Annals of Hematology (2022) 101:1887–1895
https://doi.org/10.1007/s00277-022-04907-7

REVIEW ARTICLE

Hemolytic anemia in COVID-19

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Received: 27 March 2022 / Accepted: 25 June 2022 / Published online: 8 July 2022

Abstract

COVID-19 is a global pandemic triggered by the severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2). The SARS-CoV-2 entry point involves the interaction with angiotensin-converting enzyme 2 (ACE2) receptor, CD147, and erythrocyte Band3 protein. Hemolytic anemia has been linked to COVID-19 through induction of autoimmune hemolytic anemia (AIHA) caused by the formation of autoantibodies (auto-Abs) or directly through CD147 or erythrocyte Band3 protein-mediated erythrocyte injury. Here, we aim to provide a comprehensive view of the potential mechanisms contributing to hemolytic anemia during the SARS-CoV-2 infection. Taken together, data discussed here highlight that SARS-CoV-2 infection may lead to hemolytic anemia directly through cytopathic injury or indirectly through induction of auto-Abs. Thus, as SARS-CoV-2-induced hemolytic anemia is increasingly associated with COVID-19, early detection and management of this condition may prevent the poor prognostic outcomes in COVID-19 patients. Moreover, since hemolytic exacerbations may occur upon medicines for COVID-19 treatment and anti-SARS-CoV-2 vaccination, continued monitoring for complications is also required. Given that, intelligent nanosystems offer tools for broad-spectrum testing and early diagnosis of the infection, even at point-of-care sites.

Keywords COVID-19 · SARS-CoV-2 · Autoimmune hemolytic anemia

Introduction

The normal lifespan of red blood cells (RBCs) is 120 days. In hemolytic anemia, the period is shortened to a few days due to their destruction. The hemolysis may occur when RBCs are targeted by anti-RBC membrane autoantibodies (auto-Abs) leading to induction of autoimmune hemolytic anemia (AIHA) [1]. Depending on the temperature at which auto-Abs bind optimally to RBCs, AIHA is classified as warm type mediated by IgG and C3d or cold type mediated by IgM, with their maximal reactivity at 37 °C and 4 °C, relatively. However, as even warm IgM RBC auto-Abs do exist, and secondary cold agglutinin syndrome (CAS) in some cases can be mediated by cold-reactive IgG [1, 2]. The warm and cold types of AIHA lead to hemolysis through activation of phagocytic cells and the classical complement pathway. However, extra- and intravascular hemolysis may concurrently contribute to warm or cold AIHA in some cases. The complement-mediated hemolysis in cold agglutinin diseases (CAD) or CAS is mainly extravascular (phagocytosis of C3b-opsonized RBCs), although intravascular hemolysis also occurs [1, 2].

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Moreover, a lack of standard diagnostic criteria makes the classification of AIHA and its subclasses is difficult [1, 3]. Depending on the presence or absence of underlying disease, AIHA is classified as primary or secondary. Primary or idiopathic type is in around 50% of cases, while the secondary type is caused by infections (mycoplasma and viral infections), lymphoproliferative disorders (lymphoma and chronic lymphocytic leukemia), and autoimmune diseases (systemic lupus erythematosus). Moreover, AIHA can also be triggered by drugs (methyldopa, antibiotics) and toxins (Fig. 1a) [2, 4, 5]. A significant risk factor for morbidity and mortality in AIHA patients is infection. Due to concurrent diseases harboring an inherent infectious risk, including immunodeficiency, autoimmune, and lymphoproliferative disorders, as well as immunosuppressive treatments, these patients are vulnerable to infectious agents (viruses, bacteria, fungi) which trigger onset or relapse of AIHA (Fig. 1b).

