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Metabolomic and Proteomic Profiling of Vaso-Occlusive Crises in Sickle Cell Disease: Current Evidence and Future Perspectives

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ABSTRACT

Sickle cell disease (SCD) is characterized by recurrent vaso-occlusive crises (VOCs), which are the primary contributors to morbidity and mortality globally. Conventional clinical markers, including fetal hemoglobin (HbF), reticulocyte count, and lactate dehydrogenase (LDH), offer limited predictive value because of interpatient variability and an inability to capture the complex, multifactorial pathophysiology of VOCs. Recent advances in metabolomics and proteomics have enhanced understanding of VOC biology. Metabolomic profiling has identified perturbations in glycolysis, amino acid metabolism, oxidative stress pathways, and lipid metabolism, while proteomic studies have revealed dysregulation of inflammatory mediators, adhesion molecules, coagulation factors, and endothelial markers. Although significant progress has been made, most reported metabolomic and proteomic signatures remain insufficiently reproducible and are not yet clinically applicable. This limitation is primarily attributed to biological heterogeneity, limited cohort sizes, and methodological inconsistencies across studies. Recent evidence indicates that pathway-level markers, longitudinal sampling strategies, and integrated multi-omics approaches are more likely to yield clinically relevant biomarkers than isolated single-molecule candidates. Significant challenges remain, including limited validation across diverse populations and barriers to implementation in resource-limited settings. Addressing these challenges will require collaborative, multicenter studies, improved analytical harmonization, and the development of accessible diagnostic platforms. This narrative review synthesizes current evidence on metabolomic and proteomic profiling of VOCs, highlights implications for equity and global health, and outlines priorities for translational research to advance personalized care and improve clinical outcomes in SCD.

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Introduction

Sickle cell disease (SCD) is the most prevalent inherited hemoglobinopathy worldwide, with particularly high prevalence in sub-Saharan Africa, the Middle East, and among diaspora populations in Europe and other high-income regions [1,2]. Although HbSS is typically associated with the most severe clinical phenotype, other genotypes, such as HbSC, HbS β^0 -thalassemia, and HbS β^+ -thalassemia, exhibit distinct patterns of disease severity, hemolysis, and vaso-occlusive complications. In addition, co-inherited α -thalassemia is a significant genetic modifier that

affects red cell physiology, hemolysis, blood viscosity, and clinical outcomes in SCD. These genetic and physiological factors contribute to biological heterogeneity and may account for variations in metabolomic and proteomic profiles observed among patient cohorts [3–5]. SCD results from a point mutation in the β -globin gene, leading to the production of sickle hemoglobin (HbS). Under deoxygenated conditions, HbS polymerization induces erythrocytes to assume a rigid, sickle-shaped morphology with reduced deformability and increased adhesiveness. These changes predispose individuals to microvascular obstruction and tissue ischemia [3,5].

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Sickled erythrocytes exhibit reduced deformability, membrane damage, increased cellular adhesion, and heightened susceptibility to hemolysis. These pathological features interact with vascular, inflammatory, and coagulation pathways, promoting recurrent VOCs, the hallmark clinical manifestation of SCD [1,3,4]. VOCs are the leading cause of emergency admissions and hospitalizations in affected individuals and contribute significantly to long-term morbidity, including chronic pain, cumulative organ damage, reduced quality of life, and premature mortality [1,6,7]. Endothelial dysfunction is central to the pathogenesis of VOCs. Injured endothelium expresses adhesion molecules such as vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1), facilitating interactions among sickled erythrocytes, leukocytes, and platelets. This process intensifies vascular occlusion and perpetuates local hypoxia [1]. Available proteomic studies have demonstrated dysregulation of endothelial proteins, inflammatory mediators, complement components, and coagulation factors during VOCs, underscoring the vascular injury and systemic inflammatory response that characterize these episodes [8,9].

Recent advances in disease-modifying therapies, including optimized hydroxycarbamide (hydroxyurea) use, novel anti-adhesion agents, and curative strategies such as gene therapy, have transformed the clinical management of SCD and increased the demand for robust biomarkers to guide personalized care [10–14]. Hydroxycarbamide, the cornerstone disease-modifying therapy for SCD, reduces VOC frequency by inducing fetal hemoglobin (HbF), suppressing leukocyte activation, and improving erythrocyte hydration. Nevertheless, treatment response varies substantially, highlighting the need for reliable biomarkers to support treatment optimization and personalized care [5,13,15]. The timing, frequency, and severity of VOCs remain unpredictable, underscoring the limitations of conventional laboratory markers in reflecting underlying biological heterogeneity [10,14]. At the same time, rapid progress in high-throughput metabolomic and proteomic technologies has produced a substantial body of data relevant to VOC pathophysiology [15,16]. However, the growing evidence base is fragmented, methodologically heterogeneous, and inconsistently integrated into clinical practice, which restricts its utility for patient stratification and clinical decision-making [16,17]. A comprehensive synthesis is therefore warranted to assess the consistency, biological significance, and clinical applicability of emerging omics-based biomarkers and to establish priorities that can advance precision medicine in SCD.

