis in the ICH disease course and provide a theoretical basis for using peripheral blood biomarkers to monitor disease status.[21,22]

On the one hand, peripheral immune activation may exacerbate neuroinflammation and secondary injury. On the other hand, stress responses and immune suppression tendencies after ICH may increase the risk of complications, such as pneumonia and urinary tract infection.[19,21,22] For nursing management, this means that monitoring cannot focus solely on neurological signs; dynamic changes in systemic inflammation and infection risk must also be considered.[8,10] Circulating biomarkers are particularly valuable at this intersection because they may reflect not only neuroinflammatory activity but also peripheral immune status and complication risk.

The relationship between brain injury and peripheral immune changes is also bidirectional rather than strictly one-way. Severe brain injury can trigger systemic immune remodeling, but peripheral infection, comorbid diabetes, organ dysfunction, surgery, ventilation, and treatment-related effects may, in turn, reshape biomarker profiles and influence neurological recovery. Accordingly, biomarker interpretation should always consider reverse causality and competing explanations, especially when inflammatory signals intensify after the first 24 to 72 hours.

Immunometabolic Remodeling: Linking Inflammation and Systemic Stress

The concept of immunometabolism has attracted growing attention in recent years, with the central premise that immune-cell functional states are tightly coupled to metabolic pathway selection.[23,24] Under inflammatory activation, immune cells frequently undergo metabolic reprogramming characterized by enhanced glycolysis, lactate accumulation, altered lipid metabolism, and fluctuations in redox status.[23,24] After ICH, focal injury, systemic stress, tissue hypoxia, neuroendocrine responses, and therapeutic interventions may jointly drive metabolic disturbances that further amplify inflammatory responses.[18,22–24]

From a clinical monitoring perspective, some metabolism-related indicators, such as lactate, glycemic variability, and other emerging metabolic mediators, may not merely serve as markers of severe illness but may also reflect immune activation intensity, persistence of inflammation, and compensatory capacity.[16,21] Compared with traditional inflammatory markers, these indicators may provide complementary and, in some contexts, more sensitive information regarding disease activity.[7,16] However, because immunometabolic biomarkers are mechanistically complex and affected by multiple confounders, their interpretation must be anchored to disease stage, organ function, and treatment context.

Implications of Pathophysiology for Nursing Management and Prognostic Assessment

The stage-dependent nature of post-ICH pathology implies that assessment strategies should also be dynamic.[13–19] In the ultra-early phase, priorities include blood pressure, consciousness, pupillary changes, and imaging evolution. In the acute and subacute phases, greater attention is needed for inflammatory progression, infection risk, metabolic disturbances, and multisystem stress.[3,4,21,22] In real-world nursing practice, the goal is not to identify a universal marker, but to build a comprehensive monitoring framework aligned with stage-specific risk priorities.[8–10] Accordingly, the most appropriate role of immune-related circulating biomarkers is as supplements to conventional assessment systems—enhancing risk recognition, trend judgment, and nursing decision support—rather than replacing imaging or neurological evaluation.[3,4,20]

Classification, Conceptual Scope, and Clinical Interpretation Framework of Immune-Related Circulating Biomarkers

For translational purposes, immune-related circulating biomarkers in ICH can be organized along two complementary axes: biological domain and clinical readiness. The first axis distinguishes cell-based indices, acute-phase proteins, cytokines and chemokines, immunometabolic mediators, and neuroinjury-inflammation cross-over markers. The second axis distinguishes biomarkers that are already available in routine clinical practice from biomarkers that remain mainly investigational. This dual classification helps separate monitoring roles, prognostic roles, and mechanism-oriented exploratory roles.

Peripheral Blood Cells and Derived Ratios: The Most Accessible Foundation-Layer Biomarkers

Peripheral blood cell parameters, including total WBC count, neutrophil count, lymphocyte count, monocyte count, and platelet count, are among the easiest immune-related data to obtain after admission in patients with ICH.[25,26] Derived ratios based on these parameters, such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and monocyte-to-lymphocyte ratio (MLR), integrate information on pro-inflammatory responses and immune regulation and have been widely used in stroke and ICH research in recent years.[25–28]