This risk is significant during the Coronavirus 2019 (COVID-19) pandemic [6]. COVID-19 is an infectious disease caused by severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) and is considered a global issue pandemic by the World Health Organization. SARS-CoV-2 is a positive-sense single-strand RNA that shares a genetic similarity with other beta coronaviruses, like the Middle East respiratory syndrome-related coronavirus 1 (MERS-CoV-1) and SARS-CoV-1 [7]. The primary mechanism of SARS-CoV-2 entry into host cells is binding the viral spike protein to its receptor angiotensin-converting enzyme 2 (ACE2), which is highly expressed in the lung epithelial cells, proximal renal tubules, heart, and brain. The SARS-CoV-2 infection triggers an acute host immune response, inflammatory reactions, and cytokine storm leading to acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) [8]. The virus can cause extra-pulmonary manifestations, like acute cardiac injury, arrhythmias, acute kidney injury, acute brain injury, endocrine failure, and multiple organ failure with fatal consequences [9]. Although AIHA is a relatively rare condition with an estimated incidence of 13/100,000 persons per year [10], there is a growing number of reported hemolytic anemia cases, mainly attributed to the development of auto-Abs, in the setting of COVID-19 [11]. Given the known risk of thrombosis in patients with cold agglutinin hemolytic anemia, Maslov et al. (2020) speculated that this might contribute to thrombosis and the unfavorable outcomes in COVID-19 patients [12]. The hemolysis of RBCs may also be caused by impairment of their morphology and functionality due to the virus infection [13], which is critical in cases of hemoglobinopathies or inherited anemias [14]. Severance et al. revealed that induction of hemolytic anemia in children with hereditary spherocytosis is due to provoking oxidative stress by SARS-CoV-2 infection [15]. On the other hand, sickle cell disease has been suggested to protect against fatal outcomes in COVID-19 because of reduced T cell-mediated immunity and related weakened immune response without cytokine storm [16]. Finally, anemia in AIHA patients represents a significant risk factor for a worse prognosis in COVID-19 patients [17]. Accordingly, the National Haemoglobinopathy Panel (NHP) has issued guidance on caring for patients with anemias regarding programmed blood transfusion and outpatients visits to reduce risk exposure to SARS-CoV-2 and related COVID-19 severity in the vulnerable group of patients [14].

Given the multifaceted nature of hemolytic exacerbations associated with COVID-19 infection, the review aims to highlight challenges tackling the complexity of these conditions, diagnosis, and management.

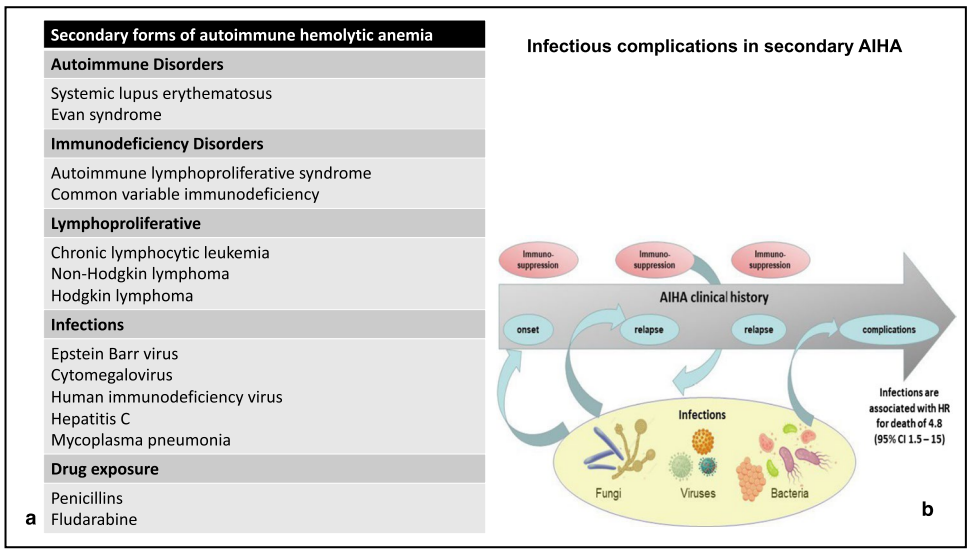

Fig. 1 Secondary forms of AIHA [5] (**a**). Infectious complications in secondary AIHA [6] (**b**)

The interplay between SARS-CoV-2 infection and AIHA

AIHA is a common hematologic autoimmune sequel in the COVID-19 patients, according to an analysis by Taherifard et al. (2021) conducted on a total reported 94 cases [18]. A cross-sectional study by Algassim et al. (2021) have revealed that COVID-19 patients with AIHA are linked with poor prognosis and prolonged hospital stay, mainly when the hemoglobin (Hb) level is below 12 g/L. The authors reported that 14.7% of patients admitted to the intensive care unit (ICU) and 9% of non-ICU patients had AIHA, with a mortality rate of 32% among the direct antiglobulin test-positive patients [17]. Lazarian et al. (2020) have reported seven cases of AIHA comprising both warm and cold types during the early COVID-19 course. Four patients had lymphoid disorders, and this per se might explain the triggering effect of SARS-CoV-2 infection in auto-immunity induction [19]. Significantly, SARS-CoV-2 infection can cause hematologic autoimmune disorders in predisposed subjects both in the elderly and children, and several cases of AIHA have been described in a pediatric setting of COVID-19 [20, 21].