Inflammatory processes further amplify vasoocclusion. Activated neutrophils and monocytes release cytokines and reactive oxygen species, inducing oxidative stress and enhancing endothelial activation [1]. Metabolomic analyses have identified disruptions in redox homeostasis, including altered glutathione metabolism and elevated oxidative stress markers, that correlate with VOC severity and indicate systemic metabolic stress during crises [18]. Concurrently, coagulation abnormalities contribute to VOC pathogenesis. Hypercoagulability in SCD is marked by increased thrombin generation and platelet activation, which promote microvascular thrombosis and further compromise blood flow [19,20]. Proteomic investigations have detected elevated concentrations of coagulation and fibrinolytic pathway components during VOCs, linking hemostatic imbalance to clinical outcomes [8]. Despite advances in supportive care and disease-modifying therapies, including hydroxycarbamide, the ability to predict and stratify risk for VOCs remains limited [2]. Current clinical markers, such as fetal hemoglobin (HbF) levels, reticulocyte counts, and lactate dehydrogenase (LDH), offer only partial insight into disease activity and are insufficient for early detection of impending crises [1,21]. In addition, genetic modifiers, including α -thalassaemia status and loci regulating HbF expression, particularly *BCL11A* and *HBS1L-MYB*, significantly influence disease severity but do not fully account for clinical variability or VOC susceptibility [3–5]. This diagnostic gap underscores the urgent need for biologically informed biomarkers that can forecast VOC onset and severity, thereby enabling personalized interventions and reducing the burden on acute care.

High-throughput omics approaches, particularly metabolomics and proteomics, provide powerful tools for capturing the complex biochemical and protein alterations underlying these interconnected pathological mechanisms. Metabolomic profiling has identified disruptions in energy metabolism, oxidative stress pathways, nitric oxide bioavailability, and lipid homeostasis in individuals with SCD, reflecting the metabolic consequences of chronic hemolysis, inflammation, and hypoxia [18,22–24]. Complementary proteomic analyses have revealed dysregulated plasma proteins associated with endothelial dysfunction, coagulation, and immune activation, all central to VOC pathophysiology [8,9,25]. Sahun et al. [26] identified a novel red blood cell deformability biomarker associated with hemolysis and vaso-occlusive crises, further supporting the contribution of altered erythrocyte rheology to disease severity.

Integrating metabolomic and proteomic data offers a systems-level view of VOC biology that overcomes the limitations of traditional hemoglobin-centric disease models. By combining information across complementary molecular layers, multi-omics approaches may enhance biological interpretation and help identify clinically relevant pathway-level biomarkers [27–29].

This narrative review examines current metabolomic and proteomic evidence on VOCs in SCD. It synthesizes existing findings to identify key molecular patterns associated with VOCs, establishes a foundation for critical discussion of clinical relevance and limitations, and introduces considerations regarding translational challenges, equity, and future directions for omics-based biomarker development in this complex hemoglobinopathy.

Materials and methods

This narrative review examines published literature on metabolomic and proteomic alterations associated with VOCs in SCD. The objective is to synthesize and critically appraise existing evidence on biological mechanisms, biomarker potential, and the translational implications of omics-based approaches in this context, rather than to conduct a systematic or meta-analytic evaluation.

Relevant literature was identified through targeted searches of major biomedical databases, including PubMed and Web of Science, using keyword combinations related to sickle cell disease (SCD), vaso-occlusive crisis (VOC), vaso-occlusive episode (VOE), metabolomics, proteomics, and biomarkers. The literature search covered publications from approximately 2010 to 2025 and was limited to English-language articles. Database searches were conducted between January and March 2026. Studies were selected based on their relevance to the objectives of this narrative review, with an emphasis on peer-reviewed original research, clinically relevant investigations, and contemporary reviews addressing the metabolomic, proteomic, and multi-omics aspects of VOCs in SCD. Conference abstracts were generally excluded; however, selected conference communications directly relevant to VOC-specific proteomic profiling were included when peer-reviewed full-length studies were unavailable. Reference lists of key review articles and primary studies were also examined to identify additional relevant publications. Priority was given to peer-reviewed original research articles and contemporary review papers addressing biochemical, molecular, or translational aspects of vaso-occlusive crisis pathophysiology.

Studies were included if they investigated metabolomic or proteomic profiles in individuals with SCD under steady-state conditions or during VOCs, or discussed the potential clinical or translational relevance of these findings. Attention was given to studies examining systemic metabolic perturbations, endothelial or inflammatory protein signatures, or integrated multi-omics approaches. No formal exclusion criteria for study design, cohort size, or analytical platform were applied; however, priority was given to studies with larger cohorts, detailed clinical annotation, robust analytical methods, longitudinal designs, and crisis-specific sampling when available.