Their principal strengths are stable availability, low cost, rapid turnaround, and suitability for emergency and bedside management. They can also be repeatedly measured, facilitating dynamic trend analysis, and are feasible even in resource-limited settings.[26,27] However, their limitations are equally important: low specificity; susceptibility to infection, stress, surgery, medication, and comorbidities; substantial variation in cut-off values across studies; and limited interpretability when used in isolation.[28] Therefore, peripheral blood cell indices and derived ratios are best used as baseline risk indicators and starting points for dynamic monitoring, while requiring joint interpretation with clinical findings and other biomarkers.[25,27]

Acute-Phase Inflammatory Proteins: Key Links Between Systemic Inflammation, Complication Risk, and Disease Trajectory

Acute-phase inflammatory proteins, such as CRP and high-sensitivity C-reactive protein (hs-CRP), are among the most commonly used and reflect systemic inflammatory burden.[29,30] In the acute phase of ICH, CRP levels may increase, and high or persistently elevated levels may indicate stronger inflammatory responses, more severe secondary brain injury, or higher complication risk.[29–31] For nursing teams, the value of CRP lies not in diagnosing ICH, but in supporting disease-trend assessment and complication surveillance, especially when interpreted alongside temperature, respiratory findings, line status, and imaging changes.[30,31]

PCT has particular relevance in ICH nursing management. After ICH, patients may be at increased risk of infection because of dysphagia, prolonged bed rest, invasive procedures, mechanical ventilation, or impaired consciousness.[4,32,33] Clinically, distinguishing sterile inflammation from infectious inflammation is

often necessary. Although PCT is not a perfect marker, it can provide useful support for infection differentiation, antimicrobial treatment assessment, and nursing escalation/reporting.[32,33] Importantly, interpretation of inflammatory proteins should emphasize dynamic changes rather than single time-point values; persistent elevation, re-elevation, or insufficient decline is often more clinically informative than an isolated high value.[29–31,34]

Inflammatory Cytokines and Chemokines: Stronger Mechanistic Relevance but Limited Clinical Translation

Inflammatory cytokines (e.g., IL-1β, IL-6, TNF-α) and chemokines (e.g., monocyte chemoattractant protein-1/C-C motif chemokine ligand 2 [MCP-1/CCL2]) are closely related to the initiation of neuroinflammation, immune-cell recruitment, blood-brain barrier disruption, and progression of cerebral edema after ICH.[35-37] Their theoretical advantage is closer proximity to the pathological process itself, potentially helping explain why some patients deteriorate neurologically despite minimal imaging change, or why patients with similar initial injury severity follow divergent disease trajectories.[17–20, 35-37]

At the same time, anti-inflammatory or inflammation-resolution-related factors (e.g., interleukin-10 [IL-10], transforming growth factor-β [TGF-β]) may reflect the host's negative feedback capacity against inflammatory responses.[38] Imbalance between pro-inflammatory and anti-inflammatory responses after ICH may lead to persistent inflammatory activation, impaired repair, or late-stage immune suppression.[21,22,38] These biomarkers support a dual-dimensional framework of inflammatory intensity plus inflammatory regulatory capacity and provide mechanistic support for patient stratification.[19,38]

However, routine clinical implementation of these biomarkers is limited by platform heterogeneity, cost, turnaround time, stability concerns, and lack of unified thresholds.[34] At present, they are more suitable for mechanistic studies, patient phenotyping, and development of combined models than for use as standalone clinical decision-making tools.

Immunometabolism-Related Mediators: A Potential Bridge from Severity Markers to Disease-state Characterization

Immunometabolism-related mediators are a major focus of this review. In conventional clinical practice, lactate, blood glucose, and certain metabolites are often treated simply as indicators of illness severity or stress. From an immunometabolic perspective, however, these indices may also reflect interactions among inflammatory activation, metabolic reprogramming, and organ compensation.[23,24] Elevated lactate after ICH may be associated with abnormal tissue perfusion, enhanced stress metabolism, inflammatory activation, and critical illness; persistent elevation or poor clearance may indicate a more complex course or sustained systemic stress.[39-42]

Blood glucose and glycemic variability also warrant attention. Hyperglycemia is common in the acute phase of ICH and may result from stress hormone release, inflammatory responses, insulin resistance, and treatment-related factors.[23,40,41] Hyperglycemia alone does not necessarily indicate immunometabolic dysregulation, but when it worsens in parallel with inflammatory markers, infection manifestations, and neurological status, it may suggest an increased pathological burden.[29,32,40-43] In nursing management, such information may influence glucose monitoring frequency, pacing of nutritional support, and fluid management strategies.[44,45]