AIHA and related anemia lead to reduce oxygen saturation, critical organs ischemia, and hemodynamic disorders [17]. When it coincides with the COVID-19 associated cytokine storm, SARS-CoV-2-mediated immune hemolysis became high. AbouYabis and Bell (2021) have summarized a growing number of reported cold and warm AIHA cases in the setting of COVID-19 infection presented during the SARS-CoV-2-induced cytokine storm. Although the exact mechanism of AIHA contributing to COVID-19 remains unknown, the alteration in antigen presentation creating cryptic antigens caused by SARS-CoV-2 cytokine-rich inflammatory response is suggested [22]. Moreover, as the intense acute-phase response in COVID-19 causes, the dysregulation of the complement system [23], immune complexes, and complement products found on the RBC cell surface have been suggested to affect their rheology promoting intravascular thrombosis [24]. This is consistent with observed disseminated intravascular coagulopathy with subsequent multi-organ failure from warm AIHA in a COVID-19 patient [25]. The hypercoagulability and exacerbated inflammatory response may affect RBCs, making membranes fragile with lower elasticity, leading to embolisms and clots in COVID-19 patients [26]. Finally, iron and serum ferritin resulting from hemolysis may drive oxidative stress. Hyperferritinemia and impaired iron homeostasis have been demonstrated to contribute to endothelial damage and cause ultrastructural changes in RBCs of COVID-19 patients. Moreover, AIHA may lead to pulmonary thrombosis [27]. Interestingly, thrombosis associated with cold-agglutinin AIHA could be the presenting symptoms in COVID-19 patients [28]. As well, warm type AIHA may cause a pulmonary embolism. Abnormal exposure to phosphatidylserine (PS), RBCs derived microparticles (MP), and nitric oxide scavenging could be the potential mechanism of thrombosis in warm type AIHA. The destruction of RBCs leads to increased exposure of PS on the RBCs outer surface. PS acts as a docking site for enzymatic complexes involved in coagulation pathways; it makes RBCs more adhesive and leads to antiphospholipid antibody formation. RBC-derived MPs are released during hemolysis, acting as tissue factors triggering thrombosis. MPs correlate with D-Dimer and thrombin-antithrombin complex formation as well. Nitric oxide is sequestrated by the released hemoglobin from hemolyzed RBCs leading to uninhibited platelet aggregation and vasoconstriction leading to thrombosis [29]. These findings suggest the causality between erythrocyte pathology and thrombosis in these patients [30].

SARS-CoV-2 and direct erythrocytes injury

Methemoglobinemia is a hemoglobin disorder caused by the oxidation of iron Hb from ferrous to ferric status with oxygen-carrying capacity failure, leading to hypoxia, cyanosis, and respiratory failure [28]. Methemoglobinemia can be induced by drugs such as dapsone, sulfonamide, local anesthetics, and ascorbic acid [31] or viral infections, such as influenza, due to induction of oxidative stress and oxidation of Hb iron as a result [32]. Lopes et al. (2021) have reported a case study of SARS-CoV-2 induced-methemoglobinemia and non-hemolytic anemia due to oxidative stress aggravated by glucose-6-phosphate dehydrogenase (G6PD) deficiency [33]. In a docking study, Liu and Li (2021) have identified two SARS-CoV-2 proteins, S and ORF3a, able to bind with the 1-beta chains of hemoglobin, therefore causing Hb denaturation and immunological agglutination [34]. Interestingly, in a cohort study, DeMartino et al. (2020) have demonstrated no direct RBCs and Hb damage during SARS-CoV-2 infection [35]. Regardless of the established findings, various possible pathophysiologic mechanisms have been highlighted. Cavezzi et al. (2020), in their narrative review, pointed out that SARS-CoV-2 infection is associated with direct cytopathic injury of circulating RBCs and their precursors in bone marrow or indirect RBCs by intravascular coagulopathy and cytokine storm. These pathological changes are supported by the presence of anisocytosis generated by conformational changes in both RBCs membrane proteins and lipids [36]. These conformational changes in RBC surface ankyrin-1 protein appear to be due to molecular similarity with the SARS-CoV-2 spike protein [37].