Primary datasets with longitudinal designs or sampling explicitly associated with VOCs were prioritized. In contrast, smaller exploratory or cross-sectional studies were considered hypothesis-generating.

Given the scope of this review, formal quality scoring, risk-of-bias assessment, and quantitative synthesis were not conducted. Findings were interpreted qualitatively, with attention to methodological heterogeneity, study limitations, and consistency across independent reports. The evidence was organized thematically to facilitate comparison of metabolomic and proteomic findings and to support discussion of emerging biological patterns, translational challenges, and future research priorities.

Evidence from metabolomic and proteomic studies

Metabolomic alterations associated with vaso-occlusive crises

Metabolomic profiling has provided significant insights into the biochemical perturbations associated with VOCs in SCD. Studies using diverse analytical platforms have consistently identified alterations in pathways involved in energy metabolism, redox balance, nitric oxide bioavailability, and lipid signaling. These findings underscore the complex interactions among hemolysis, hypoxia, inflammation, and endothelial dysfunction that define VOCs [18,22–24]. Table 1 summarizes key metabolomic studies and their principal pathway-level findings.

Alterations in glycolytic intermediates and tricarboxylic acid cycle metabolites indicate heightened energetic stress and altered substrate utilization. Additionally, disruption of amino acid metabolism, particularly of L-arginine and glutamine, has been associated with impaired nitric oxide signaling during acute crises [18,24].

Table 1. Metabolomic and metabolic biomarker studies relevant to vaso-occlusive crisis pathophysiology in sickle cell disease.

Study	Cohort characteristics	Sample type	Sampling timing	Analytical platform	Principal metabolic signatures
[18]	40 adults with SCD sampled during steady-state and VOC	Plasma and erythrocytes	Steady-state and VOC	Targeted LC-MS metabolomics (188 metabolites)	Arginine-NO metabolism; hypoxia-related adaptation; energetic stress; erythrocyte membrane remodeling
[22]	90 SCD patients and 50 controls	Whole blood/erythrocytes	Steady-state and VOC	Oxidative stress biomarker assays	Oxidative stress; lipid peroxidation; antioxidant depletion; nitric oxide dysregulation; endothelial dysfunction-associated metabolic disturbances
[24]	12 children with SCD admitted with acute VOC pain	Platelet-rich plasma	Acute VOC	Mitochondrial enzyme activity assays and oxidative stress profiling	Arginine-nitric oxide metabolism; mitochondrial bioenergetic dysfunction; oxidative stress pathways; metabolic recovery following arginine supplementation
[23]	596 patients with SCD from the WALK-PHaSST cohort, including HbSS and HbSC genotypes	Plasma	Steady-state cohort sampling	Large-scale plasma metabolomics	Reduced arginine and S1P; elevated kynurenine; altered acyl-carnitine and bile acid metabolism; metabolic signatures associated with hemolysis, cardiorenal dysfunction, disease severity and therapeutic response

VOC: vaso-occlusive crisis; SCD: sickle cell disease; LC-MS: liquid chromatography-mass spectrometry; NO: nitric oxide; RBCs: red blood cells; S1P: sphingosine-1-phosphate

Note: Included studies are original investigations relevant to VOC-associated metabolic dysregulation in SCD. Due to methodological heterogeneity, pathway-level findings, rather than individual metabolite-level findings, are summarized.

Across independent cohorts, the most consistent metabolomic alterations occur at the pathway level rather than at the level of individual metabolites. Perturbations in arginine–nitric oxide metabolism, glutathione-centered redox pathways, and lipid-mediated inflammatory signaling are consistently identified and demonstrate strong biological plausibility with respect to endothelial dysfunction and vaso-occlusion [18,22–24].

Lipidomic analyses have identified altered phospholipid composition, sphingolipid signaling, and eicosanoid production in SCD, implicating membrane remodeling and inflammatory amplification during VOCs [18,22]. However, reported lipid signatures vary substantially across studies, likely due to differences in analytical platforms, sample handling, and disease state at the time of sampling [22].

Several reported metabolite classes are confounded by hemolysis, treatment exposure, and sampling timing. Metabolites associated with free hemoglobin, intracellular energy, and certain amino acids may primarily reflect red cell rupture or acute-phase responses rather than biology specific to VOCs [21]. Additionally, the inconsistent consideration of the metabolic effects of disease-modifying therapies, such as hydroxycarbamide, limits comparability and interpretability across studies, particularly in cross-sectional designs [21]. Acute sampling of established VOCs further complicates interpretation, as many observed metabolic changes likely reflect downstream effects of systemic stress rather than serving as predictive or causal biomarkers.

Taken together, current evidence indicates that pathway-level metabolomic signatures associated with endothelial function, oxidative stress, and lipid-mediated inflammation should be prioritized over isolated single-metabolite changes. Employing longitudinal sampling strategies, comprehensive clinical annotation, and integration with proteomic data is essential to distinguish VOC-specific mechanisms from confounding effects such as hemolysis and therapy, thereby enhancing translational potential [18,22–24].