In addition, some emerging metabolic mediators, such as specific lipid inflammatory mediators, amino-acid metabolism-related products, and resolution-related metabolites, have shown potential value in basic and early clinical studies.[42,43] These markers may more sensitively reflect the balance between inflammatory amplification and inflammation resolution and represent a promising direction for precision monitoring in ICH.[23,24,42,43] However, given the currently limited evidence base, their significance should be framed as frontier exploratory value rather than established clinical utility.[43,46]

Neuroinjury-Inflammation Cross-over Biomarkers: Expanding the Basis for Combined Assessment

Neuroinjury-related biomarkers, such as S100 calcium-binding protein B (S100B), neuron-specific enolase (NSE), and glial fibrillary acidic protein (GFAP), more directly reflect brain tissue injury severity and changes in blood-brain barrier permeability.[44] Although they are not immune biomarkers in the strict sense, neuroinjury and inflammation are tightly coupled after ICH; thus, combining these markers with immune-inflammatory biomarkers may improve the

completeness of disease assessment.[17,18,44] For example, among patients with similar inflammatory burden, markedly higher neuroinjury marker levels may suggest more severe primary or secondary damage.[44] Conversely, when neuroinjury markers remain relatively stable but inflammatory markers continue to rise, infection or systemic inflammatory complications should be considered.[29–33,44]

Accordingly, in prognostic assessment and nursing risk stratification for ICH, a composite perspective integrating injury markers, inflammatory markers, and metabolic markers may better reflect true disease status than any single dimension alone.[44]

Core Principles for Clinical Interpretation of Biomarkers: Avoiding Number-Centered Thinking

In both review discussions and clinical applications, several principles should be emphasized when interpreting biomarkers:

1. Time window first: The same biomarker may have different meanings at different disease stages.[29]

2. Trend over single value: Persistent elevation, rate of rise, and delayed decline are often more informative than isolated measurements.[27,31,45,46]

3. Scenario-based interpretation: Priorities differ across contexts, such as neurological deterioration, infection screening, nutritional assessment, and postoperative observation.[32,35,40,43,45]

4. Combined judgment: Biomarkers must be interpreted together with imaging, neurological function, vital signs, and nursing observations.[3,4,8,45]

5. Confounder awareness: Infection, surgery, medications, comorbidities, and organ dysfunction can all influence biomarker levels.[28,34]

These principles are essential for improving the practical clinical value of this field and for addressing concerns about how biomarker findings can be translated into real-world use.

A practical extension of these principles is to standardize when biomarkers are sampled. For routine markers used in early bedside management, a pragmatic framework is baseline testing at admission, repeat assessment at approximately 24 hours, reassessment at approximately 72 hours, and additional testing when triggered by neurological worsening, fever, respiratory decline, suspected infection, or marked metabolic instability. For investigational cytokines or broader immunometabolic mediators, fixed research windows should be reported explicitly because interpretation is highly stage dependent. This approach may improve comparability across studies and make biomarker trends more actionable for clinical teams.

Clinical Value of Immune-Related Circulating Biomarkers in Nursing Management of ICH

Acute-phase Nursing Risk Stratification: from Surface Clinical Stability to Recognition of Pathological Activity

After admission of a patient with ICH, nursing teams typically must complete an initial assessment in a short time and determine monitoring priorities, including consciousness, limb movement, pupillary findings, cardiorespiratory status, body temperature, blood pressure, line status, and baseline complication risks.[8–10,45] Incorporating immune-related circulating biomarker data into this process can provide an additional dimension for risk stratification, especially for patients who appear relatively stable clinically but may harbor a high inflammatory or stress burden.[25,29,40,45]

For example, when imaging shows no obvious expansion and vital signs are temporarily stable, a marked rise in inflammatory ratio indices, rapidly increasing CRP, or coexisting lactate abnormalities may indicate a higher level of pathological activity, justifying increased observation frequency, closer neurological tracking, and strengthened vigilance for complications.[25,29–31,40,45] Conversely, in patients with stable biomarker trends and stable clinical findings, nursing resources may be optimized under safe conditions.[45,46] It should be emphasized that this approach does not replace established severity scoring systems, but rather supplements them with additional risk information.[3,4,45]

In practice, the most useful trigger is often a pattern rather than a universal cutoff. Examples include NLR or total WBC counts that continue to rise over the first 24 to 72 hours, CRP that re-elevates after an initial decline, PCT elevation accompanied by worsening sputum or oxygenation, persistent lymphopenia after early inflammatory activation, and lactate that fails to clear on serial testing. These patterns do not establish a diagnosis by themselves, but they can justify predefined nursing responses, such as shortening observation intervals, intensifying aspiration precautions, reviewing catheter necessity, increasing the precision of handoff alerts, and notifying physicians earlier.