Besides ACE2, the virus tropism for erythrocytes is associated with the cluster of differentiation 147 (CD147), also known as basigin or extracellular matrix metalloproteinase inducer (EMMPRIN), a transmembrane glycoprotein highly expressed in RBCs [38]. CD147 mediates SARS-CoV-2 entering RBCs by endocytosis [39], leading to dysregulation of RBCs CD147-cyclophilin A signaling pathway with subsequent hemolysis [40]. So, antibodies against CD147 like mepolizumab may attenuate SARS-CoV-2 invasion and hemolysis [41]. Similarly, azithromycin and other macrolides can also inhibit the interaction between SARS-CoV-2 and CD147 on RBC membranes and other host cells. Therefore, these antibiotics can also be considered a potential therapeutic drug in COVID-19 management and associated hemolytic anemia [42]. However, Shilts et al. (2021) have demonstrated no interactions between SARS-CoV-2 and CD147. In their experiment, no changes in susceptibility to this virus were observed in human lung epithelial cells after removing by CRISPR/Cas9 basigin from their surface [43]. As a matter of fact, the CD147 expression is stimulated by hyperinflammation status [44]. Raony and Figueiredo (2020) have confirmed that in a COVID-19-induced cytokine storm, there is an overexpression of CD147 facilitating the SARS-CoV-2 spike protein binding to retinal cells [45]. Therefore, the higher expression of RBCs CD147 may mediate the interaction between RBCs and SARS-CoV-2 even in the absence of ACE2. Indeed, it has been reported that ACE2-deficient T cells can be infected with SARS-CoV-2 via CD147 [46].

Moreover, inducing intra-erythrocytic oxidative stress by viral load has been demonstrated to be detrimental to proteins in erythrocytes, including those involved in membrane function, antioxidant defense, and transport and delivery of oxygen [47]. The RBCs' susceptibility is increased to being damaged by the associated micro-angiopathic inflammations [48]. In a case study, Lancman et al. (2021) have reported intravascular hemolysis with Coombs-negative hemolytic anemia in COVID-19 patients, suggesting direct RBCs injury due to SARS-CoV-2/CD147 interaction [49]. The latter, along with associated inflammatory reactions, is suggested to induce erythrocyte structural membrane changes and complement activations that together provoke intravascular and extravascular hemolysis [47, 50].

As regards the virus tropism to erythrocyte, Cosic et al. (2020), using the resonant recognition model, have proposed that SARS-CoV-2 might also infect RBCs via binding to the RBC Band3 protein [51]. Band3, the anion exchanger 1 protein, is most abundant in mature RBCs and controls, among others, bicarbonate/chloride homeostasis. This protein is regarded as a docking site for structural proteins necessary for membrane integrity [52] and is mandatory for oxygen release and metabolic processes [51]. Thus, SARS-CoV-2 spike protein binding to RBC Band3 protein disturbs oxygen transport function causing severe hypoxia and metabolic alterations that increase the risk of RBC injury and hemolytic effect [13, 51]. Band3 protein inhibits glycolytic enzyme function during normal oxygen saturation. However, during hypoxia, oxy-Hb competes with Band3 protein to favor the glycolytic pathway that increases RBCs ATP to promote oxygen release and prevent tissue hypoxia [53]. Moreover, Thomas et al. (2020), in an observational study involving 29 COVID-19 patients and 23 healthy controls, have revealed that RBCs from COVID-19 patients had a high glycolytic pathway with oxidation and fragmentation of membrane protein, including Band3 protein, spectrin beta, and ankyrin [47]. This alteration in membrane protein is associated with RBC lipid metabolism changes, particularly sphingolipids, acyl-carnitine, and fatty acids. High RBC glycolytic metabolite is regarded as a compensatory pathway against SARS-CoV-2 induced hypoxia to improve Hb oxygen load [54]. Because Band3 protein stabilizes deoxy-Hb and control oxygen loading, so it is shifting RBC metabolism toward hexose-monophosphate shunt and prevents the susceptibility of RBC to the effects of oxidative stress during COVID-19-induced hypoxia [55]. These findings suggest a potential impact of SARS-CoV-2 infection on the RBCs' structural proteins and lipid metabolism. Thus, COVID-19-induced hypoxia or SARS-CoV-2 may inhibit Band3 protein, disrupting RBC metabolism, structural integrity, oxygen transport, and circulation in the bloodstream [56].