Proteomic signatures associated with endothelial dysfunction and inflammation

Proteomic analyses have provided complementary insights into the molecular mechanisms underlying VOCs, particularly inflammation, endothelial activation, coagulation, and immune dysregulation. Plasma-based proteomic studies in SCD have identified differential expression of inflammatory mediators, adhesion molecules, and hemostatic proteins during VOCs, reflecting the systemic inflammatory and prothrombotic environment characteristic of acute pain episodes [8,30]. Recent studies have further highlighted substantial biological heterogeneity among VOC episodes, suggesting that distinct inflammatory phenotypes may exist within clinically similar crises. Collectively, these findings support the potential utility of proteomic profiling for VOC biomarker discovery and patient stratification. Table 2 summarizes representative proteomic investigations relevant to VOC biomarker discovery.

Table 2. Proteomic studies relevant to VOC biomarker discovery in sickle cell disease.

Study	Cohort characteristics	Sample type	Sampling timing	Analytical platform	Principal proteomic signatures
[30]	HbSS and HbSβ ⁰ -thalassemia patients and healthy controls	Plasma	Steady-state and VOC	Olink PEA	Inflammatory pathway activation; cytokine signaling; immune dysregulation
[8]	46 individuals with SCD; 39 paired VOC and baseline plasma samples	Plasma	VOC and baseline follow-up	Olink Explore (>1,000 proteins)	Inflammatory heterogeneity; innate immune activation; VOC-associated proteomic signatures
[25]	189 adults with SCD from the OMG-SCD cohort	Plasma	Steady-state sampling	Large-scale mass spectrometry proteomics	Proteomic signatures associated with sickle cell nephropathy and pulmonary hypertension; extracellular matrix remodeling and cell adhesion pathways.
[31]	376 individuals with SCD and 103 healthy controls	Plasma	Cross-sectional sampling	Large-scale plasma proteomics (5,411 proteins)	Mortality-associated proteomic signatures; inflammation-related pathways (including IL-18 signaling); biomarkers of disease severity and accelerated biological aging.

VOC: vaso-occlusive crisis; SCD: sickle cell disease; PEA: proximity extension assay.

Note: The table summarizes original proteomic investigations relevant to biomarker discovery in sickle cell disease, including studies that directly examined vaso-occlusive crises and those that identified proteomic signatures associated with disease severity, mortality, and major disease complications.

The interpretation of proteomic findings is strongly influenced by methodological factors, including sample type, protein depletion strategies, and analytical platforms. Most published proteomic studies in SCD use plasma rather than serum to preserve coagulation factors; however, plasma proteomes are dominated by a few high-abundance proteins, which can obscure detection of lower-abundance, disease-relevant signals. Variability in depletion strategies, sample preparation, analytical platforms, and bioinformatic pipelines further complicates cross-study comparability and reproducibility [29,32]. Many reported proteomic VOC signatures are dominated by high-abundance acute-phase proteins, raising concerns about disease specificity and long-term translational relevance. Consistent increases in C-reactive protein, serum amyloid A, complement components, and fibrinogen likely reflect general acute inflammatory responses rather than VOC-specific or predictive biological processes [8,9,30].

Proteins linked to endothelial activation and coagulation pathways underscore the central role of vascular dysfunction in VOC pathophysiology. The identification of inflammatory and vascular-associated proteomic signatures during VOCs aligns with established models of endothelial injury, hemostatic activation, and hypercoagulability in SCD [8,19,20].

Despite these findings, reproducibility across proteomic platforms remains limited. Variations in mass spectrometry workflows, antibody-based assays, sample preparation, and data normalization strategies contribute to inconsistent identification of candidate biomarkers. Furthermore, many studies use small, cross-sectional cohorts sampled during established VOCs, limiting statistical power and making it difficult to determine whether observed changes are causal, predictive, or secondary to acute inflammation

[8,30,32]. The limited number of published proteomic investigations directly examining VOCs further constrains validation across independent cohorts and analytical platforms. Notably, several recent proteomic datasets relevant to VOC biology are available only as conference abstracts or proceedings, highlighting both the rapid development of the field and the need for additional peer-reviewed studies to confirm and extend these findings.

In summary, progress in this field will depend on harmonized sample processing, standardized analytical workflows, larger multicenter cohorts, and longitudinal study designs capable of distinguishing predictive biomarkers from secondary inflammatory responses. Greater emphasis on pathway-level proteomic signatures and integrated network-based approaches, rather than isolated protein changes, is likely to improve biological interpretation, enhance reproducibility, and facilitate clinical translation [27–29].

