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EDITED BY
Halvard Bönig,
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REVIEWED BY
Marvyn T. Koning,
Leiden University, Netherlands
Andres Felipe Escobar,
Hospital Pablo Tobon Uribe, Colombia

*CORRESPONDENCE
Juan Bautista De Sanctis
juanbautista.desanctis@upol.cz

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A perfect storm: the deadly intersection of sickle cell disease and COVID-19

Arturo José Martí-Carvajal[1,2] and Juan Bautista De Sanctis[3,4]*

[1]Cátedra Rectoral de Medicina Basada en la Evidencia, Universidad de Carabobo, Valencia, Venezuela, [2]Facultad de Medicina, Universidad Francisco de Vitoria, Madrid, Spain, [3]Faculty of Medicine and Dentistry, Institute of Molecular and Translational Medicine, Palacky University., Olomouc, Czechia, [4]The Czech Advanced Technology and Research Institute (Catrin), Palacky University, Olomouc, Czechia

This review critically examines the latest research on the intersection of sickle cell disease (SCD) and COVID-19, highlighting meaningful immunopathological interactions. It reveals significant knowledge gaps, particularly in the analysis of inflammatory markers in clinical studies and the oversight of SCD in malaria-COVID-19 research conducted in African contexts. The investigation explores shared pathophysiological mechanisms, including the cytokine storm phenomenon, vascular complications, and autoimmune responses, which exemplify the perilous interplay between SCD's chronic inflammatory state and the acute inflammatory response triggered by COVID-19. Furthermore, it provides a comprehensive analysis of hyperhaemolysis syndrome (HHS), related autoimmune conditions, and avascular necrosis (AVN) as critical complications affecting SCD patients during the COVID-19 pandemic. The aim is to establish a comprehensive framework for understanding this crucial intersection while proposing vital directions for future research and therapeutic interventions.

KEYWORDS

sickle cell disease, SARS-CoV-2, inflammation, cytokines, cytokine storm

1 Introduction

SCD is characterised by chronic inflammation, endothelial dysfunction, and an increased thrombotic risk, which can be exacerbated by the inflammatory and prothrombotic effects of SARS-CoV-2 infection (1).

Concerns about severe outcomes in this patient population spurred quick research and surveillance efforts globally. Early findings from France, particularly those by Arlet et al. (2), challenged the assumption of uniformly poor outcomes, documenting considerable variability in disease severity and highlighting the importance of early intervention. Azerad et al. (3) reported several atypical presentations with surprisingly favourable

outcomes, emphasising the complexity of this clinical intersection and the need for individualised assessment and management approaches. The paper examined the complex pathophysiological environment affecting multiple organ systems—from acute chest syndrome in paediatric patients (4) requiring significant adaptation of traditional management algorithms, to severe hepatic dysfunction leading to encephalopathy and multi-organ failure (5), and catastrophic neurological events requiring heightened surveillance and prompt intervention (6). A detailed analysis of susceptibility and clinical severity patterns by Sayad et al. (7) reveals complex interactions among genetic factors, environmental influences, and therapeutic interventions. This suggests that while some patients demonstrate remarkable resilience, others face significantly increased risks of severe complications. Special attention is given to vulnerable populations, particularly pregnant women with SCD during the pandemic (8–10). Joseph et al. (8) documented elevated maternal and fetal morbidity rates requiring modified obstetric and haematological management approaches, findings further supported by Gibson et al. (9) and Kolanska et al. (10), emphasising the need for enhanced monitoring and specialised care protocols. Current treatment approaches assess established SCD protocols alongside emerging COVID-19 therapies, highlighting red blood cell exchange transfusion as essential for severe respiratory issues (11), the potential role of disease-modifying therapies such as hydroxyurea (12), and the implementation of standardised screening and management protocols to guide decision-making in various clinical scenarios (13–15).

In an extensive French study, children with SCD had rates of COVID-19 exposure that were similar to those of their healthy peers (13). However, these children did not experience severe complications, which suggests that activation of the basal interferon type I (IFN-I) pathway may help control the virus (13, 14). The humoral immune response in these children appears to be temporary, raising the risk of reinfection (15). The adverse outcomes reported in other studies may be related to disparities in healthcare access or underlying comorbidities, rather than solely due to SCD. Martin et al. (16) explored the unique challenges faced by paediatric populations and analysed mortality patterns, emphasising the influence of healthcare access and socioeconomic factors on survival (16). Additionally, the research addresses autoimmune interactions—including SCD's association with systemic inflammatory diseases, autoimmune haemolytic anaemia, and immune thrombocytopenia—and devastating musculoskeletal complications affecting 50-70% of patients (17), particularly avascular necrosis of the femoral head, where inflammation and vaso-occlusion create a cycle of tissue damage (16, 17). This paper highlights the evolving SARS-CoV-2 variants and SCD pathophysiology, stressing the need for ongoing vigilance and adaptable management strategies (17–19). Emerging evidence indicates that long-term complications require specialised follow-up protocols and rehabilitation strategies to optimise outcomes (18–20). This review focuses on the underlying mechanisms of the pathology, revises the gaps in global health literature and provides an overview of management strategies.

2 Pathophysiological foundation of sickle cell disease

2.1 Molecular and cellular mechanisms

In 1910, in Chicago, Dr James B. Herrick officially described the first clinical case of what would later become known as sickle cell disease (SCD) (21). SCD was the first molecularly characterised disorder. It is defined by a specific mutation in the beta-globin gene at the sixth codon, which leads to the production of abnormal haemoglobin S (HbS) in place of the normal haemoglobin A (HbA) (22, 23). More than 7.5 million people worldwide are affected (24).

When deoxygenated, HbS undergoes polymerisation, resulting in the distortion of erythrocytes into a rigid, sickle-shaped form. This alteration in the morphology and functionality of erythrocytes contributes to several clinical manifestations associated with the disease (25):

1. Vaso-occlusion from rigid cells obstructing microvasculature.
2. Chronic haemolysis due to the premature destruction of sickled erythrocytes.
3. Endothelial activation and damage from repeated exposure to sickled cells
4. Chronic inflammation from ongoing tissue injury and cell damage

The abnormal features of sickle red blood cells (RBCs), which disrupt patients' blood rheology, are responsible for chronic haemolytic anaemia and frequent painful vaso-occlusive crises (VOCs).

2.1.1 Epidemiological context and confounding factors

SCD is most prevalent in malaria-endemic regions, particularly sub-Saharan Africa, where up to 2% of births are affected, as well as in the Mediterranean, the Middle East, and parts of India (24). These areas have unique epidemiological characteristics that influence COVID-19 patterns and complicate the relationship between malaria, SCD, and COVID-19 (24). SCD-endemic regions are primarily lower and middle-income countries with younger populations, lower obesity rates, and housing that is more crowded yet better ventilated than in high-income areas. These factors can affect COVID-19 transmission and severity, potentially obscuring the impact of SCD on COVID-19 susceptibility. However, Dawudi et al. reported, in a meta-analysis, an increased risk of hospitalisation and death in SCD patients (26).

Concurrent malaria exposure may alter immune responses and influence both SCD and COVID-19 outcomes due to shared inflammatory pathways. Limitations in healthcare infrastructure further complicate the management of SCD and the detection of COVID-19, leading to surveillance bias. This highlights the need for carefully designed studies that consider regional epidemiological contexts when examining interactions between SCD and COVID-

19, especially in comparative analyses across different socioeconomic backgrounds.

2.2 Inflammatory state in SCD

Even in steady state, patients with SCD exist in a chronic proinflammatory state characterised by elevated levels of pro-inflammatory cytokines, including IL-1β, IL-6, IL-8, IL-33, and TNF-α (25). This inflammatory milieu is further intensified by dysregulation of anti-inflammatory cytokines, including IL-2, TGF-β, IL-10, IL-27, IL-35, and IL-37 (27). The chronic inflammatory state is characterised by increased expression of adhesion molecules (28) and neutrophil activation, as well as the formation of neutrophil extracellular traps (NETs) (29–31). Additionally, persistent endothelial activation (32) and platelet activation (33, 34) contribute to the hypercoagulable state (35) that characterises SCD. The proinflammatory state facilitates red blood cell alloimmunization in paediatric SCD patients (36).

Chronic inflammation reshapes the hematopoietic landscape, particularly within the bone marrow, affecting monocyte programming, increasing cytokine production, and promoting myeloid skewing. This understanding is essential for grasping why SCD patients are more susceptible to COVID-19-related complications (37). Ferroptosis also plays a crucial role in sickle cell disease, as free iron is essential for the formation of reactive oxygen species (38).

2.3 Pro-Inflammatory mechanisms in SCD

Evidence suggests persistent inflammation is central to SCD pathophysiology, exacerbating endothelial dysfunction, vascular occlusion, and multi-organ failure (39). The pro-inflammatory essence of SCD can be understood through several key mechanistic pathways:

2.3.1 Oxidative stress and endothelial activation

The pathophysiological cascade in SCD is driven by recurrent cycles of hypoxia-reoxygenation, leading to the excessive production of reactive oxygen species (ROS) (40). Oxidative stress triggers endothelial activation, promoting the expression of adhesion molecules such as VCAM-1, ICAM-1, E-selectin, and P-selectin, which facilitate the adhesion of leukocytes and platelets to the vascular endothelium (16, 32). Elevated endothelial-derived extracellular vesicles also contribute to a hypercoagulable state, exacerbating vaso-occlusion (32–34).

2.3.2 Neutrophil activation and NET formation

Neutrophils are major effectors of SCD-associated inflammation. Circulating iron and cell-free haem released during haemolysis activate neutrophils, inducing the formation of NETs, which amplify endothelial damage and vaso-occlusion (41, 42). Targeting NET formation has emerged as a potential therapeutic strategy to mitigate inflammatory exacerbation in SCD (43).

Argueta et al. (44) recently reported the formation of mast extracellular traps in SCD, suggesting that tissue mast cells may also play a role in the disease's physiopathology.