Moreover, SARS-CoV-2 reduces RBC antioxidant capacity, including G6PD activity, and causes deformability of RBCs associated with a high risk of hemolysis [47]. The reduced G6PD activity contributes to the oxidation of structural proteins resulting in RBCs deformability and their susceptibility to coagulation and thromboembolic disorders in patients with severe COVID-19 [57].

Likewise, sphingosine-1-phosphate (S1P), also known as lysosphingolipid, is a bioactive lipid mediator mainly released from RBCs and to a lesser extent from platelets and endothelial cells. S1P has immune-modulating effects in mitigation of SARS-CoV-2 and viral infection-induced inflammatory disorders. The reduction of S1P serum level correlates with COVID-19 severity and reduces RBCs production or SARS-CoV-2-induced injury [58, 59].

Overall, the net effect of SARS-CoV-2 infection-induced hemolytic anemia is either direct RBC injury or indirectly through induction of auto-Abs against the RBC membrane (Fig. 2).

COVID-19 management in the scenario of AIHA

The rapid spread and high fatality of SARS-CoV-2 requires a rapid discovery of effective antiviral agents to control this pandemic. The lack of treatment options caused clinical

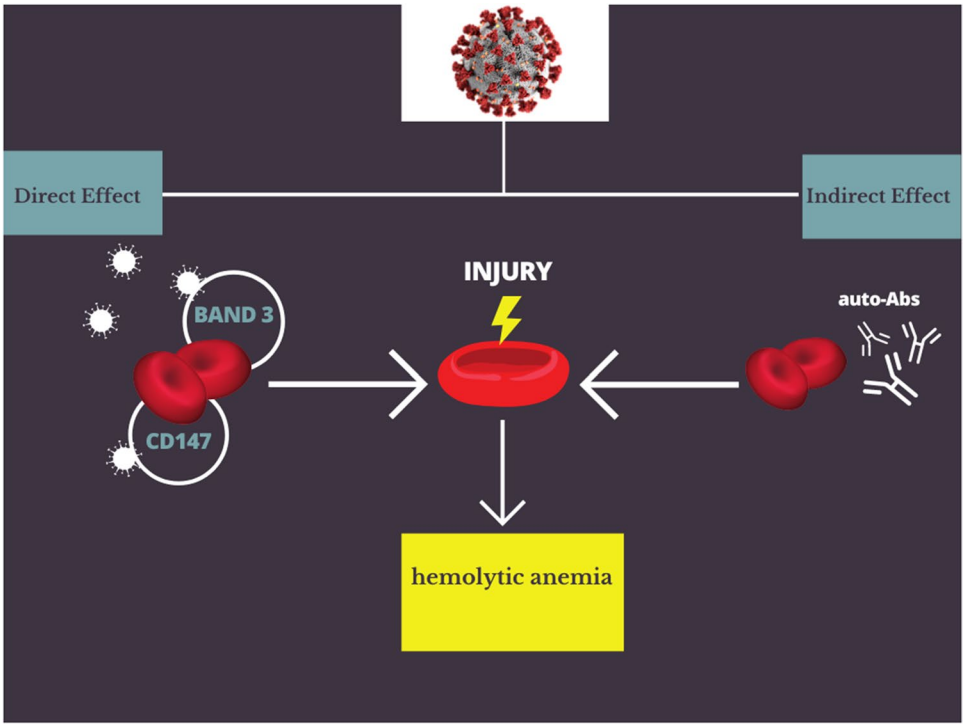

Fig. 2 Mechanism of SARS-CoV-2-induced hemolytic anemia

trials to test existing pharmacological drugs such as remdesivir, chloroquine, hydroxychloroquine, ivermectin, lopinavir-ritonavir, azithromycin, doxycycline, rivaroxaban, and protease inhibitors to repurpose them for the treatment of COVID-19. Since some of these agents may be implicated in the pathogenesis of AIHA, the risk should be considered in evaluating the efficacy and safety of prospective repurposing drugs in the treatment of COVID-19 infections [60, 61].