Multi-omics integration: current evidence

Metabolomic and proteomic investigations have each advanced understanding of the biology of vaso-occlusive crisis (VOC). However, single-omic approaches have plateaued in their ability to yield reproducible, clinically actionable biomarkers. Although researchers repeatedly identify biologically plausible signals, findings from isolated omics layers show limited concordance across cohorts and platforms and rarely progress beyond the discovery phase [21,28]. Table 3 outlines examples of multi-omics integration approaches relevant to VOC biomarker research.

These challenges reflect both the inherent biological complexity of SCD and the inability of any single molecular layer to capture the dynamic, multisystem processes underlying VOCs.

Table 3. Examples of multi-omics integration approaches relevant to VOC biomarker research.

Study	Cohort characteristics	Sampling timing	Omics integrated	Integration approach	Principal outcomes
[28]	SCD patient cohorts	Mixed disease states	Metabolomics + Proteomics	Correlative and pathway-based analysis	Convergent inflammatory and metabolic signaling
[29]	Methodological and multi-disease frameworks	Not applicable	Multi-omics frameworks	Network-based integration	Pathway-level systems biology models
[33]	Multi-disease precision medicine datasets	Not specified	Metabolomics + Proteomics	System-level network modeling	Endothelial–metabolic interaction hubs
[27]	Methodological multi-omics studies	Not applicable	Multi-layer omics	Pathway- and network-centric analysis	Improved biomarker coherence and prioritization

Notes: The listed studies are illustrative of the existing literature and are not exhaustive. Some publications are methodological or framework-focused and therefore do not report disease-specific cohort characteristics or sampling time points.

Multi-omics integration addresses these limitations by enabling biological triangulation across complementary molecular domains. Integrative analyses can identify pathway-level signatures consistently supported by convergent changes in metabolites and proteins, thereby distinguishing robust disease mechanisms from platform-specific noise or acute-phase artifacts [29,33]. By reinforcing mechanistic signals across molecular layers, multi-omics approaches improve reproducibility and strengthen confidence in candidate biomarkers. Furthermore, these approaches enhance clinical relevance by aligning findings with endothelial dysfunction, oxidative stress, inflammation, and coagulation processes central to VOC pathophysiology [28,34].

From a systems biology perspective, VOCs are emergent phenomena arising from coordinated interactions among erythrocytes, leukocytes, endothelial cells, and plasma factors within a dynamically changing metabolic environment. Systems-level frameworks are essential for contextualizing omics data within interacting biological networks, rather than treating individual molecules as independent predictors. Network- and pathway-centric models help examine how metabolic, inflammatory, and hemostatic pathways converge to drive vaso-occlusion, providing a more accurate and biologically coherent representation of disease processes than reductionist approaches [27,29].

Despite its conceptual appeal, previous efforts to integrate multiomics data in SCD have had limited impact, largely because integration was often superficial rather than analytical. Many studies presented parallel metabolomic and proteomic datasets without unified modeling frameworks. Additionally, small sample sizes, cross-sectional designs, inconsistent VOC timing, and limited phenotypic annotation have constrained interpretability [21,28]. Variability in preprocessing, normalization, and data integration methods

has further undermined reproducibility across studies [29].

Future investigations should be explicitly designed for multi-omics integration rather than relying on *post hoc* data aggregation. Key priorities include longitudinal sampling from steady state through pre-VOC and acute-VOC phases, harmonized biospecimen collection and processing, and integrated analysis pipelines capable of modeling interactions across molecular layers. Analytical focus should shift toward pathway- and network-level frameworks, supported by validation in independent cohorts, to enable robust biomarker prioritization and clinically meaningful stratification [27,33]. These approaches are essential for translating multi-omics discoveries into predictive, mechanistically informed tools for precision medicine in SCD. Figure 1 presents an integrated systems-level framework linking VOC pathophysiology to metabolomic and proteomic alterations and their translation into biomarker discovery and precision medicine applications.

Discussion and conclusions

This review synthesizes metabolomic and proteomic evidence to elucidate the systems-level biological processes underlying VOCs in SCD. The findings demonstrate that VOCs arise from coordinated disruptions across metabolic, inflammatory, endothelial, and hemostatic pathways, thereby extending understanding beyond traditional hemoglobin-centric models.

Integrative interpretation of omics findings

Metabolomic and proteomic findings reinforce established concepts of VOC pathophysiology and provide additional mechanistic detail. Metabolic perturbations in energy demand, oxidative stress, nitric oxide dysregulation, and lipid metabolism align with recognized contributors to erythrocyte rigidity, endothelial activation,