2.3.3 Monocyte dysfunction and cytokine dysregulation

Aberrant monocyte activation plays a central role in SCD inflammation (45–47). Studies have reported an increased prevalence of immature monocyte subsets expressing pro-inflammatory markers such as CD14+CD16- and CD14+HLA-DR- phenotypes associated with impaired immune responses (27, 45–47). These monocytes secrete elevated levels of TNF-α, IL-6, and IL-1β, thereby perpetuating systemic inflammation (46, 47) through the TLR4 pathway (48). The higher expression of TLR4 in SCD patients was inferred to be responsible for the increased secretion of IL-12, IL-17, and IL-10 cytokines, as well as for the increased number of circulating activated CD4+CD19+ lymphocytes (49).

As Felicio et al. (50) demonstrated, B lymphocytes are also crucial in the physiopathology of SCD. B-cell alterations in the memory subpopulation appear to be critical in this process.

T regulatory cells were shown to be increased in paediatric patients with SCD, and treatment with hydroxyurea was able to decrease the amount of T reg (51). Additionally, CD8 and CD8 +CD45RA cells were reduced compared to the controls (52). The decrease in CD8 could reduce SARS-CoV-2 clearance in these patients. T cells can play a crucial role in modulating B1 cells, suggesting that the antibody response to viral infection is affected in SCD (53). Moreover, Marchesani et al. (54) reported, in paediatric patients, lower values of CD4+ T cells (with a higher number of memory and central memory T lymphocytes) with increased frequency of CD8+ T cells (with a predominant naive pattern) and, higher values of CD39+ Tregs and lower HLA-DR+ and CD39- T cells, along with an increased Th17, Th1-17, and Th2 response.

2.3.4 Haeme-mediated inflammation and MicroRNA regulation

Free haem is a potent damage-associated molecular pattern (DAMP) that exacerbates inflammation by upregulating NF-κB and TLR4 signalling pathways. The modulation of haem-induced inflammation through microRNA-loaded liposomes has shown promise in experimental models, with miR-451a and let-7i-5p reducing inflammatory responses and promoting haem clearance via haemopexin and HO-1 (55). In addition, a phase 2 open-label trial with food rich in docosahexaenoic acid has shown promising results in SCD (56).

3 COVID-19 pathophysiology and immune response

3.1 Virology and Cellular Entry

The SARS-CoV-2 virus, first identified in December 2019 in Wuhan, China, primarily enters host cells through the angiotensin-

converting enzyme 2 (ACE2) receptor. This tropism for ACE2 is significant as this receptor plays a crucial role in regulating inflammatory responses through the bradykinin signalling pathway. ACE2 downregulation during infection can lead to dysregulated inflammation (57, 58).

3.1.1 Viral evolution and contemporary relevance

The literature reviewed primarily discusses earlier SARS-CoV-2 variants, particularly the original Wuhan strain, Alpha, and Delta (15–18, 25, 26). These variants exhibited greater virulence than the Omicron subvariants (59). This raises important questions about the relevance of findings for SCD patients and ongoing risk assessment. Despite Omicron's generally reduced virulence in healthy individuals, SCD patients may still face an increased risk of vaso-occlusive crises (VOCs) (60). Their baseline inflammatory conditions and immune dysregulation could exacerbate even mild viral infections. Chronic organ damage and functional asplenia may go beyond variant-specific severity.

Vaccination also complicates the picture; while vaccines help reduce severe disease, SCD patients may have weaker immune responses due to underlying conditions (59) or a lower vaccination rate (60). Most reports have been based on mRNA vaccines, rather than using attenuated or protein vaccines (59). The risk of complications, such as haemolytic-uremic syndrome, persists due to immune evasion by variants and waning immunity. However, antiviral therapy may be a good option for these patients (61).

Mechanistic pathways such as cytokine dysregulation and thrombo-inflammatory responses remain relevant across variants, necessitating a focus on SCD-specific complications alongside acute COVID-19 outcomes in future surveillance.

3.2 Inflammatory cascade in COVID-19

COVID-19 initiates a complex inflammatory cascade characterised by an early innate immune response, where the infection of epithelial cells in the upper respiratory tract triggers mucus production, antiviral metabolites, type I interferons, and other cytokines (55). In severe cases, a dysregulated immune response produces excessive proinflammatory cytokines, including IL-6, IL-1β, IL-8, and TNF-α, along with various chemokines, resulting in widespread inflammation and tissue damage known as cytokine storm (57, 58, 62–68). IL-6 plays a critical role in the response to bacterial infection in SCD (64–67), while IL-8 is increased in patients with SCD (57, 58, 62, 68).

SARS-CoV-2 infection directly and indirectly damages the vascular endothelium, leading to coagulation abnormalities, microvascular thrombosis, and increased vascular permeability (57, 58). The inflammatory cascade extends beyond the respiratory system, affecting multiple organs and systems, including the cardiovascular, neurological, renal, and haematological systems (57, 58, 69, 70). This pathophysiological progression aligns dangerously with the pre-existing inflammatory state in SCD, setting the stage for potentially catastrophic interactions (71–74).

4 Epistemic zones in SCD-COVID-19 research

4.1 Mechanistic insight: foundational understanding

Several key studies provide mechanistic frameworks essential for understanding the SCD-COVID-19 interaction:

Swirski et al. (37) outline a fundamental framework for understanding the increased susceptibility of patients with SCD to complications associated with COVID-19. Their research elucidates how chronic inflammation modifies the haematopoietic landscape, particularly within the bone marrow niche, which subsequently alters monocyte programming and leads to increased cytokine production and myeloid skewing. Within the context of COVID-19, this framework assumes critical importance, as patients with SCD typically exist in a state of immunological activation.

Saxena and Muthu (72) explored the intersection of haematological disruptions and immune dysregulation during COVID-19 relevant to SCD. Dobkin et al. (73) significantly re-examined the evolutionary and immunological effects of red blood cell adaptations to malaria, particularly regarding how these adaptations influence the host response to critical illnesses, such as COVID-19. The authors argue that adaptations such as haemoglobin S, alpha-thalassemia, G6PD deficiency, and Duffy antigen mutations have remapped erythroid immunology across entire populations (73). These report offer a molecular and evolutionary justification for integrating SCD and malaria into the analysis of COVID-19 pathology

4.2 Descriptive silence: the missing mechanisms

Most clinical studies on SCD and COVID-19 demonstrate significant limitations, including the general documentation of clinical presentations and outcomes without analysis of underlying mechanisms, as well as the absence of measurement of inflammatory markers. Several studies observe but do not question. They document presence without meaning, reflecting a recurring epistemic pattern of describing symptoms in inflammatory diseases without addressing inflammation. The patients' physiology is treated as a black box—observed only from the outside (74). Several registry-based studies document hospitalisations, oxygen requirements, and VOC in SCD patients with COVID-19 but avoid interpreting these outcomes in biological terms. This represents a missed opportunity to understand the pathophysiological interaction between these conditions.

4.3 Africa without malaria or SCD: a geographic and conceptual omission

Perhaps the most revealing epistemic gap is found in studies conducted in Africa that examine COVID-19 and malaria without considering SCD:

Woodford et al. (75) present an extensive longitudinal cohort study in Mali evaluating whether recent *Plasmodium falciparum* infection affects susceptibility to COVID-19 or alters clinical outcomes. However, nowhere in this comprehensive study—conducted in a region with high prevalence of SCD and sickle cell trait—is there any mention of "sickle," "haemoglobinopathy," or "SCD." This reveals a significant epistemic flaw: sickle cell disease is hidden in vague categories, dismissed as analytically irrelevant, or overlooked in research.

Achan et al. (76) conducted a multicenter, prospective cohort study in Uganda to investigate the effect of recent malaria exposure on COVID-19 outcomes. Among the 597 hospitalised COVID-19 patients studied, they observed elevated inflammatory markers associated with poorer outcomes. Nevertheless, there is a total absence of any mention of SCD, despite Uganda having a significant prevalence of sickle cell trait exceeding 13% in many regions. Excluding SCD from COVID-19 research in areas with high prevalence and known interactions with malaria is not just a data gap, but an epistemic erasure with clinical implications.

Feit et al. (77) conducted a methodologically robust 2.5-year longitudinal study involving 178 patients diagnosed with COVID-19 and 356 matched controls. Similarly, Bodla et al. (78) analysed 66,415 adult patients hospitalised for sickle cell crises, documenting an adjusted odds ratio of 8.49 for in-hospital mortality with concurrent COVID-19 infection. Despite the fact that the studies had a broad temporal scope, sample size, and good statistical analysis, their design limited the ability to explore mechanistic insights, evaluate inflammatory biomarkers, or generate hypotheses about pathophysiological interactions. Thus, the resulting dataset offers limited guidance for clinical intervention or theoretical advancement.

5 Immunopathogenesis in SCD-COVID-19 Interaction

5.1 Synergistic inflammatory cascades

The interaction between SCD and COVID-19 culminates in a perilous synergy within inflammatory processes that extends beyond the baseline inflammatory priming present in SCD patients. Upon exposure to SARS-CoV-2, this already activated system elicits an exaggerated release of inflammatory mediators (57, 58). The onset of COVID-19 in SCD patients may trigger increased haemolysis, releasing additional free haem that further stimulates inflammatory pathways (79). This interconnected relationship highlights the significantly increased mortality risk seen in patients with both conditions. COVID-19 and splenic dysfunction alter red blood cell behaviour and vesiculation, thereby impairing oxygen delivery and increasing the risk of thrombosis (80). B cells play a pivotal role in both the pathophysiology of COVID-19 (57, 58) and exhibit enhanced activity in SCD (48, 78), warranting further investigation of this intersection.

SCD and COVID-19 damage the endothelium through distinct yet complementary mechanisms, which may result in catastrophic vascular dysfunction (81–84). This interconnected relationship highlights the significantly increased mortality risk seen in patients who have both conditions. One study shows that parvovirus B19-induced aplastic anaemia in SCD worsens immune dysregulation, raising concerns about chronic inflammation. Another study highlights that COVID-19 and splenic dysfunction alter the behaviour and vesiculation of red blood cells, impairing oxygen delivery and increasing the risk of thrombosis (80, 82).

Additionally, B cells play a pivotal role in the pathophysiology of COVID-19 (57, 58) and can exhibit enhanced activity in SCD, as previously documented by Felicio et al. (50) and Dhawan (83). Further exploration in this area is essential to uncover vital insights.