Dynamic Monitoring and Nursing Decision Support: Building a Trend-signs-action Assessment Chain

A core strength of nursing management is continuous observation, and the greatest value of circulating biomarkers likewise lies in dynamic monitoring.[9,10,45-49] Unlike one-time testing, serial or staged measurements can help identify key turning points in the disease course and improve sensitivity to abnormal trends.[38,45,46] For instance, persistently rising inflammatory markers may suggest unresolved inflammation and should prompt closer monitoring of temperature, consciousness, airway status, and neurological signs; re-elevation after a transient decline may raise concern for complications (especially infection) or secondary disease fluctuations; prolonged abnormalities in metabolic stress markers may indicate sustained systemic stress and warrant greater attention to nutrition, glucose management, and fluid balance; declining inflammatory markers with persistent lymphopenia may indicate an immune suppression tendency and increased susceptibility to infection.[21,22,25,29–33,40,46]

Linking these trends with nursing observations can transform laboratory data into nursing action language, such as increasing neurological observation frequency, earlier escalation/reporting, intensified airway care, rechecking catheter management, strengthening repositioning and chest physiotherapy, or optimizing execution of nutritional support.[8–10,45-47]

Complication Warning: Especially for Infection Risk Identification

Patients with ICH are vulnerable to multiple complications, among which infection—particularly pneumonia—is a major determinant of in-hospital outcomes and rehabilitation progress.[32,33,49] Impaired consciousness, dysphagia, prolonged bed rest, invasive procedures, mechanical ventilation, indwelling catheters, and malnutrition all increase infection risk.[32,33,49] In this context, the role of immune-related circulating biomarkers in nursing management is primarily to support early warning and differential assessment, helping nursing staff recognize abnormalities earlier and escalate findings more promptly, rather than replacing diagnosis.[41,49]

Supporting Differentiation Between Sterile and Infectious Inflammation

ICH itself may trigger systemic inflammatory responses, leading to leukocytosis, elevated CRP, and even temperature fluctuations, which can overlap with early signs of infection.[21,22,29–31,41] If nursing teams integrate PCT, dynamic CRP changes, leukocyte differential counts, sputum characteristics, breath sound changes, imaging findings, and oxygenation status into a comprehensive assessment, potential infection can be recognized and reported earlier, reducing delays or over-alerting associated with experience-based judgment alone.[32,33,40,41,49]

Identifying Immune Suppression Tendency and Infection-prone Phases

Some patients may transition into a relatively immunosuppressed phase after early inflammatory activation, manifested as persistent lymphopenia and discordance between inflammatory indices and clinical presentation.[21,22,25,42] Although mature clinical criteria are still lacking, identifying such infection-prone patients has practical relevance in nursing management and may prompt enhanced oral care, suctioning management, catheter maintenance, early mobilization, and more rigorous implementation of nutritional support.[8–10,42,49]

Auxiliary Role in Monitoring Neurological Deterioration and Secondary Injury Risk

During hospitalization, patients with ICH may develop secondary neurological deterioration due to hematoma expansion, edema progression, rebleeding, metabolic disturbances, infection, or systemic deterioration.[5,13,14,43] Circulating biomarkers cannot replace neurological examination or repeat imaging, but they may assist in several ways: providing clues to pathological activity (abnormal inflammatory/metabolic markers prompting heightened vigilance), helping interpret abnormal phenomena (e.g., consciousness fluctuation or fever potentially reflecting inflammatory fluctuation vs infection), and optimizing re-evaluation timing (high-risk trends triggering earlier clinical reassessment).[29–31,40,43,45-47] Thus, in this scenario, the value of biomarkers lies more in improving sensitivity and shortening recognition time than in establishing a diagnosis.[43,45]

Potential Value in Nutritional Support, Metabolic Management, and Global Condition Assessment