It has been shown that both chloroquine and hydroxychloroquine inhibit SARS-CoV-2 in Ver E6 at a micromolar concentration range through blocking of cathepsin L and PH-dependent interference with viral endocytosis. Both chloroquine and hydroxychloroquine were used to manage COVID-19 based on the preliminary data suggesting their abilities to limit viral replications [62, 63]. Doyno et al. (2020), however, have revealed that hydroxychloroquine might increase the risk of hemolysis in COVID-19 patients with G6PD deficiency. Thus, a measurement of this enzyme activity should be done before initiation of therapy [62]. Surprisingly, a large-scale study did not support these findings [63].

Despite the fact that controversy about the potential benefit of ribavirin in the management of COVID-19 [64], Eslami et al. (2020) have revealed the effectiveness of ribavirin in the inhibition of the replication of SARS-CoV-2 [65]. However, its prolonged intake can increase the risk of hemolytic anemia due to accumulation within the RBCs and induction of oxidative membrane damage [66]. Moreover, Nabil et al.'s (2020) study has disclosed that repurposing antiviral drugs such as arbidol, remdesivir, ritonavir, and lopinavir may cause hemolytic anemia by unknown mechanisms in patients with COVID-19 [67]. Finally, the World Health Organization recommended against the use of chloroquine, hydroxychloroquine, remdesivir, and lopinavir/ritonavir in the treatment of SARS-CoV-2 infection [60]. Therefore, an extensive review of used drugs in the management of COVID-19 for the potential hemolytic effect is necessary and warranted since anemia is correlated with COVID-19 severity [68].

Recently, discussion of the hematologic complications after SARS-CoV-2 vaccination has been starting. Besides developing vaccine-associated immune thrombosis with thrombocytopenia, as Fattizzo et al. (2021) reviewed, hemolytic flares occurred in patients with cold and warm AIHA who received either Moderna or Pfizer-BioNTech vaccines [69]. Fatima et al. (2022) also have reported a case of a patient who developed IgG-mediated AIHA after vaccination with the Moderna COVID-19 vaccine [70]. Overall, hemolytic exacerbations occurring during COVID-19 are more severe than those appearing after the SARS-CoV-2 vaccine [69, 70].

AIHA diagnosis in the setting of COVID-19 infection

The AIHA diagnosis is based on the detection of hemolytic anemia by Hb level and biochemical markers of hemolysis (often supported by blood smear and absolute reticulocyte

count), followed by a demonstration of autoimmune pathogenesis by DAT. The further classification depends primarily on the pattern by monospecific DAT (Ig class and/or complement protein on the RBC surface) and only occasionally on autoantibodies in RBC eluate and serum, while anemia and hemolysis are identified based on complete blood count (CBC), reticulocyte count, peripheral blood smear, serum biomarkers including bilirubin, lactate dehydrogenase (LDH), haptoglobin, and urine hemoglobin level [10].

According to Lazarian et al. (2020), the time between the COVID-19 symptoms and AIHA onset with marked signs of hemolysis ranged from 4 to 13 days [19]. Positive direct DAT or Coombs tests for IgG and C3 were reported in several COVID-19 cases [71–74] and warm antibodies in four of the seven cases reported by Lazarian et al. [19]. Hemolysis markers, including anemia, defects in the red cell membrane–spherocytosis (Fig. 3a and b) [74], reticulocytosis (Fig. 3c) [75], unconjugated bilirubinemia, increased serum LDH activity, ferritin, and low haptoglobin were also observed [10, 73, 74, 76]. Moreover, increased D-dimer and C-reactive levels were reported due to hypercoagulability and hyperinflammatory response in most SARS-CoV-2-associated AIHA cases [19, 72–74, 76]. Extended examinations, including chest X-rays, showed bilateral opacities (Fig. 3d) [73, 76], while chest computed tomography showed typical COVID-19 infection changes in the lung (Fig. 3c) [74, 75].