5.2 Historical and current perspectives on cytokine dysregulation

Understanding the involvement of cytokines in SCD has evolved significantly over the past three decades. Early work by Chappey et al. (84) established the first experimental frameworks using endothelial cell cultures to study vascular dysfunction in SCD, demonstrating how cytokines such as TNF-α and IL-1 can activate endothelial cells and influence the expression of adhesion molecules. A breakthrough came in 1999 when Croizat and Nagel (85) identified distinct cytokine response patterns related to HbF levels, finding that patients with HbF levels below 8-9% showed different cytokine profiles compared to those with higher HbF levels, particularly in terms of SCF and TGF-β concentrations.

The role of TGF-β1 has been further elucidated by Santiago et al. (86), who demonstrated that its plasma levels are significantly elevated in HbSS patients compared to HbSC and healthy controls. This cytokine correlates with monocyte activation, leukocyte counts, and inflammatory mediators such as TIMP-1 and MMP-9, providing mechanistic insights into the immunopathological heterogeneity of SCD and its association with vascular dysfunction (86). These findings suggest that TGF-β1 contributes to vascular remodelling, vasculopathy, angiogenesis, and inflammatory processes in SCD patients, which may become particularly relevant in SARS-CoV-2 infection.

Early advances in understanding cytokine functions in SCD emerged in the early 2000s. Schnog et al. (87) investigated sVCAM-1 levels in adults with SCD, establishing connections between adhesion molecules and disease severity. Assis et al. (88) demonstrated how specific cytokines influenced sickle neutrophil adhesion to fibronectin, whilst Brittain and Parise's (89) review consolidated the growing knowledge about plasma factors and cytokines in SCD, highlighting the emerging role of platelets in cytokine release and the importance of angiogenic and inflammatory factors.

Modern understanding of cytokine involvement in SCD has benefited from advanced technical capabilities. Paulson et al. (90) introduced new perspectives on stress erythropoiesis and its relationship with cytokine signalling. Recent studies have identified the crucial role of inflammatory dendritic cells in regulating immune responses in SCD. Sesti-Costa et al. (91) demonstrated that inflammatory dendritic cells (CD14+ DCs) are key contributors to immune dysregulation in SCD, producing the

cytokines IL-6, IL-8, and IL-17, which are critically involved in both SCD and severe COVID-19 cases. Their study suggests that an upregulated haeme oxygenase (HO-1) pathway in monocytes promotes the differentiation of these inflammatory dendritic cells (DCs), potentially exacerbating endothelial inflammation and thrombo-inflammatory complications in SCD patients infected with SARS-CoV-2 (91).

The cytokine interplay between SCD and COVID-19 involves several shared pathways. Chiang et al. (71) described the shared inflammatory mechanisms of thrombo-inflammation in SCD and COVID-19, particularly in the activation of the coagulation cascade, endothelial damage, and platelet-leukocyte adhesion. The role of thromboxane A2 (TxA2) and lipid mediators in both diseases is emphasised as a potential therapeutic target, with platelet-derived microvesicles potentially exacerbating both vaso-occlusive crises in SCD and endothelial injury in COVID-19 (71).

Emerging evidence suggests that basal interferon-1 activation in SCD may confer a protective advantage against severe COVID-19 manifestations (92–94). Interferon signalling in SCD patients modulates the immune response, potentially mitigating the full impact of a SARS-CoV-2-induced cytokine storm (94). In contrast to previous assumptions that SCD patients have a heightened vulnerability to COVID-19, some studies report that specific interferon-related mechanisms may confer protective effects, which is counterbalanced by exacerbated thrombo-inflammatory responses (94, 95).

Several cytokine-targeting therapies have shown promise in both SCD and COVID-19, including tocilizumab (an IL-6 inhibitor), fostamatinib (an SYK inhibitor), regadenoson (an A2A receptor agonist), and vitamin D modulation (96–99). Additionally, hydroxyurea's established anti-inflammatory and cytoprotective effects in SCD may also potentially mitigate inflammation in COVID-19 (95). Targeting the TGF-β1 and TIMP-1/MMP-9 axis could enhance therapeutic strategies to reduce cytokine-driven complications in both conditions (86, 89).

The role of platelet activation in the pathophysiology of both SCD and COVID-19 has led to increasing interest in antiplatelet therapies as potential disease-modifying agents. Martí-Carvajal et al. (100) conducted a systematic review assessing the clinical benefits and risks of antiplatelet agents in preventing VOC events in SCD. Their analysis of five randomised controlled trials involving 747 participants examined the effects of prasugrel, ticagrelor, crizanlizumab, and aspirin (100). However, due to the high risk of bias and the heterogeneity of the study populations, the authors concluded that there is insufficient evidence to support or refute the routine use of antiplatelet agents in preventing VOCs.

Future research should focus on cytokine-based biomarkers for risk stratification and the development of targeted therapies. Advances in genetic susceptibility studies have shed light on the role of cytokine polymorphisms in determining the severity of both SCD and COVID-19. Additionally, novel anti-inflammatory adenosine pathway modulators warrant further investigation as therapeutic candidates for managing the cytokine-mediated complications that characterise the intersection of these two conditions.

5.3 Resolution of inflammation: role of specialised pro-resolving mediators

Recent research underscores the protective effects of 17R-Resolvin-D1 (17R-RvD1) in alleviating cardiovascular dysfunction associated with SCD. 17R-RvD1 has diminished neutrophil-mediated cardiac hypertrophy and fibrosis by modulating the NF-κBp65 and TGF-β1/Smad2–3 signaling pathways (101). This finding supports the therapeutic potential of pro-resolving lipid mediators in managing SCD, which may be especially pertinent in hyperinflammation induced by COVID-19 (101, 102).

5.4 Anti-inflammatory cytokine modulation

The existing imbalance between pro-inflammatory and anti-inflammatory cytokines SCD has generated considerable interest in targeting pathways that enhance the activity of IL-10, TGF-β, and IL-27 (30, 103). Recent studies suggest that dietary interventions, particularly omega-3 fatty acids and vitamin D supplementation, may help mitigate inflammation and reduce the frequency of VOCs (30, 57, 103–105). These strategies may also alleviate the cytokine storm associated with severe COVID-19 in patients with SCD.

5.5 Redox-based interventions and antioxidant therapy

Nitro-fatty acids have shown promise in preclinical models, exerting anti-inflammatory effects by modulating transcription factors and reducing endothelial dysfunction (106). Antioxidant therapies targeting ROS-induced vascular injury may hold potential as adjunctive treatments for SCD patients with COVID-19, particularly given the oxidative stress that characterises both conditions (107, 108).

5.6 Ferroptosis at the crossroads of sickle cell disease and COVID-19

Ferroptosis, an iron-dependent form of regulated cell death driven by lipid peroxidation, has emerged as a crucial player in the pathophysiology of SCD and may represent a significant mechanistic link to COVID-19 complications (109). Characterised by chronic haemolysis and iron dysregulation, SCD creates an environment conducive to ferroptotic damage. Excess haeme promotes ferroptosis via haeme oxygenase-1 upregulation, exacerbating cardiac complications in SCD patients (109). Moreover, ferroptosis-driven lipid peroxidation contributes to endothelial dysfunction and systemic inflammation, highlighting its significance as a potential therapeutic target (109–114).

The intersection of SCD and COVID-19 may magnify ferroptotic stress through multiple converging pathways (109–114). First, chronic haemolysis in SCD releases free haem, which upregulates haem oxygenase-1 (HMOX1), a driver of iron release and subsequent

ferroptosis (110). Second, SARS-CoV-2-induced hyperinflammation further perturbs iron homeostasis, increasing ferroptotic susceptibility (78). Third, endothelial dysfunction, a shared feature of both conditions, may be exacerbated by ferroptotic endothelial cell death, contributing to vasculopathy, thrombosis, and multiorgan failure (109, 111–114).

Recent evidence suggests that the transsulfuration (TSS) pathway is a primary defence mechanism against ferroptotic stress in SCD by maintaining cysteine availability for glutathione biosynthesis (115). Cystathionine beta-synthase (CBS) activation via NRF2-mediated epigenetic modifications significantly enhances cellular antioxidant capacity, reducing ferroptotic damage in erythroblasts (115). This proposed mechanism influences chromatin architecture and ferroptosis susceptibility, with findings indicating that NRF2 regulates L-2-hydroxyglutarate (L2HG) metabolism. Koklesova et al. (116) identified homocysteine as a marker for tailored treatment in SARS-CoV-2 infection.

Beyond erythrocyte dysfunction, ferroptosis plays a key role in organ pathology in SCD. GBT1118, a voxelotor analogue, mitigates sickle hepatopathy by reducing iron overload, inflammation, and fibrosis, thereby limiting ferroptotic activity (117). Similarly, leonurine, a natural alkaloid, protects against iron-induced hepatotoxicity by upregulating NRF2 and suppressing NF-κB-mediated inflammation, reinforcing the interplay between antioxidant defence mechanisms and ferroptosis regulation (117, 118).

Given the central role of ferroptosis in SCD-COVID-19 pathophysiology, targeted interventions to mitigate ferroptotic stress may offer therapeutic benefit. Ferroptosis inhibitors such as ferrostatins, liproxstatins, and iron chelators (e.g., deferoxamine) have shown promise in preclinical models (119–121). Additionally, upregulation of GPX4 via pharmacological agents or nutritional strategies (e.g., selenium supplementation (122) may counteract ferroptotic damage (119–121). Emerging gene therapy approaches targeting ferroptosis-associated pathways could provide novel avenues for intervention in this high-risk population (119–121).

This mechanistic insight underscores the urgency of integrating ferroptosis-targeted therapies into clinical strategies for managing SCD patients infected with SARS-CoV-2 (119–123). Although this study focuses on COVID-19, its findings on ferroptosis may have translational relevance for SCD, particularly in advancing understanding of the shared mechanisms of inflammation and oxidative stress in both conditions, and in exploring novel combined therapeutic strategies (119–123).

Future research must prioritise translational studies to validate these findings and develop effective interventions to mitigate ferroptosis-driven complications in this vulnerable population.