Nursing management of ICH extends beyond neurological care and must also address the quality of

systemic supportive treatment. Critically ill patients often exhibit hypermetabolism, negative nitrogen balance, glycemic fluctuations, challenging fluid management, and gastrointestinal dysfunction.[49] Immunometabolism-related indicators (e.g., lactate and glucose dynamics) lack neurological specificity but can reflect overall stability from the perspective of systemic stress burden.[40-42] When analyzed together with inflammatory markers and clinical findings, they may help nursing teams better understand why a patient recovers slowly, why infection risk increases, or why vital signs fluctuate frequently, thereby enabling more targeted observation and feedback regarding nutrition delivery, glucose monitoring, fluid balance recording, and complication prevention.[29–3,40-42,47]

Information Integration Value in Nursing Handoffs and Multidisciplinary Collaboration

High-quality handoffs are a cornerstone of safe nursing management in ICH.[8–10,45] In practice, handoffs often focus on vital signs, consciousness, line status, and completed nursing procedures, whereas laboratory interpretation may remain limited to whether a value is simply high or low, making it difficult to generate action-oriented risk alerts.[45,47] Incorporating immune-related circulating biomarkers into a structured handoff framework may convert them into more actionable information, such as inflammatory trends, infection-risk judgment, neurological deterioration warning points, metabolic stress status, and triggers for focused reporting.[32,33,40-42,45,47] This approach may enhance shared understanding of disease dynamics within nursing teams and improve communication with physicians, respiratory therapists, dietitians, and rehabilitation therapists.[8–10,47]

Exploratory Prospects for Rehabilitation Transition and Post-discharge Follow-up Stratification

As survival after ICH improves, rehabilitation transition and long-term management are becoming increasingly important.[1,2] Some patients continue to experience slow functional recovery, recurrent infection, cognitive or emotional problems, or persistent systemic instability even after imaging stabilization.[40,49] In the future, identifying different recovery trajectories through inflammatory and immunometabolic biomarkers may help tailor rehabilitation nursing plans, follow-up frequency, and family caregiving education.[40-42] Although evidence in this area remains limited, it has substantial translational potential and warrants further validation in nursing pathway-embedded studies.

Research Progress in Prognostic Assessment Using Immune-related Circulating Biomarkers in ICH

A Hierarchical Understanding of Prognostic Endpoints

Prognosis in ICH is not a single construct, but rather comprises multiple levels: ultra-early or acute endpoints (hematoma expansion, early neurological deterioration, intracranial pressure crisis, in-hospital mortality risk), short-term endpoints (in-hospital complications, duration of mechanical ventilation, in-hospital death), intermediate endpoints (30- or 90-day functional outcomes, such as modified Rankin Scale categories), and long-term endpoints (6- or 12-month functional recovery, cognition, quality of life, and readmission risk).[44,50-52] Different biomarkers may have different predictive value for different endpoint levels. Therefore, interpretation of prognostic utility must first clarify which endpoint, which time window, and which patient population are under consideration.[44,52,53]

Traditional Immune-inflammatory Markers: Abundant Evidence but Marked Heterogeneity

Peripheral blood cell counts and derived ratios (especially NLR) are among the most frequently reported biomarkers in ICH prognostic research and are often used to assess disease severity and risk of poor outcomes.[25–28,52] Their popularity derives from ease of acquisition, suitability for large retrospective cohorts, and relative consistency across different acute brain injuries.[25–27,45,52] However, major differences in sampling timing, cut-off values, study populations, and outcome definitions make results difficult to compare directly or synthesize robustly.[28,52,53]

Acute-phase inflammatory proteins, such as CRP, have also been widely investigated, and some studies suggest that high or persistently elevated CRP is associated with poor functional outcomes, mortality risk, or infectious complications.[29–31,53] However, CRP is strongly affected by infection and comorbidities; without adequate confounder adjustment, its direct predictive value for neurological outcomes may be overestimated.[32,52,54] Thus, these markers may be most appropriately positioned as candidate variables in prognostic models or as adjunctive indicators for disease-course monitoring.[50,52]

Across the current literature, the most reproducible prognostic signals concern NLR, total WBC count, and CRP, although their performance varies widely by cohort, endpoint definition, and sampling window. Published meta-analyses and large observational studies generally support an association between higher early inflammatory burden and worse short-term outcome or mortality, but single-marker discrimination is usually modest, and reported cutoffs are inconsistent. This means that biomarkers with the best validation are not necessarily those with the highest biological specificity. From a translational standpoint, currently available evidence supports using these markers as additive variables within combined clinical-imaging-laboratory models rather than as stand-alone prognostic tests.