Challenges and future perspectives

Challenges remain, including hemolysis diagnosis in COVID-19 patients, which may be masked by the infection-related elevated acute phase haptoglobin [74]. Given that the complexity of the pathophysiologic interplay between SARS-CoV-2 infection and hemolytic events still requires further studies, more research on developing comprehensive diagnostic approaches tailored to the individual pathophysiological features of each disease is necessary. The improved understanding of the interconnected pathogeneses will enable the development of specific biomarkers alongside exact therapy. Since hemolytic anemias are increasingly associated with COVID-19, early detection and management of these conditions may prevent poor prognostic outcomes in these patients. In this context, the emerging sensitive, rapid, selective, and at the point-of-care (POC) diagnostic systems for the virus detection are a response [77, 78]. Moreover, biomonitoring related to coagulopathy and other pathologies may be the subject of POC analyses assisting clinicians in planning clinical interventions relating to individualized management [30]. This is even more important, considering that the NHP recommended minimalization outpatient visits to limit exposure of anemia patients to SARS-CoV-2 infections. In fact, these patients are at risk of non-efficient diagnostics and withdrawal of effective trial therapy [14]. This problem is the more serious as the COVID-19 pandemic is constantly surprising healthcare systems, and continuous variations in the structures of SARS-CoV-2 contribute to newly emerged variants making the viral infection more transmissible, contagious, and severe [79]. In this context, a broader application of current knowledge on technologies that use high-performance antibacterial and antiviral nanosystems can also mitigate the SARS-CoV-2 transmission [80].

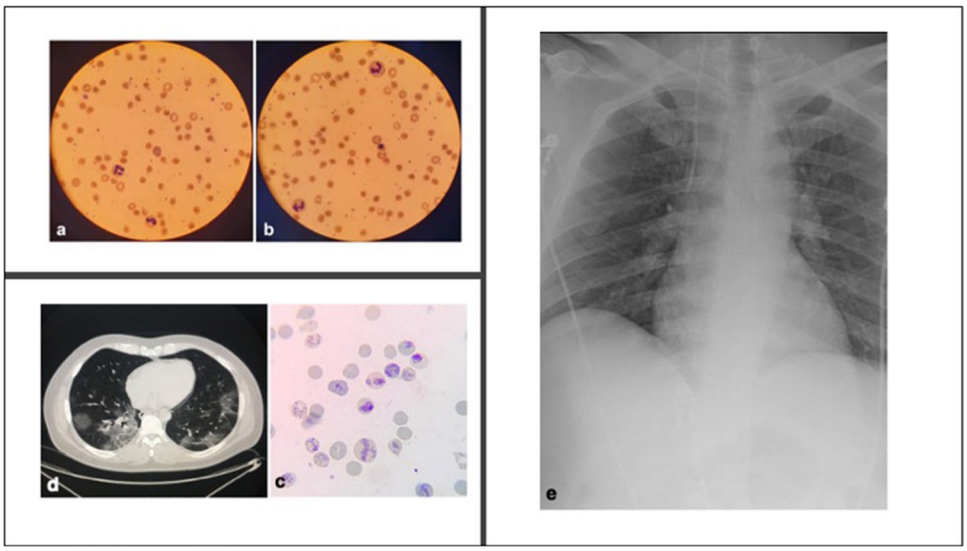

Fig. 3 Diagnosis of hemolysis: polychromasia (**a**), nucleated red blood cells (**b**) [74], and reticulocytosis (**c**) [75]. COVID-19 infection-induced changes in the lung: Computed tomography scan shows bilateral lung infiltration (**d**) [81]; chest X-ray shows diffuse bilateral opacities **(e)** [81]

Conclusions

Taken together, the data discussed here highlight that SARS-CoV-2 infection may lead to hemolytic anemia directly through cytopathic injury or indirectly through induction of auto-Abs. Therefore, extensive research on the potential mechanisms of SARS-CoV-2-induced hemolytic anemia and related specific diagnostics covering the complex etiology is required. Diagnostics tailored to the individual pathophysiological features of each disease demand comprehensive and continuous examination. Challenges remain, however, including the recommendation of limited outpatient visits. A more comprehensive application of intelligent nanosystems may contribute to broad-spectrum testing and early diagnosis of the SARS-CoV-2 infection even as well as can mitigate the SARS-CoV-2 transmission thus be part of protecting strategy of these vulnerable group of patients.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00277-022-04907-7.

Author contribution HMA and AIA conceptualized the study; HMA, AIA, MK, and AK collected the data. HMA, GEB, and MK interpreted the data. AIA and MK drafted the initial version; HMA, GEB, MK, and AK revising it critically for important intellectual content approved the final version to be published. All authors remain in agreement to be accountable for all aspects of the work.

This article does not contain any studies with human participants or animals performed by any of the authors.

Data availability Not applicable.

Declarations

Conflict of interest The authors declare no competing interests.

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