5.7 Vascular dysfunction and coagulopathy

The vascular endothelium represents the critical interface between SCD and COVID-19 pathophysiology. In SCD, chronic exposure to sickled erythrocytes, free haem, and inflammatory cytokines generates endothelial dysfunction through recurrent cycles of hypoxia-reoxygenation, leading to excessive production of ROS (39). This oxidative stress triggers endothelial activation, promoting the expression of adhesion molecules such as VCAM-1, ICAM-1, E-selectin, and P-selectin, which facilitate the adhesion of leukocytes and platelets to the vascular endothelium (16, 32). Elevated endothelial-derived extracellular vesicles contribute to a hypercoagulable state, exacerbating vaso-occlusion (32–34). COVID-19 exacerbates this dysfunction by directly infecting endothelial cells through ACE2 receptors and triggering widespread endothelial injury via inflammatory mediators, complement activation, and NETs (57). Neutrophils, activated by circulating iron and cell-free haem released during haemolysis, form NETs that amplify endothelial damage and vaso-occlusion (41, 42).

High-mobility group box 1 (HMGB1) regulates inflammation and promotes platelet activation via Toll-like receptor 4 (TLR4) (124). HMGB1-induced platelet activation involves ADP-dependent P2Y12 (purine receptor) signalling, and HMGB1 sensitises platelets for ADP signalling (125). This synergistic interaction between ADP and HMGB1 enhances the understanding of thromboinflammatory signalling in SCD and provides insights for therapeutic P2Y12 inhibition (124, 125).

5.8 Pulmonary vulnerability

The lungs represent a particular point of vulnerability in the SCD-COVID-19 interaction:

Acute chest syndrome (ACS) is already a leading cause of mortality in SCD, characterised by pulmonary infiltrates, hypoxemia, and respiratory distress. The pathophysiology of ACS involves sickling within the pulmonary vasculature, fat embolism resulting from bone marrow infarction, and inflammation triggered by infection (126, 127).

Asthma, a common comorbidity, affects up to 48% of SCD patients, exacerbating risks of acute chest syndrome, stroke, and VOCs. Its coexistence reflects complex inflammatory interactions, with studies showing altered cytokine profiles (e.g., elevated IL-6, IL-8) and heightened airway reactivity (126, 127). Recognising this interplay is critical for multidisciplinary management and improved outcomes in affected individuals.

COVID-19 primarily affects the lungs through direct viral infection of pneumocytes, inflammation-induced alveolar damage, and microvascular thrombosis (57, 58).

The clinical presentations of these conditions can overlap, making diagnosis and management more complicated. More importantly, the underlying mechanisms can synergise, with COVID-19 potentially triggering and severely exacerbating ACS through:

Hypoxemia that triggers sickling; 2) Inflammatory activation of adhesion molecules; 3) Endothelial injury; 4) Hypercoagulability, and 5) Cytokine storm.

This interaction may explain the significantly increased mortality observed in co-affected patients (57, 58).

5.9 Hyperhaemolysis syndrome: a critical complication in the context of COVID-19

Hyperhaemolysis syndrome (HHS) in SCD is a significant example of immune-mediated haemolysis, where both transfused and autologous red blood cells (RBCs) are rapidly destroyed, leading to severe anaemia. The emergence of SARS-CoV-2 may exacerbate the chronic pro-inflammatory state in SCD, thereby increasing the severity of hyperhaemolysis episodes.

5.9.1 Considerations and diagnostic variability

It is worth noting that inconsistencies in the diagnostic criteria for HHS across the literature significantly impact the interpretation of findings (128–133). Some studies apply stringent criteria requiring a post-transfusion haemoglobin concentration lower than the pre-transfusion level with evidence of donor and recipient red cell destruction. In contrast, others employ more lenient definitions (130, 131). This diagnostic heterogeneity potentially explains some of the variability in reported therapeutic responses and complicates efforts to establish whether COVID-19-associated HHS constitutes a distinct clinical entity.

The current evidence base is insufficient to delineate specific subtypes of COVID-19-associated HHS versus traditional HHS in SCD. Cases reported demonstrate overlapping and distinctive characteristics; however, larger cohorts with detailed immunological characterisation would be necessary to justify a distinct classification system.

5.9.2 Immunopathological mechanisms in COVID-19-associated HHS

5.9.2.1 Complement dysregulation

The role of complement dysregulation in COVID-19 and long COVID-19 is particularly striking (132, 133). Studies demonstrate that SARS-CoV-2 triggers the activation of the alternative pathway, leading to the deposition of the C3 and C5b-9 membrane attack complex (MAC) on red blood cells (RBCs) (134–138). This mechanism parallels findings in patients experiencing severe HHS (138, 139), where uncontrolled complement activity accelerates RBC clearance and contributes to profound anaemia.

Whilst this mechanistic overlap is compelling, it is essential to acknowledge that direct evidence examining complement activation in patients with concurrent COVID-19 and SCD experiencing HHS remains limited (137, 138). Most inferences are drawn from separate bodies of literature on COVID-19 immunopathology and HHS in SCD, with a paucity of studies directly measuring complement components and activation products in this specific patient population.

In a report by Ita et al. (135), a teenage patient with SCD developed a spontaneous extradural haematoma during a vaso-occlusive crisis, with concomitant hyperinflammation, thrombotic microangiopathy, and HHS. The rapid deterioration of this patient despite conventional management necessitated the use of eculizumab, a C5 inhibitor, which ultimately reversed the cascade of complement-mediated destruction (134–138). The implication is clear: targeting complement activation could offer a lifeline in patients experiencing HHS in COVID-19. However, this represents a single case report, and the absence of controlled studies limits the strength of conclusions that can be drawn regarding the efficacy of this approach.

5.9.3 Macrophage overactivation and cytokine dysregulation

Macrophages play a key role in inflammation in both SCD and COVID-19 (139, 140).

Madu et al. (141) reviewed the mechanism by which activated macrophages are responsible for HHS. They demonstrated that changes in the red blood cell membrane resulted in immunological reactions against exposed membrane phospholipids in the erythrocytes (141). Integrin α4β1 in SCD erythrocytes, binding to VCAM-1 in macrophages, and ICAM-4, expressed in transfused erythrocytes, binding to CD11c/CD18 in macrophages, are critical in macrophage activation in HHS syndrome (80).

Beyond complement dysregulation, macrophage overactivation is a central driver of hyperhaemolysis in SCD (139). The phenomenon of macrophage priming in COVID-19 is well recognised, with IL-6 and IFN-γ implicated in the heightened phagocytic activity observed in severe cases (139–141). This cytokine surge may potentiate the excessive clearance of both transfused and autologous RBCs in HHS, a hypothesis supported by the findings of Fuja et al. (142), who documented a patient with SCD and recent COVID-19 hospitalisation presenting with HHS. This patient exhibited a complex alloimmune and autoimmune antibody profile, including anti-Fya, anti-Fyb, and anti-Lea, as well as strong cold agglutinins. The administration of tocilizumab, an IL-6 receptor antagonist, stabilised the patient's haemoglobin levels, marking one of the first documented cases of successful IL-6 blockade in post-COVID-19 hyperhaemolysis (80, 142–144). This observation reinforces that immune hyperactivation in COVID-19 patients with SCD serves as a precipitating factor for severe HHS episodes, and that early immunomodulation may prevent catastrophic haemolysis.

However, it is worth noting that the literature has not adequately addressed potential contradictions between studies (80, 142–144). The variability in response to specific therapies could indicate heterogeneity in underlying mechanisms or differences in the definitions used for HHS (129, 130). The absence of comparative studies also limits our ability to determine whether specific immunological signatures might predict response to particular therapeutic interventions.

5.10 Emerging therapeutic paradigms for HHS in the COVID-19 context

5.10.1 Complement inhibition

Using eculizumab in HHS represents a targeted approach to interrupting the complement cascade, potentially limiting intravascular and extravascular haemolysis. Whilst case reports

suggest promising outcomes, several limitations must be considered:

- Significant cost implications, which result in limited availability in many healthcare settings.
- Increased risk of meningococcal infections necessitating prophylaxis
- Absence of comparative efficacy data versus established therapies

The evidence base for eculizumab in other complement-mediated haemolytic disorders such as paroxysmal nocturnal haemoglobinuria (PNH) shares similar limitations (137, 145). A Cochrane review by Martí-Carvajal et al. (146) highlighted the paucity of high-quality evidence supporting the use of eculizumab in PNH, with conclusions based on a single small trial that had a risk of bias due to attrition and selective reporting (146). These parallels underscore the need for robust clinical trials before widespread implementation of complement inhibition in HHS.

5.10.2 Cytokine blockade

Applying tocilizumab for IL-6 blockade in HHS follows the recognition of hypercytokinaemia as a feature of both severe COVID-19 and HHS. The successful case reported by Fuja et al. (142) provides preliminary support for this approach, but important caveats include:

- There is limited evidence base with HHS.
- Potential for increased infection risk in an already vulnerable population.
- Uncertain optimal timing of administration in the disease course.
- Cost and accessibility concerns in resource-limited settings.

5.10.3 Alternative oxygen carriers

Alternative oxygen carriers provide a novel therapeutic approach for patients in whom conventional transfusion strategies prove futile. Mei et al. (145) reported three cases in which polymerised haemoglobin-based oxygen carriers (HBOC-201) were deployed under expanded access protocols, successfully stabilising patients who were otherwise refractory to transfusion therapy. This finding is particularly relevant in the context of COVID-19, where alloimmunization and transfusion restrictions may limit treatment options for patients experiencing severe hyperhaemolysis (143, 147). The ability to sustain oxygen delivery without further exacerbating immune-mediated haemolysis represents a crucial advance in managing HHS, especially in the context of emerging viral threats.

Key limitations include:

- Experimental status with limited availability
- Potential adverse effects include hypertension and nephrotoxicity
- Unknown long-term safety profile
- Regulatory hurdles to widespread implementation

5.10.4 JAK inhibition: a theoretical avenue

The advent of JAK inhibitors as potential modulators of immune-driven haemolysis adds another layer to this discussion. The inhibitors have been proposed for the treatment of thalassemia (147) and haemophagocytic lymphohistiocytosis.

Recent preclinical studies suggest that ruxolitinib, a JAK1/2 inhibitor, may attenuate macrophage-mediated haemolysis by dampening pro-inflammatory signalling cascades (148, 149). Although clinical data remain limited, the theoretical underpinnings of JAK inhibition in HHS warrant further exploration, particularly in the subset of patients with post-viral immune activation.