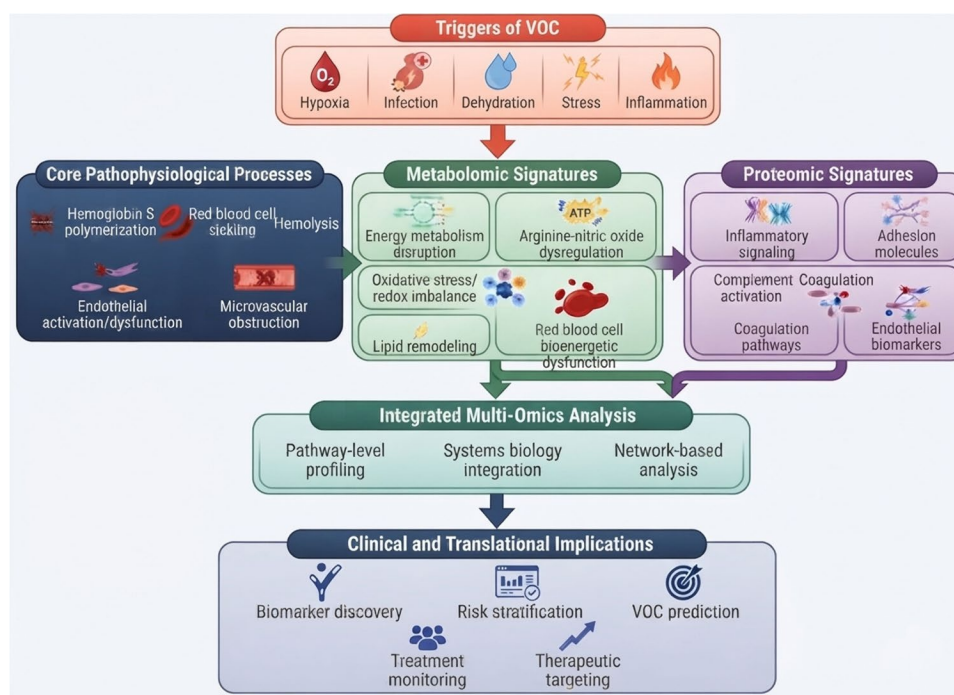


Figure 1. Integrated metabolomic and proteomic framework illustrating the pathophysiology of vaso-occlusive crises (VOCs) in sickle cell disease. Physiological and environmental triggers promote hemoglobin S polymerization, red-cell sickling, hemolysis, endothelial dysfunction, and microvascular obstruction. These processes generate characteristic metabolomic and proteomic alterations that reflect metabolic stress, inflammation, vascular injury, and coagulation abnormalities. Integrating these complementary omics layers through multi-omics approaches supports pathway-level biomarker discovery, risk stratification, VOC prediction, treatment monitoring, and therapeutic targeting.

and vascular dysfunction [1,18,22–24]. Concurrently, proteomic signatures implicating adhesion molecules, inflammatory mediators, coagulation factors, and immune-related proteins highlight the central role of vascular inflammation and hemostatic imbalance in VOC development [8].

The convergence of metabolic stress and protein-level dysregulation supports a model in which VOCs arise from coordinated, multi-system disturbances rather than isolated pathological events. This integrative perspective reconciles clinical observations with molecular evidence and provides insight into inter-individual variability in VOC frequency and severity [1,8].

Translational relevance and clinical implications

Although significant progress has been made in metabolomic and proteomic profiling of VOCs, integration into routine clinical practice remains limited. Most identified biomarkers reflect downstream effects of hemolysis, inflammation, or tissue injury rather than serving as early or predictive indicators, thereby limiting their immediate clinical utility [35,36]. However, consistent patterns across studies suggest that omics-based markers could influence clinical

practice if key methodological and validation challenges are addressed.

Prediction of vaso-occlusive crisis onset

Currently, the most promising candidates for predicting VOC onset are pathway-level metabolomic signatures linked to endothelial dysfunction, nitric oxide bioavailability, oxidative stress, and lipid-mediated inflammation, particularly when evaluated longitudinally rather than solely at crisis presentation [18,22–24]. These pathways align with established mechanisms of vaso-occlusion and tissue hypoxia. Nevertheless, the predictive value of these markers remains unproven because most studies collect samples during established VOCs rather than in pre-crisis states, limiting causal inference and early-warning capability [35].

Stratification of crisis severity and risk

Proteomic and metabolomic signatures reflecting inflammatory burden, endothelial activation, and coagulation dysregulation may stratify VOC severity and identify patients at risk of prolonged hospitalization or complications [9,28]. Combined pathway-level signatures may outperform conventional laboratory markers in capturing disease heterogeneity. However,

omics signatures associated with severity currently lack standardized thresholds and external validation across diverse cohorts, limiting their reliable clinical application [21,36].

Monitoring therapeutic response

Omics-based biomarkers may ultimately prove valuable for monitoring responses to disease-modifying therapies, including hydroxycarbamide, anti-adhesion agents, and emerging gene-based interventions. Longitudinal changes in metabolic or proteomic pathways linked to reduced inflammation, improved redox balance, or decreased endothelial activation could serve as pharmacodynamic indicators [28,36]. Currently, these applications remain exploratory because treatment effects are often confounded by baseline variability, small sample sizes, and non-standardized sampling intervals [35].