Cytokines and Chemokines: Mechanistic Advantages Coexisting with Practical Barriers

Compared with traditional markers, cytokines and chemokines participate more directly in post-ICH neuroinflammatory cascades and are therefore theoretically better indicators of secondary brain injury activity.[35-37,48] Some studies report associations between IL-6, TNF-α, and certain chemokines with cerebral edema, clinical worsening, or poor functional outcomes; others suggest that abnormalities in inflammation-resolution-related factors may be linked to poor recovery or increased infection risk.[38,48] Such findings reinforce the potential value of mechanism-related biomarkers for prognostic stratification while underscoring the need to interpret them in relation to disease phase and clinical endpoints.[35-38,48]

From the perspective of clinical implementation, however, these biomarkers face substantial barriers: high testing cost, slow turnaround, platform variability, limited standardization and reproducibility, and strong sensitivity to sampling windows.[34,48,53] Even when strong associations are observed in research settings, multicenter validation and assessment of incremental value remain necessary before routine clinical use can be considered.[48,50,51,54] At present, their main utility lies in mechanistic interpretation, patient phenotyping, and development of integrated prognostic models.[48,51]

Another reason for interpretive caution is that conflicting and negative findings remain common. For several cytokines and chemokines, apparently discrepant results may reflect different sampling windows, disease severity distributions, infection burden, assay platforms, and analytical adjustment strategies rather than a true biological contradiction. Accordingly, the strength of evidence should be judged not only by statistical significance in single studies but also by reproducibility, external validation, and incremental value beyond established clinical variables.

Emerging Immunometabolic and Neuroinflammatory Mediators: A New Direction for Prognostic Assessment

Emerging immunometabolic mediators provide a new perspective for prognostic assessment in ICH.[40-43,49] Compared with traditional inflammatory markers, these mediators may simultaneously capture inflammatory status and metabolic compensation, thereby better reflecting disease complexity. For example, lactate elevation is not only a marker of hypoxia or perfusion abnormality; it may also indicate systemic stress and immunometabolic remodeling, and persistent abnormalities may suggest ongoing instability.[40-42,49] Similarly, certain lipid inflammatory mediators and resolution-related molecules may help identify patient subgroups with persistent inflammatory activation versus inflammation-resolution recovery patterns.[39,42,43,49]

The major challenge in this area is the fragmented evidence base: diverse indicators, generally small sample sizes, inconsistent endpoints, and heterogeneous assay methods.[43,49,52,53] Therefore, these biomarkers should currently be regarded as a direction with strong theoretical promise and research potential, rather than established tools for routine prognostic use.[49,52,54]

Dynamic Changes and Trajectory Analysis: Potentially Superior to Single Baseline Measurements

Inflammatory and metabolic responses after ICH are highly dynamic, and a single baseline measurement cannot fully characterize the pathological process[40] Increasingly, research is shifting toward dynamic features such as peak value, time to peak, duration of sustained elevation, rate of decline, and synergistic patterns among multiple indicators.[38,39,55] For prognostic assessment, these dynamic features may offer stronger explanatory power than one-time measurements. For example, an inflammatory marker that is only mildly elevated at admission but continues to worsen may indicate a higher risk of poor outcome than a marker that is initially high but declines rapidly.[29–31]

This perspective is naturally aligned with nursing management, which emphasizes continuous observation, trend recognition, and time-point documentation.[9,1045-47] Future studies integrating nursing observational data with biomarker trajectories may generate prediction models better suited to real-world clinical scenarios.[50,51,56,57]

Combined Prediction Models and Incremental Clinical Value Assessment

The central clinical need in ICH prognostic assessment is not to identify a single best biomarker, but to build an interpretable, actionable, and generalizable combined prediction system.[50,51,58] An ideal model should integrate at least baseline clinical information, neurological severity indicators, imaging findings, treatment/support variables, biomarker data, and dynamic nursing information.[3,4,44,50,51,58] In such a framework, the key question for a biomarker is not merely whether it is statistically significant, but whether it provides incremental value beyond traditional models.[50,51,58] Future research should place greater emphasis on model calibration, clinical net benefit, reclassification performance, and implementability, rather than reporting only improvements in AUC.[50-52,54,58]