5.10.5 N-acetylcysteine treatment

The proposal to use N-acetylcysteine as an antioxidant has been discussed for many years, as reviewed by Wand and Zennadi (150). Nur et al. (151) evaluated treatment in SCD years ago in a small clinical trial; however, contrasting results were reported (152).

N-acetylcysteine has been used in COVID-19 patients (153), with a decrease in C-reactive protein and D-dimer levels. The potential use of N-acetylcysteine in viral and lung inflammation, aside from COVID-19, should benefit SCD patients (107); however, well-designed clinical trials are needed.

5.11 Autoimmunity in SCD: implications for COVID-19 patients

The interplay between SCD and autoimmunity (154, 155) represents an important but often overlooked dimension of disease pathophysiology, particularly relevant to patients with SARS-CoV-2 infection (156). Recent studies have highlighted the association between SCD and various autoimmune phenomena, including systemic inflammatory diseases (SIDs) (157), autoimmune haemolytic anaemia (AIHA) (158, 159), and immune thrombocytopenia (ITP) (160, 161).

The critical issue is that autoimmune responses generate a secondary immune deficiency, which is responsible for the impaired antiviral response (155–157). It would be interesting to analyse how many SCD patients have prolonged COVID-19 and what clinical characteristics are observed in long-term studies. In addition, monitoring antibodies to viral proteins and boosting vaccinations may also provide new elements to study in SCD.

5.11.1 Immune dysregulation and chronic inflammation

The chronic inflammatory state characteristic of SCD serves as a precursor to autoimmunity through several mechanisms (162). Haemolysis-induced oxidative stress, endothelial dysfunction, and recurrent VOCs collectively create an environment conducive to immune dysregulation, leading to aberrant autoantibody production and immune-mediated cytopenias (163–166). Elevated

levels of pro-inflammatory cytokines such as IL-6, TNF-α, and IL-18 have been implicated in the pathogenesis of SCD and autoimmune conditions (69, 70, 163). This creates a concerning overlap with the cytokine profiles observed in severe COVID-19, which is particularly relevant for COVID-19 patients with SCD, as the virus-induced cytokine storm may amplify pre-existing immune aberrancies and potentially trigger or exacerbate autoimmune complications. The dysregulated release of cytokines in response to SARS-CoV-2 infection could tip the delicate balance in SCD patients toward autoimmune manifestations, further complicating their clinical course.

5.11.2 Autoimmune cytopenias and COVID-19

AIHA and ITP are increasingly reported in SCD patients and represent significant clinical challenges when they occur in the context of SARS-CoV-2 infection (164). AIHA in SCD is often refractory to conventional immunosuppressive therapies but has shown responsiveness to proteasome inhibitors, such as bortezomib, as demonstrated by Alanssari et al. (164). Similarly, cases of ITP in SCD have demonstrated positive responses to corticosteroids, highlighting the immune-mediated nature of these cytopenias, as noted by Alkhars et al. (165).

The emergence of autoimmune cytopenias after SARS-CoV-2 infection is particularly concerning for SCD patients, as it complicates their already fragile haematological status. Recent case reports highlight COVID-19-related autoimmune cytopenias in the general population, raising alarm about severe outcomes in SCD patients with compromised haematopoiesis.

5.11.3 Pathophysiological mechanisms and COVID-19 interactions

Several key pathophysiological mechanisms link SCD, autoimmunity, and COVID-19:

1. Complement dysregulation: Deficiencies in complement regulatory proteins contribute to increased autoimmune susceptibility in SCD. Abnormal activation of the complement cascade leads to increased opsonisation and immune complex deposition, exacerbating both haemolysis and systemic autoimmunity, as described by Floch et al. (166). SARS-CoV-2 infection has been shown to activate the complement system (167, 168), potentially creating a synergistic effect that increases the risk of autoimmune complications in SCD patients (169).
2. T cell and B cell aberrancies: SCD patients exhibit skewed T and B cell subsets, characterised by an increase in memory T cells and a reduction in regulatory B cells (52, 170, 171) and immature NK cells (172). This imbalance promotes chronic immune activation and may contribute to alloimmunisation following transfusion therapy. Memory T stem cells (TSCMs) have been identified as key drivers of autoimmunity in SCD, linking chronic inflammation to persistent immune activation, as reported by Fazeli et al. (173). SARS-CoV-2 infection can further disrupt T and B cell homeostasis, potentially exacerbating these pre-existing immune abnormalities (57, 58, 156).
3. Red blood cell alloimmunization and hyperhaemolysis: The risk of alloimmunization in SCD patients undergoing transfusion therapy during COVID-19 may be heightened due to the pro-inflammatory milieu. Alloantibody formation bridges transfusion-related immune responses and systemic autoimmunity, as noted by Pirenne and Pondarré (174). HHS is a severe complication of alloimmunisation, sharing mechanistic similarities with immune-mediated haemolysis seen in AIHA. It may be triggered or worsened by COVID-19-induced inflammation.

5.11.4 Therapeutic considerations for autoimmunity in SCD-COVID-19 patients

The management of autoimmune complications in SCD patients with COVID-19 requires careful consideration of both conditions:

1. Immunomodulatory interventions: The use of immunosuppressive agents, including corticosteroids, rituximab, and IVIG, remains crucial in managing autoimmune complications in SCD. However, their application in the context of active SARS-CoV-2 infection must be cautiously approached due to potential suppression of antiviral immune responses. Recent case reports by Alanssari et al. (164) highlight the efficacy of bortezomib in refractory AIHA, suggesting a role for proteasome inhibition in modulating autoimmune haemolysis in selected cases. Additionally, tocilizumab has been explored as treatment for severe COVID-19 and SCD-associated autoimmune manifestations, as described by De Luna et al. (175), representing a therapeutic convergence point.
2. Coexistence of SCD and systemic autoimmune disorders: Systemic lupus erythematosus (SLE), juvenile idiopathic arthritis (JIA), and inflammatory bowel disease (IBD) have been documented in paediatric and adult SCD cohorts (23, 161, 175). Inflammatory arthritis in SCD can mimic musculoskeletal manifestations of SCD, complicating diagnosis. Although treatments such as steroids, methotrexate, and anti-TNF agents are applied similarly, the heightened risk of infections and SCD crises requires tailored therapeutic strategies to ensure patient safety (19, 155, 176, 177). These conditions complicate diagnosis and management due to overlapping clinical features such as arthropathy, anaemia, and systemic inflammation. Notably, patients with concurrent SCD and SLE exhibit significant dysfunction of regulatory B cells, leading to a loss of immune tolerance, as demonstrated by Boulassel et al. (177). These patients may be particularly vulnerable to COVID-19 due to the triple hit of SCD, autoimmunity, and viral infection on their immune system function (177).

3. Alloimmunisation prevention and transfusion strategies: Genotypic matching for red blood cell transfusions is increasingly essential for SCD patients requiring transfusion support during SARS-CoV-2 infection (178). According to Wong et al. (179), HLA class II allelic polymorphisms have been identified as key genetic determinants influencing alloantibody formation, highlighting the importance of personalised transfusion strategies. Extended phenotype matching should be prioritised whenever possible to minimise the risk of alloimmunization and subsequent autoimmune complications.
4. Targeting the complement and cytokine axis: Emerging therapies targeting complement activation and pro-inflammatory may address both the virus-induced hyperinflammation and the autoimmune sequelae, potentially improving outcomes in this vulnerable patient population, as suggested by Poutrel et al. (180).
5. The coexistence of SCD, autoimmunity, and COVID-19 presents a complex clinical challenge that demands a multidisciplinary approach. Future research should aim to clarify the impact of COVID-19 on autoimmune manifestations in SCD and develop targeted therapies for this triad.

5.12 Splenic complications: the epicentre of a perfect storm

The spleen, already compromised by the relentless onslaught of vaso-occlusive crises in SCD, becomes the epicentre of a harrowing sequence of events upon SARS-CoV-2 infection, amplifying the morbidity and mortality risks inherent to both conditions (181).

The spleen is pivotal in host immunity, serving as a filtration site for abnormal erythrocytes and a key orchestrator of humoral defence (182). However, in SCD, recurrent microvascular occlusion precipitates progressive infarction and fibrosis, leading to functional autosplenectomy early in life (183). This leaves SCD patients profoundly vulnerable to infections, particularly by encapsulated bacteria such as Streptococcus pneumoniae and *Haemophilus influenzae* (184).

Superimposed on this immunological deficit, SARS-CoV-2 infection precipitates severe B-cell depletion within the splenic tissue, mirroring the immunoparesis observed in sepsis (185). Reductions in memory B cells critically impair antibody responses, predisposing individuals to secondary bacterial infections and prolonged viral persistence (186–188). The dual insult of chronic immunodeficiency from SCD and COVID-19-induced lymphoid atrophy culminates in a perilous state of immune collapse, rendering these patients extraordinarily susceptible to overwhelming infection and sepsis.

5.12.1 A thrombotic maelstrom: the catastrophic hypercoagulability of COVID-19 in SCD

SCD is intrinsically prothrombotic, with endothelial dysfunction, platelet activation, and chronic inflammation fostering a state of persistent hypercoagulability (187, 188). COVID-19 further exacerbates this hypercoagulable milieu by inducing widespread endothelial injury, cytokine-driven thrombogenesis, and the formation of microvascular thrombi (188). The spleen, already a site of extensive microvascular compromise in SCD, becomes acutely vulnerable to thrombotic insults, culminating in widespread infarction and accelerated splenic atrophy (189).

Clinical reports highlight the increased incidence of splenic infarction in COVID-19 patients, attributed to systemic endothelial dysfunction and disseminated microthrombosis (190). In the context of SCD, where splenic infarction is an established consequence of chronic vaso-occlusion, the superimposed thrombotic burden of SARS-CoV-2 infection threatens to accelerate the trajectory towards complete autosplenectomy and catastrophic multiorgan failure.