Equity and global health considerations

SCD disproportionately affects populations in low- and middle-income countries (LMICs), where the burden of VOCs is highest and access to comprehensive care remains limited. In 2021, an estimated 7.7 million people were living with SCD globally, with nearly 80% in sub-Saharan Africa. That year, SCD accounted for more than 80,000 deaths among children under age five [37,38]. These epidemiological realities underscore the need to ensure that advances in metabolomics and proteomics are accessible to populations bearing the greatest burden, rather than disproportionately benefiting high-income settings.

Most current omics-based investigations rely on technologies and infrastructure that are not practical for routine use in low- and middle-income countries (LMICs). High-resolution mass spectrometry platforms, reliance on ultra-cold storage, and complex bioinformatic workflows require sustained investment and specialized expertise, which are seldom available in regions with the highest prevalence of SCD [21,35]. Long-term preservation of metabolomic and proteomic biospecimens often requires storage at ultra-low temperatures (typically -80°C), creating additional logistical challenges in resource-constrained settings. Alternative approaches, including dried blood spot sampling, stabilizing reagents, lyophilization, and targeted assays with shorter processing timelines, may reduce dependence on ultra-cold storage and improve feasibility in resource-constrained settings [21,35]. As a result, discovery-phase research conducted predominantly in high-resource settings risks limited global applicability unless implementation constraints are explicitly addressed during study design.

Despite this, successful biomarker and metabolomic studies have been conducted in several LMIC settings, including Ghana and other African countries, showing that collaborative research networks, regional reference laboratories, and international partnerships can implement advanced analytical approaches. These examples suggest that the main barriers often relate to sustainable infrastructure and workforce development rather than technical feasibility alone [22,37].

Sample handling and pre-analytical variation pose additional challenges. Metabolomic and proteomic profiles are highly sensitive to processing delays, temperature fluctuations, and repeated freeze-thaw cycles. These conditions are common in settings with limited laboratory infrastructure or an unreliable power supply [38]. Such factors can introduce systematic bias and reduce reproducibility when samples from LMIC cohorts are analyzed alongside those from high-income environments.

From an implementation perspective, resource-appropriate technologies are essential for translating omics discoveries into equitable care. Targeted assays that use small panels of pathway-level biomarkers, streamlined analytical workflows compatible with current laboratory infrastructure, and integration with point-of-care or near-patient testing are considered more practical for clinical translation than comprehensive discovery-omics platforms [28,35]. These strategies align with global health assessments that prioritize robustness, scalability, and cost-effectiveness over maximal molecular depth [21].

However, targeted metabolomic approaches may introduce selection bias by limiting analyses to pre-defined metabolites and pathways. Untargeted metabolomic strategies remain essential for biomarker discovery because they enable the identification of novel metabolites and previously unrecognized biological mechanisms without prior assumptions. Future studies should integrate untargeted discovery approaches with subsequent targeted validation to balance biological breadth with translational feasibility [21,29].

Applicability in low- and middle-income country settings also depends on study designs that explicitly include diverse populations and healthcare contexts. Many published omics studies rely on small cohorts from high-income countries, limiting generalizability across genetic backgrounds, environmental exposures, and treatment paradigms [37,38]. Without deliberate inclusion of LMIC populations and equitable research partnerships, candidate biomarkers may perform inconsistently or fail entirely in the regions most affected by SCD.

Addressing these challenges requires coordinated global investment and a pragmatic approach to translation. Peer-reviewed assessments of SCD care consistently underscore the importance of capacity building, regional laboratory development, and integrating SCD services into primary healthcare systems to achieve equitable and scalable progress [35,36,38]. Biomarker strategies that align with local diagnostic capabilities and established clinical workflows are more likely to improve global outcomes than technically advanced approaches that are not feasible for large-scale implementation.

Methodological limitations and reproducibility challenges

A significant challenge identified in the literature is substantial methodological heterogeneity. Variations in cohort characteristics, disease state at sampling, analytical platforms, and data-processing pipelines complicate comparisons across studies and hinder the synthesis of findings [18,21]. Additionally, small sample sizes and predominantly cross-sectional designs limit statistical power and constrain the ability to establish temporal relationships between molecular changes and clinical events.

Addressing these limitations is essential to advancing the field. Increased standardization of omics workflows, improved reporting practices, and multicenter collaboration may enhance reproducibility and facilitate biomarker validation [21].

Priorities for advancing omics-based biomarkers in SCD

Although metabolomic and proteomic studies have significantly advanced understanding of the biology of vaso-occlusive crisis (VOC), progress toward clinically actionable biomarkers remains constrained by persistent methodological and design challenges. To move beyond descriptive discovery and toward meaningful clinical impact, a coordinated, prescriptive shift in research priorities is required [21,35].

Practices requiring cautious interpretation

Although underpowered and cross-sectional studies conducted during established VOCs have important methodological limitations, they continue to provide valuable biological information, particularly in understudied populations and resource-constrained settings. Future studies should transparently report methodological constraints, interpret findings cautiously, and validate results in larger longitudinal cohorts, rather than excluding such data from consideration [21,28,35].