Application Boundaries and Ethical Considerations in Prognostic Assessment

While emphasizing biomarker potential, it is equally important to guard against misuse in clinical practice.[50,51,58] Patients with ICH and their families often face major treatment decisions, and overreliance on inadequately validated biomarker results may lead to unnecessary pessimism or excessive intervention.[50,51] Prognostic tools should support communication, stratification, and management optimization, rather than function as conclusion machines that replace comprehensive clinical judgment.[51,58] Therefore, biomarkers should be considered auxiliary evidence and used within a framework of standardized clinical assessment and multidisciplinary discussion.[3,4,50,51,58]

Major Limitations of Current Research and Evidence Quality Issues

Taken together, the current evidence base is best regarded as exploratory to intermediate rather than definitive. The field has generated many promising associations, but translation remains constrained by design limitations, heterogeneity, residual confounding, and limited linkage between biomarker information and real clinical actions. These concerns are especially relevant when biomarkers are proposed for nursing workflows, because bedside value depends on timing, interpretability, and actionability rather than on statistical association alone.

Predominance of Observational Designs and Generally Low Evidence Level

Most biomarker studies in ICH are currently single-center retrospective observational studies with limited sample sizes and problems such as inconsistent inclusion criteria, heterogeneous case mix, loss to follow-up, and information bias.[52-54] Some studies fail to adequately adjust for key confounders or draw strong conclusions based only on univariate analyses, thereby reducing the credibility of findings.[52,54,55] For emerging immunometabolic and neuroinflammatory mediators, exploratory studies far outnumber validation studies.[43,49,52]

Nonstandardized Sampling Windows and Testing Procedures

Inflammatory and metabolic responses after ICH change rapidly and are stage-dependent, yet sampling time definitions vary widely across studies (e.g., on admission, within 24 hours of onset, day 3), often corresponding to very different pathological stages.[52,53,56] In addition, differences in serum/plasma processing, centrifugation and storage conditions, assay reagents, and platforms can all affect result stability.[34,52,53] These issues limit the comparability of biomarker values across studies and hinder external validation of cut-off thresholds.[52-54,56]

Heterogeneity in Endpoint Definitions, Follow-up Duration, and Statistical Methods

Some studies use in-hospital mortality as the endpoint, some use 90-day modified Rankin Scale outcome, some focus on hematoma expansion or infectious complications, and others combine multiple endpoints.[44,52-54] Such inconsistency means that studies may appear comparable while actually addressing different outcomes, complicating evidence synthesis.[52-54] Moreover, differences in statistical strategies—such as whether baseline severity is adjusted for, whether time-dependent analyses are performed, and whether competing risks are considered—can substantially affect

interpretation. Endpoint and modeling heterogeneity is therefore a central barrier to translation.[50-54,58]

Insufficient Confounder Control, Especially Neglect of Nursing-Related Variables

Immune-inflammatory and metabolic markers in ICH are influenced by multiple factors, including infection, invasive procedures, postoperative status, nutritional support, antimicrobial treatment, steroid use, liver/kidney function, and comorbid diabetes or immune disease.[32,33,40,52,55] Many studies record these variables incompletely, and nursing process variables, such as mechanical ventilation management, suction frequency, catheter dwell time, and oral care quality, are especially often overlooked, despite their influence on infection and inflammatory trajectories.[8–10,45,49,55] This weakens causal interpretation and limits assessment of the real-world utility of biomarkers in nursing management scenarios.[55]

Lack of Translational Research Linking Biomarkers to Actions

Most current studies answer which biomarkers are associated with which outcomes, but far fewer address how biomarker information should change management pathways.[52,54,55] For nursing management, the most important practical questions include: Which biomarkers are worth routine tracking? Which testing windows are most meaningful? What trend patterns should trigger intensified monitoring or escalation? How should biomarker information be integrated into existing nursing assessment scales and handoff workflows?[45-47,55,56] High-quality evidence addressing these questions remains limited and should be prioritized in future translational studies.[55,58]

Future Research Directions and Clinical Translation Pathways

Establishing a Standardized, Stage-Specific Monitoring Framework

Future research should build stratified monitoring frameworks around different phases of the ICH course rather than broadly reporting testing after admission.[53,56] At minimum, studies should distinguish key windows, such as the ultra-early phase (admission/shortly after onset), acute phase (24–72 hours), and subacute phase (days 4–7), while clarifying the main clinical questions at each stage (e.g., hematoma progression, cerebral edema, infection risk, metabolic stress).[44,53,56] Such stage-specific design can improve clinical interpretability and reproducibility, while also helping nursing teams develop stratified monitoring strategies.[45-47,56]

Focusing on Dynamic Trajectories and Patient Subtypes Rather Than Average Effects

ICH is a highly heterogeneous condition, and the same biomarker may follow very different trajectories in different patients.[52,57] Future studies may use trajectory modeling, clustering, or stratified modeling to identify subtypes, such as persistent high-inflammation, early peak followed by decline, and persistent metabolic stress, and then examine their associations with nursing risk and prognostic outcomes.[57] Such approaches are more likely to yield clinically useful stratification results and are more consistent with the logic of dynamic observation in nursing practice.