5.12.2 The spectre of acute splenic sequestration and rupture

Though many adults with SCD have lost splenic function due to autosplenectomy, residual splenic activity persists in some individuals, leaving them susceptible to acute splenic sequestration crisis (ASSC)—a phenomenon wherein large volumes of sickled erythrocytes become entrapped within the spleen, precipitating profound anaemia, hypovolaemic shock, and sudden circulatory collapse (190–192). COVID-19, which can exacerbate hypoxia and trigger erythrocyte adhesion, may act as a potent precipitant of ASSC, escalating the risk of rapid haemodynamic deterioration (192).

Moreover, emerging case reports have documented instances of spontaneous splenic rupture in patients with severe COVID-19 attributed to inflammation-induced architectural fragility and microvascular injury (193–195). In an SCD patient harbouring residual splenic tissue, the combined effects of vaso-occlusion, thrombotic congestion, and viral endothelial aggression could precipitate catastrophic splenic rupture, a rare yet potentially fatal sequela necessitating emergent surgical intervention.

5.13 Global variability of splenic complications and co-infections: implications for the SCD–COVID-19 interaction

Splenic dysfunction in SCD is not a monolithic entity. Instead, it is shaped by complex interactions between genetic predispositions, co-infectious landscapes, and systemic immunological burdens, which vary dramatically by geography. This heterogeneity has become increasingly salient in the context of COVID-19 as emerging data reveal that splenic status may critically influence disease outcomes and vaccine responses (193–195).

A systematic review by Ladu et al. (194) covering 14 African nations documented that splenomegaly persists into late childhood and even adulthood in substantial proportions of individuals with SCD, challenging the canonical view of early and universal auto-

splenectomy. Acute splenic sequestration crises (ASSC) and hypersplenism were less frequent, while data on functional splenic capacity were almost entirely lacking, exposing a key blind spot in regional clinical research.

Tubman and Makani (195) coined the term "turf war" to describe the immunological tension between SCD and endemic malaria. In such regions, the spleen may remain enlarged but functionally compromised, particularly in its marginal zone B cell compartment, which undermines host defence against encapsulated bacteria and possibly viral pathogens. Malaria may delay autosplenectomy yet induce an altered immune phenotype.

The concept of immune decoupling is highlighted by Joice et al. (196), who found that HIV-positive paediatric patients with malaria had higher splenic parasite burdens and reduced phagocytic clearance, despite intact spleen structure. While SCD was not included in the study, the observed macrophage dysfunction and immunological stasis in the red pulp provide insights into the immune vulnerabilities of SCD patients exposed to SARS-CoV-2.

Insights from COVID-19 highlight important immunological issues. A review by Lenti et al. (197) described how SARS-CoV-2 targets the spleen, resulting in a significant depletion of IgM memory B cells, a sign of functional hyposplenism. This damage, confirmed by postmortem studies, persists even after clinical recovery, raising concerns about immune memory. Lenti et al. (197) refer to this as a "Janus-faced issue": patients with existing asplenia or hyposplenism face higher risks of severe COVID-19. At the same time, COVID-19 may also induce new functional asplenia, complicating vaccination responses and immune defence against secondary infections.

These findings highlight that spleen size does not correlate with spleen function, particularly for SCD patients in malaria- or HIV-endemic areas. Splenic dysfunction in SCD–COVID–19 co-morbidity should be viewed as a spectrum rather than a binary state. Clinical protocols must incorporate function-based screening tools, such as pitted red cell counts and flow cytometry for B cell analysis (185). Vaccination should be prioritised for asplenic and hyposplenic individuals, especially in areas with endemic infections (198).

In conclusion, functional hyposplenism—whether congenital, infection-induced, or COVID-19-related—significantly impacts infection susceptibility, vaccine responses, and sepsis risk. Acknowledging this complexity is crucial for creating effective responses for SCD patients facing various infectious threats.

6 Avascular necrosis in SCD: exacerbation by COVID-19

6.1 Pathophysiology of AVN in SCD

The pathogenesis of AVN in SCD begins with the sickling of red blood cells, leading to vascular occlusion and subsequent ischaemia (199, 200). This process is particularly significant in the femoral head due to its unique vascular supply, which makes it vulnerable to ischaemic events. The initial VOC triggers a cascade of events, including endothelial activation, leukocyte adhesion, and platelet aggregation, which further compromise blood flow (199, 200). Osteonecrosis has been described in SCD (201).

Hypercoagulability plays a crucial role in the development of AVN in SCD, with this hypercoagulable state correlating with prevalent complications, including retinopathy and osteonecrosis (200).

6.2 Inflammatory mechanisms in AVN

Inflammation is a significant feature of SCD and a key contributor to the pathophysiology of AVN. Several inflammatory markers have been associated with SCD complications, including AVN. Domingos et al. (62) found that patients with higher levels of IL-6 had a significantly higher frequency of osteonecrosis compared to those with lower levels ($p = 0.0006$). Similarly, elevated IL-8 levels have been associated with other SCD complications, suggesting a broader role of inflammatory cytokines in disease manifestations (68).

The role of T cells in AVN development has been increasingly recognised. Daltro et al. (201) demonstrated that SCD patients with osteonecrosis have distinct CD4+ T cell profiles compared to those without this complication. Specifically, they found an increased frequency of circulating CD4+ T cells capable of simultaneously producing IFN-γ, IL-4, and IL-17 in SCD patients compared to healthy controls.

Tregs, characterised by the expression of CD4+CD25+FoxP3+, have also been implicated in the complications of SCD. Rêgo et al. (202) evaluated these cell populations in SCD patients with leg ulcers. They found that patients with a history of osteonecrosis showed higher IL-10 production in stimulated and unstimulated cultures, suggesting an altered immune response that may contribute to bone necrosis.

6.3 Genetic modifiers in AVN development

The clinical heterogeneity of SCD, including the variable occurrence of AVN, suggests the influence of genetic modifiers. Several studies (203–206) have identified polymorphisms in genes involved in inflammation, bone morphology, and vascular biology that may predispose SCD patients to AVN.

Baldwin et al. (203) found associations between single-nucleotide polymorphisms (SNPs) in the bone morphogenetic protein 6, annexin A2, and klotho genes and osteonecrosis in SCD patients. These genes are essential in bone morphology, metabolism, and vascular disease, providing insight into the genetic basis of AVN susceptibility.

Tozatto-Maio et al. (204) identified polymorphisms in inflammatory genes, including TLR2 and HLA-G, that modulate clinical complications in SCD patients. Specific genotypes were associated with fewer complications, suggesting potential protective effects.

The Duffy antigen receptor for chemokines (DARC) has been suggested as another potential genetic modifier in SCD. Farawela et al. (205) and Drasar et al. (206) investigated the relationship

between DARC expression and disease severity, finding that Duffy-positive patients had higher white blood cell counts, which could contribute to increased inflammation and vaso-occlusion.

6.4 COVID-19 and AVN: emerging evidence

A retrospective analysis conducted by Sinha et al. (207) involving ten patients hospitalised due to COVID-19 who subsequently reported hip pain revealed degenerative changes consistent with AVN of the femoral head by magnetic resonance imaging (MRI). Notably, one patient with prior femoral surgery exhibited favourable recovery; however, they developed AVN following SARS-CoV-2 infection, indicating a possible association between COVID-19 and the onset of AVN. Additionally, the authors reported elevated IgG antibody levels, joint abnormalities, and moderately severe symptomatology, with a favourable response to supportive therapy and anti-inflammatory medications, which alleviated joint pain and acute inflammatory symptoms. Thus, COVID-19 may lead to significant musculoskeletal complications, AVN, likely due to corticosteroid use and microembolism (207). Further studies and long-term follow-up are suggested.

6.5 Mechanisms of COVID-19-Induced AVN in SCD

Several mechanisms may explain how COVID-19 could increase the risk of AVN in SCD patients:

1. Enhanced inflammation: COVID-19 may exacerbate the pre-existing inflammatory state in SCD, which has been linked to osteonecrosis (25, 207).
2. Hypercoagulability: Both COVID-19 and SCD are associated with a hypercoagulable state, potentially leading to a synergistic effect that increases the risk of vascular occlusion and subsequent AVN (35, 204–207).
3. Steroid use: The use of high-dose corticosteroids may contribute to the development of AVN, especially in SCD patients.
4. Microembolism: COVID-19-associated endothelial dysfunction and microthrombus formation may contribute to bone necrosis, particularly in patients with SCD.

7 Takotsubo syndrome in sickle cell disease during COVID-19

SCD patients live under relentless physiological and psychological pressure due to chronic haemolysis, recurrent VOCs, and systemic inflammation (208). The COVID-19 pandemic intensified this burden, resulting in an unprecedented level of biological stress. This confluence of hypoxia, inflammation, and emotional trauma dramatically increases the risk of Takotsubo syndrome (TTS)—a stress-induced cardiomyopathy that mimics acute coronary syndrome yet lacks coronary obstruction (209). Though TTS has traditionally been associated with postmenopausal women, it now emerges as a critical endpoint in SCD patients facing the compounded insults of COVID-19. In malaria-endemic regions, where many of these patients reside, additional physiological strain from co-infections and structural healthcare limitations exacerbate this fragile balance, tipping it toward cardiovascular collapse (210).

7.1 Takotsubo syndrome: historical context and pathophysiology

First described in 1990 by Japanese cardiologists Sato et al. (211), TTS derives its name from the takotsubo (Japanese for "octopus trap"), reflecting the characteristic apical ballooning of the left ventricle observed on echocardiography. While initially linked to postmenopausal women experiencing emotional trauma, TTS is now recognised as a systemic response to severe physiological or psychological stress (211). Its pathophysiology involves interrelated mechanisms:

1. Catecholamine Surge

Acute stress triggers excessive sympathetic nervous system activation, flooding the myocardium with adrenaline and noradrenaline (212). This disrupts cardiomyocyte metabolism, induces calcium overload, and impairs mitochondrial function (213). In SCD, chronic pain, hypoxia, and anxiety sustain elevated catecholamine levels, sensitising the heart to TTS (214).

2. Direct Myocardial Stunning

High catecholamine concentrations downregulate β-adrenergic receptors and impair cyclic AMP signalling, leading to transient left ventricular dysfunction (215). The apical myocardium, which has a higher density of β-receptors, becomes hypo-contractile, while the base hypercontracts, creating the classic "apical ballooning" appearance (216).