Non-standardized definitions of VOCs should be avoided. Variability in clinical criteria, inconsistent documentation of treatment exposure, and differences in biospecimen collection timing reduce cross-study comparability and obscure disease-specific molecular signals, thereby limiting translational relevance [35,36].

Research practices that should be strengthened

Longitudinal sampling strategies should be adopted as standard practice. Serial biospecimen collection across steady-state, pre-VOC, acute VOC, and recovery phases is necessary to distinguish biomarkers of susceptibility, onset, severity, and resolution from downstream effects of inflammation or tissue injury [18,21].

Post-VOC recovery sampling may be equally important because it can help distinguish persistent biological abnormalities from transient crisis-associated changes and provide insight into biological recovery trajectories and the risk of recurrent VOCs. For biomarker discovery studies, steady-state sampling should ideally be standardized and defined as an interval free of acute VOCs, infection, blood transfusion, or major treatment modifications, thereby reducing biological variability and improving comparability across studies.

Pre-VOC sampling designs should be prioritized. Although logistically challenging, outpatient monitoring and peri-trigger sampling are critical for identifying early biological changes that precede pain presentation and hospitalization; without such designs, predictive biomarker development will remain speculative [28,35].

Implementing harmonized analytical and bioinformatics pipelines across centers is recommended. Standardizing sample handling, data preprocessing, normalization, and statistical modeling is essential to enhance reproducibility and facilitate the meaningful integration of metabolomic and proteomic datasets across studies and platforms [21].

Strategic priorities for future research

Pathway-level signatures should be prioritized over isolated single-molecule markers. Independent studies consistently show that the most reproducible findings implicate shared biological pathways, particularly those involving endothelial dysfunction, oxidative stress, inflammation, and coagulation. These results support adopting pathway-centric analytical approaches [18,28].

Multi-center and multi-population consortia should be prioritized to ensure sufficient statistical power and generalizability. Collaborative studies that include diverse geographic regions, healthcare settings, and patient populations are essential for validating candidate biomarkers and minimizing the risk of overfitting to single-institution cohorts [21,28].

Prospective integration of omics data with clinically meaningful endpoints must be established from the outset. Biomarker discovery should be explicitly linked to outcomes such as vaso-occlusive crisis (VOC) frequency, time to the next crisis, hospital length of stay, treatment response, and organ-specific complications. Without prospective alignment with clinical endpoints, omics findings are unlikely to advance beyond exploratory significance [8,35].

In summary, prioritizing longitudinal, harmonized, and pathway-level multi-omics research, anchored in clinically relevant outcomes and inclusive study design, offers the most credible approach to translating metabolomic and proteomic insights into precision care for individuals with SCD [21,35].

Conclusions and future perspectives

Metabolomic and proteomic investigations have significantly advanced understanding of the biological processes underlying VOCs in SCD. These studies reveal coordinated perturbations across energy metabolism, redox homeostasis, endothelial activation, inflammation, and coagulation pathways. The reviewed evidence suggests that VOCs arise from dynamic, multisystem interactions rather than from isolated hemoglobin-centric mechanisms. This perspective offers a more integrated framework for biomarker discovery and disease stratification [8,18,21].

Despite these advances, the translation of omics-derived biomarkers into routine clinical practice remains limited. Most reported candidates reflect downstream consequences of acute inflammation or hemolysis rather than predictive or mechanistically causal signals. Few biomarkers have undergone robust longitudinal validation or prospective linkage to clinically actionable endpoints [35,36]. Consequently, no metabolomic or proteomic biomarker is currently suitable for routine clinical decision-making in SCD, underscoring the need for continued methodological refinement and translational realism.

The most credible path toward precision medicine in SCD is longitudinal, harmonized, and pathway-level multi-omics research. Integrating metabolomic and proteomic data with detailed clinical phenotyping, standardized analytical pipelines, and prospectively defined outcomes is essential for distinguishing biomarkers of VOC susceptibility, onset, severity, and treatment response from nonspecific molecular noise [18,22–24,28]. Multi-center consortia and inclusive study designs are particularly important for ensuring statistical power, reproducibility, and global applicability.

Aligning biomarker strategies with real-world clinical workflows and health-system capacity is equally critical. Targeted, pathway-based panels that prioritize robustness, scalability, and feasibility are more likely to influence care than technically sophisticated discovery-omics platforms that cannot be implemented at scale. This consideration matters most in low- and middle-income settings, where the burden of SCD is greatest [35,36].

In conclusion, although metabolomic and proteomic studies have reshaped the conceptual understanding of VOC biology, their ultimate clinical impact depends on deliberate shifts in study design, analytical strategy, and translational intent. Embedding longitudinal sampling, pathway-centric analysis, clinical endpoint integration, and equity-conscious implementation into future research may enable omics-based biomarkers to fulfill their promise of providing more precise, anticipatory, and personalized care for individuals living with SCD.

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