Promoting Multimodal and Interpretable Combined Models

In model development, future work should avoid algorithm-only thinking and instead emphasize interpretability, simplicity, and implementability.[50,51,58] An ideal model should not only be accurate, but also explain to clinicians and nurses where the risk comes from and what should be monitored next.[50,58] Accordingly, biomarkers should be integrated with imaging, neurological scores, vital-sign trends, and nursing observation variables to develop stratified warning tools, followed by validation of clinical net benefit in prospective cohorts or real-world studies.

Conducting Prospective Studies Embedded in Nursing Pathways

Given the focus of this review, future research should prioritize nursing pathway embedding rather than prediction performance alone.[55] Possible directions include incorporating selected highly accessible biomarkers into ICH nursing handoff templates; establishing escalation triggers based on biomarker trends plus clinical signs; applying biomarkers to infection-risk stratification while observing effects on nursing resource allocation and intensity of basic nursing care; and combining rehabilitation follow-up with inflammatory/immunometabolic trajectories to optimize rehabilitation nursing pathways.[45-47,49,55] Such studies are more likely to demonstrate the practical value

of nursing management and support broader clinical adoption.

Feasible next-step studies would include prospective multicenter cohorts with predefined sampling windows at admission, approximately 24 hours, approximately 72 hours, and day 5 to 7; standardized adjudication of pneumonia and other complications; explicit recording of treatment exposures and major comorbidities; and nursing outcomes, such as escalation frequency, time to physician notification, ICU length of stay, and handoff completeness. Such designs are more likely to show whether biomarkers truly improve care processes rather than merely correlate with outcomes.

Stepwise Validation of Emerging Immunometabolic and Neuroinflammatory Mediators

For emerging biomarkers, a stepwise validation pathway is recommended: mechanistic plausibility → analytical feasibility → clinical association → incremental value → practical accessibility.[42,43,49,58] Only when a biomarker shows stable associations across multiple independent cohorts, provides clear incremental value in combined models, and is supported by acceptable cost and turnaround time for clinical use, should it proceed to studies of routine application.[49,50,51,58] This strategy can help prevent enthusiasm for novel biomarkers without real clinical usability.

Building a Collaborative Clinical-nursing-laboratory-imaging Research Model

Translation of ICH biomarker research requires multidisciplinary collaboration.[55,58] Laboratory medicine contributes assay platforms and standardization support; neurology/neurosurgery and critical care provide disease stratification and treatment context; nursing teams contribute continuous observational data and workflow-embedded application scenarios; and imaging specialists provide structural and progression information.[3,4,8–10,50,58] Future studies that include nursing variables and process-related outcomes at the design stage will be more likely to produce truly applicable evidence.

DISCUSSION

Immune-related circulating biomarkers provide a useful additional window into the evolving biology of ICH, particularly when the aim is to recognize dynamic risk rather than to describe injury severity at a single time point. Among currently available options, routine blood-cell indices, CRP, and PCT are the most practical for serial bedside use because they are accessible, repeatable, and already embedded in many hospital workflows.

At the present stage of evidence, these biomarkers should be interpreted as adjuncts to imaging, neurological examination, vital signs, and nursing observation. The most clinically relevant question is not whether one biomarker can independently predict outcome, but whether biomarker trajectories can improve stage-specific monitoring, complication warning, handoff quality, and multidisciplinary response.

Accordingly, near-term implementation should focus on standardized sampling windows, trend-based interpretation, and integration into explicit nursing protocols rather than on single cutoff-driven decisions. Future prospective studies should test whether biomarker-informed workflows improve clinically meaningful outcomes and care processes, especially infection surveillance, escalation timing, and transition planning after ICH.

STATEMENT OF ETHICS

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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DATA AVAILABILITY

The data that support the findings of this study are available from the corresponding author upon reasonable request.

AI ASSISTANCE DISCLOSURE

Not applicable.

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