7.2 Microvascular dysfunction

Endothelial damage in SCD reduces nitric oxide (NO) bioavailability, limiting coronary vasodilation (217). COVID-19 exacerbates this via ACE2 receptor-mediated endothelial injury, promoting microthrombosis and vasospasm (218). The resultant mismatch between oxygen supply and demand precipitates myocardial ischaemia (219).

7.3 Inflammatory crosstalk

Chronic inflammation in SCD (elevated IL-6, TNF-α, CRP) synergises with COVID-19's cytokine storm to amplify oxidative stress and cardiomyocyte apoptosis (220). Reactive oxygen species (ROS) from recurrent haemolysis and virus-induced hypoxia further destabilise myocardial contractility (218).

7.4 Neurohormonal factors

Oestrogen deficiency, common in postmenopausal women, may reduce cardioprotective effects (e.g., antioxidant activity, NO synthesis) (219). SCD patients, particularly women, often experience premature endocrine dysfunction due to chronic illness, potentially heightening TTS susceptibility (218, 220).

7.5 Purinergic system dysregulation

Burnstock first described purinergic nerves in 1972, establishing the foundation for understanding purinergic signalling (221). His later work highlighted the historical roles of purinergic signalling in blood cells, providing critical insights into how these pathways influence haematological disorders, such as SCD (221–223).

Emerging evidence implicates the purinergic system—a network of signalling molecules (e.g., ATP, adenosine) and receptors (P1, P2)—in TTS pathophysiology (223). During stress or viral infection, ATP is released from damaged cells or sympathetic nerve terminals, activating P2X and P2Y receptors. These receptors exacerbate catecholamine release, calcium overload, and microvascular spasm (224, 225). In COVID-19, the cytokine storm amplifies ATP spillage, creating a feedforward loop that intensifies myocardial stunning (222). Conversely, adenosine (via P1 receptors) modulates vasodilation and anti-inflammatory responses, but its overproduction during hypoxia may paradoxically suppress cardiac contractility (226). Zhang et al. (227) demonstrated that adenosine signalling has detrimental effects in SCD, potentially contributing to cardiovascular complications. Recent studies by Vandorpe et al. (228) confirmed that purinergic signalling is essential for full Psickle activation (i.e., activation of the deoxygenation-induced cation conductance pathway in sickle red blood cells, which leads to ion imbalance, cell dehydration, and increased sickling) by hypoxia and acidic pH, linking this system directly to SCD pathophysiology.

Targeting purinergic pathways (e.g., P2 receptor antagonists, adenosine modulators) could mitigate TTS progression by interrupting this syndromic cascade (229).

SCD and COVID-19: A Global Catalyst for Cardiac Stress

In SCD, chronic anaemia triggers compensatory mechanisms, such as increased cardiac output, which can lead to ventricular hypertrophy and diastolic dysfunction (230). COVID-19 amplifies this burden through:

- Hypoxia-Driven Crises: SARS-CoV-2 pneumonia exacerbates sickle cell-related hypoxia, accelerating HbS polymerisation and VOC frequency (231).
- Thrombotic Pathways: Platelet activation and hypercoagulability in COVID-19 increase the risk of pulmonary embolism or myocardial injury, often mimicking TTS (232).
- Psychosocial Stress: Pandemic-related isolation, delayed healthcare access, and fear of infection elevate cortisol and catecholamines, directly potentiating TTS (233).

Globally, these mechanisms increase the risk of TTS in patients with SCD. However, in malaria-endemic regions, overlapping pathologies—SCD, COVID-19, and malaria—create a 'triple burden' that magnifies cardiac strain (234).

7.6 Malaria co-endemicity: a compounding factor

In regions where malaria coexists with SCD, Plasmodium falciparum infection exacerbates haemolysis, inflammation, and endothelial dysfunction (235):

- Haemolytic Burden: Malaria-induced red cell destruction worsens anaemia, increasing cardiac workload (236).
- Inflammatory Synergy: Malaria's cytokine release (e.g., IFN-γ, IL-1β) amplifies SCD- and COVID-19-driven inflammation, accelerating myocardial injury (237).
- Diagnostic Challenges: Overlapping symptoms (fever, fatigue) delay recognition of VOCs, COVID-19, or TTS, prolonging untreated cardiac stress (238).
- Healthcare Limitations: Resource constraints in these regions restrict access to therapies like hydroxycarbamide (hydroxyurea), transfusions, or ventilatory support, leaving stressors unmitigated (239).

This "triple burden" creates a vicious cycle, overwhelming compensatory mechanisms and increasing the incidence and severity of TTS (240). The connection between red blood cell pathology and inflammation in SCD, as elucidated by Nader et al. (241), further emphasises how this disease predisposes patients to cardiac complications during infectious challenges (241, 242).

7.7 Clinical management and challenges

Diagnosing TTS in SCD requires distinguishing it from acute coronary syndrome (ACS) or VOC-related pain. Key indicators include (243):

- Transient left ventricular dysfunction with apical ballooning.
- Absence of obstructive coronary disease on angiography.
- Precipitating stressors (e.g., recent COVID-19 diagnosis, severe infection).

7.8 Multidisciplinary management strategies

Given the complexity of overlapping conditions, patients with SCD presenting with acute coronary symptoms should be managed by a multidisciplinary team including:

1. Cardiologists: To assess ventricular function, rule out ACS, and guide heart failure therapies (e.g., beta-blockers, diuretics) (244).

2. Haematologists: Optimise SCD-specific care (e.g., hydration, analgesia, transfusion) (245).
3. Psychologists: To address anxiety, depression, and chronic stress, which exacerbate catecholamine surges (246).
4. Social Workers: To mitigate socioeconomic stressors (247).

Researchers have already documented several cases of Takotsubo syndrome triggered by COVID-19, including one that introduced the term "COVIDsubo" (248, 249). Nevertheless, no studies have reported this syndrome in individuals with sickle cell disease, alone or in combination with COVID-19. Despite overlapping stress-related pathophysiological mechanisms, this conspicuous absence calls for greater clinical vigilance and systematic case reporting in this vulnerable population.

Takotsubo syndrome represents a critical intersection of physiological and emotional stressors in SCD patients, amplified globally by COVID-19 and catastrophically worsened in malaria-endemic regions. The purinergic system plays a pivotal role in this complex pathophysiology, mediating stress responses, inflammation, and cardiac dysfunction.

While TTS is reversible, delayed recognition in high-risk cohorts, particularly where healthcare resources are limited, can lead to fatal arrhythmias or heart failure (42). Addressing this requires a dual focus: improving access to cardiac diagnostics and therapies worldwide, while prioritising malaria control and pandemic preparedness in vulnerable regions (249, 250).

Future research should explore biomarkers (e.g., cytokines, microRNA profiles, catecholamine metabolites) and pharmacological interventions targeting the purinergic system (e.g., P1/P2 receptor modulators) to disrupt the stress-catecholamine-cardiac injury axis (229, 251).

8 Placental pathophysiology in pregnant women with SCD and COVID-19: the hidden nexus

8.1 Placental vulnerability

The placenta is a critical interface between the maternal and foetal circulatory systems, regulating nutrient exchange, oxygenation, and immune defence (165, 252). Placental homeostasis may be severely compromised in systemic conditions such as SCD (253, 254) or SARS-CoV-2 infection (255). When these two entities converge in pregnancy, the result is a compounded burden of vascular dysfunction, inflammatory amplification, and immune dysregulation (256). This pathological convergence may precipitate pre-eclampsia, intrauterine growth restriction (IUGR), preterm birth, or stillbirth (26–261).

SCD contributes through chronic haemolysis, oxidative stress, and endothelial injury, while COVID-19 has been shown to induce trophoblast necrosis, intervillous fibrin deposition, and decidual inflammation. Histopathological studies have identified maternal vascular malperfusion (MVM), increased syncytial knots, and reduced placental branching in pregnancies with SCD (255, 261, 262). Meanwhile, SARS-CoV-2 placental infection is associated with chronic histiocytic intervillositis, CD68+ macrophage infiltration, and thrombotic microangiopathy (256).

8.2 Endothelial dysfunction and vascular insufficiency: a dual threat

Endothelial dysfunction is central to the pathogenesis of both SCD and COVID-19:

- In SCD, elevated placental growth factor (PlGF) levels drive endothelial activation and pulmonary hypertension via endothelin-1 (ET-1) upregulation (262). Free iron regulates PiGF (263). VOCs impair perfusion and promote infarction.
- In COVID-19, direct viral invasion of the placental endothelium through ACE2 and TMPRSS2 receptors leads to inflammation and fibrin deposition (57, 264).

The confluence of these mechanisms may result in chronic placental hypoperfusion, impaired nutrient delivery, and increased foetal distress.

8.3 Exacerbation of inflammatory pathways and immune dysregulation

SCD and COVID-19 are both characterised by systemic inflammation. Their co-occurrence intensifies leukocyte activation, cytokine release, and immunological imbalance:

- In SCD, PlGF promotes leukotriene synthesis and monocyte infiltration, sustaining a pro-inflammatory microenvironment (265, 266).
- SARS-CoV-2 infection alters the decidual immune profile: third-trimester infection increases macrophage, NK cell, and T cell activity, while second-trimester exposure leads to partial immune resolution (267–269).

This inflammatory synergy has been linked to pre-eclampsia, foetal inflammatory response syndrome, and early labour (268–271).

8.4 Hypoxia, pulmonary hypertension, and placental hypoperfusion

Both diseases impair maternal-foetal oxygen exchange:

- SCD results in chronic anaemia and hypoxia-induced erythropoiesis, which exacerbates placental resistance and microvascular damage (272).

- COVID-19 contributes via pulmonary microthrombosis and hypoxaemia, further restricting oxygen transfer to the fetus (273).

This cumulative hypoxic burden raises the likelihood of placental abruption, IUGR, and perinatal loss.

8.5 The prothrombotic state and placental vascular pathology

Both SCD and COVID-19 promote a hypercoagulable state:

- In SCD, increased PAI-1 expression inhibits fibrinolysis, while VOCs induce platelet activation (268).
- COVID-19 introduces microthrombi, intervillous haemorrhage, and diffuse fibrin deposition within the placenta (269).

This prothrombotic milieu accelerates placental infarction and stillbirth risk.

The catastrophic events may be increased with flavivirus infections (58).

8.6 Diagnostic and prognostic utility of placental pathology

Placental histology may offer predictive and diagnostic insights in SCD-COVID-19 pregnancies:

- Histopathological markers (e.g., MVM, intervillous thrombosis, syncytial knots) help differentiate between SCD- and COVID-19-driven injury (256, 261).
- Biomarkers such as PlGF, thrombospondin, and VEGF may assist in identifying at-risk pregnancies and guiding management (270).

These findings underscore the need for systematic placental examination and longitudinal follow-up in affected cohorts.

8.7 Clinical and therapeutic implications

Pregnant patients with coexisting SCD and COVID-19 warrant enhanced surveillance (271):

Clinical management approach, incorporating:

- Close maternal-foetal monitoring using Doppler ultrasound and biomarker profiling.
- Preventive anticoagulation therapy to reduce thrombotic risks.
- PlGF-targeted therapies for vascular and inflammatory control in SCD.
- Vaccination as a priority.

9 Therapeutic considerations and management strategies

9.1 Challenges in management

Managing patients with SCD and COVID-19 presents unique challenges, particularly in distinguishing COVID-19 pneumonia from acute chest syndrome. Uncertainty around transfusion strategies and achieving proper anticoagulation complicates treatment. Immunomodulatory therapies used for severe COVID-19, like steroids and IL-6 inhibitors, have not been thoroughly studied in SCD and could affect VOC (274). Monitoring for signs of acute splenic sequestration, splenic infarction, or rupture is mandatory. The goal is to avoid risks of hypoxia-induced sickling and thrombosis. Prophylaxis against bacterial infections is crucial, especially for those with functional hypersplenism.

9.2 Approaches for AVN management in SCD and COVID-19

Managing AVN in SCD is challenging due to limited effective interventions. A Cochrane Review by Martí-Carvajal et al. (274) found no significant improvement in SCD patients with AVN when hip core decompression was added to physical therapy, based on a single trial with high attrition rates. Al-Otaibi's review (272) suggests that initial treatments may include pharmacological agents, bone morphogenetic protein stimulation, and surgical options, such as total hip arthroplasty. A multidisciplinary approach is essential for effective patient management. Supportive care for SCD patients in vaso-occlusive crises includes intravenous hydration, pain management, and sometimes blood transfusion (273). These measures can help prevent progression to AVN by addressing vaso-occlusion and ischaemia.

In the context of COVID-19 management strategies, AVN in SCD patients may need adaptation:

1. Anti-inflammatory therapy: Targeted anti-inflammatory treatments may benefit patients with SCD and COVID-19. Low-dose methotrexate has shown promise (275).
2. Anticoagulation: Prophylactic anticoagulation may be considered for SCD patients with COVID-19 (14); however, this requires further investigation.
3. Careful steroid use is essential due to the potential link between high-dose corticosteroids and AVN in SCD patients with COVID-19. Almeida et al. (276) found that both conventional (prednisolone) and dissociative (vamorolone) corticosteroids worsen liver injury in sickle cell mice, raising concerns about their use in SCD patients.
4. Increased vigilance for early signs of AVN in SCD patients recovering from COVID-19 may allow for earlier intervention and better outcomes. Regular assessments and imaging studies should be included in the post-COVID-19 follow-up for these patients.

9.3 Management of autoimmune complications in SCD-COVID-19

1. Tailored immunosuppression: In patients with SCD, autoimmunity, and COVID-19 treatment must be customised to avoid compromising antiviral immunity. In select cases, targeted therapies such as bortezomib for refractory autoimmune haemolytic anaemia (AIHA) may be preferable to broad immunosuppression (162, 164).

2. Monitoring for immune cytopenias: It's essential to monitor for AIHA and ITP in SCD patients with COVID-19, as viral infections can trigger or worsen these autoimmune cytopenias (277).

3. Balancing transfusion needs and the risk of alloimmunization: SCD patients with autoimmune complications often require transfusion support, but this carries an increased risk of alloimmunization, particularly in the pro-inflammatory state induced by COVID-19. SCD patients with the FcγR2B 2B.4 haplotype have an increased risk of RBC alloimmunization (278). Genetic polymorphism studies in these high-risk patients it is strongly recommended (279).

In these complex cases, extended phenotype matching and alternative strategies, such as erythropoiesis-stimulating agents, may be considered for treatment.

4. Managing systemic autoimmune diseases: For patients with SCD and systemic autoimmune diseases (such as SLE or JIA), COVID-19 may trigger flares that require prompt intervention (280). Hydroxychloroquine may be particularly beneficial in this subset of patients, although the evidence is limited (156).

9.4 Recommended preventive approaches for SCD patients

1. Prevention strategies: Vaccination should be prioritised.
2. Infection control measures and remote healthcare. Telemedicine can be used to maintain necessary monitoring and management.
3. Prophylactic strategies: Early therapeutic interventions.

Pregnant patients with SCD require specialised management protocols as detailed in obstetric considerations elsewhere in this review.

9.5 Treatment adaptations

Early hospitalisation is recommended, as well as aggressive hydroxyurea optimisation to ensure optimal HbF induction to reduce COVID-19-related hypoxemia.

A prophylactic exchange transfusion for selected high-risk patients, along with preventive anti-inflammatory therapy and management of hyperhaemolysis, is recommended in clinical settings.

A clinical decision-making algorithm is proposed for SCD patients that includes: 1) vigilant monitoring of post-transfusion haemoglobin levels in SCD patients, 2) monitoring inflammatory markers, complement activation, and parameters indicative of haemolysis; 3) stratify severity based on the rate of haemoglobin decline, presence of end-organ damage, and associated comorbidities; 4) adopt an escalating therapeutic approach: administer corticosteroids and intravenous immunoglobulin as first line of treatment and evaluate the potential use of biological therapies.

For refractory cases, consider evaluating alternative oxygen carriers by applicable regulatory guidelines.

Suggestions for the autoimmune complication management: 1) prompt differentiation between alloimmune and autoimmune haemolysis through comprehensive antibody screening and direct antiglobulin testing; 2) consider proteasome inhibition for refractory AIHA cases; 3) monitor for the emergence or exacerbation of systemic autoimmune manifestations during and after SARS-CoV-2 infection; 4) multidisciplinary patient management.

9.6 Socioeconomic considerations

Several socioeconomic considerations should be taken into account. SCD patients may be particularly vulnerable due to their financial situations. Patients must have access to necessary tests, treatments, and vaccinations. There should be a specialised centre with well-designed protocols for immunological testing, pain management, and emergency care, despite the high costs associated with specialised treatment and care.

10 Future research directions

Our analysis identifies several critical areas for future research:

10.1 Mechanistic studies

Longitudinal studies focusing on genetic markers, immune cell populations, cytokine profiles, neutrophil activation, and endothelial markers in patients with SCD, across both paediatric and adult populations, are essential for a better understanding of the disease's pathophysiology. Furthermore, research is needed to explore the mechanisms of endothelial damage in SCD patients who have contracted COVID-19 or are experiencing long COVID (281, 282).

More studies are required on genetic modifiers in SCD. Studies examining how genetic factors that modify SCD severity interact with COVID-19 outcomes, including the analysis of specific inflammatory cells and biomarkers or genetic markers for AVN risk.

Prospective investigation of macrophage and complement activation products (C3a, C5a, soluble C5b-9) in SCD patients with COVID-19 with a particular focus on those who develop HHS.

A comprehensive analysis of autoimmune signatures in SCD-COVID-19 patients is essential. Characterising autoantibody profiles and B cell subsets before and after COVID-19 infection will help identify predictors of autoimmune complications, guiding clinical decisions.

10.2 Clinical research priorities

In SCD, there is a need for specific trials and registry-based studies of therapeutics for viral infections, particularly in COVID-19 and long-COVID-19. Moreover, comparative studies are required to examine the differences between simple versus exchange transfusion, liberal versus restrictive approaches, and prophylactic versus therapeutic strategies.

There is a need for controlled trials of complement inhibitors, cytokine blockade, and alternative oxygen carriers in patients with SCD. It is clinically relevant to develop and validate standardised imaging protocols for the early detection of AVN in SCD patients, along with testing for autoimmune diseases and autoimmune therapy and response to vaccines to prevent complications in these patients.

10.3 Epistemic integration

Integrated multidisciplinary studies that explore the interaction among malaria, SCD, and COVID-19, along with biomarker validation, are essential for understanding the relationship among these conditions and other viral infections. Additionally, well-designed studies are needed to develop effective prevention and treatment strategies for patients with SCD. The studies should include Recommendations for Interventional Trials (SPIRIT) statement for trial conduct and the Consolidated Standards of Reporting Trials (CONSORT) statement for reporting, including detailed medical history and treatments.

11 Conclusion

The interplay between SCD and COVID-19 represents a complex intersection with significant clinical implications. There are concerning epistemic gaps in the current literature, particularly in mechanistic investigations, clinical studies, and the omission of SCD in African COVID-19 research.

The immunopathogenesis involves synergistic inflammatory processes, vascular dysfunction, and an increased risk of haemolytic-uremic syndrome and avascular necrosis. While the evidence base consists predominantly of case reports and small series, promising therapeutic avenues have emerged, necessitating a transition from anecdotal successes to evidence-based approaches that prioritise early recognition and targeted intervention.

The evidence synthesised in this review predominantly reflects experiences with earlier, more virulent SARS-CoV-2 variants. While currently circulating variants demonstrate reduced population-level virulence, the mechanistic vulnerabilities identified in SCD patients—chronic inflammation, immune dysregulation, and organ dysfunction—suggest that vigilance remains warranted regardless of viral evolution. The pathophysiological intersections described herein represent host response patterns that may be triggered across the spectrum of viral variants, particularly in this immunologically vulnerable population.

Future research must address both mechanistic questions and socioeconomic contexts. Through integrating epistemic awareness with rigorous pathophysiological investigation, we can develop more effective approaches to protect this vulnerable population.

Author contributions

AM-C: Formal Analysis, Writing – original draft, Writing – review & editing, Data curation, Investigation, Conceptualization, Methodology, Validation, Visualization. JD: Writing – review & editing, Conceptualization, Funding acquisition, Resources, Investigation, Validation, Project administration, Formal Analysis, Supervision, Methodology, Visualization, Data curation.

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