International Journal of Immunopathology & Pharmacology

Inflammatory Mediators in COVID-19 and Other Diseases-Original Research Article

International Journal of Immunopathology and Pharmacology
Volume 36: 1–7

DOI: 10.1177/03946320221103151
journals.sagepub.com/home/iji
SAGE

COVID-19 and erythrocrine function: The roller coaster and danger

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Abstract

Erythrocrine function refers to erythrocytes' ability to synthesize and release active signaling molecules such as ATP and nitric oxide (NO). Erythrocyte NO regulates its deformability and increases its perfusion and circulation that prevent tissue hypoxia. Recently, there is a connotation between SARS-CoV-2 infection and erythrocrine function due to alteration in the release of NO and ATP from erythrocytes. SARS-CoV-2 binds erythrocyte band3 protein, which has a similar characteristic of ACE2, leading to alteration of erythrocyte physiology like oxygen transport with development of hypoxia. Similarly, SARS-CoV-2 infection activates erythrocyte protein kinase C alpha (PKC-α), causing significant changes in the erythrocyte functions. The erythrocytes can bind SARS-CoV-2 and its active particles with subsequent virus delivery to the liver and spleen macrophages. Thus, the erythrocytes act as elimination for SARS-CoV-2 in COVID-19. Moreover, the erythrocyte stored, release sphingosine-1 phosphate (S1P) improves endothelial and regulates lymphocyte functions. SARS-CoV-2 ORF8 protein binds the porphyrin part of hemoglobin heme at the β1 chain, causing hemolysis and dysfunctional hemoglobin to reduce oxygen-carrying capacity. In conclusion, SARS-CoV-2 infection and associated pro-inflammatory disorders lead to abnormal erythrocrine function with subsequent inflammatory complications and endothelial dysfunction due to deficiency of protective released molecules (NO, G1P, and ATP) from functional erythrocytes. In vitro, preclinical, and clinical studies are mandatory in this regard.

Keywords

Erythrocrine function, SARS-CoV-2, COVID-19

Date received: 19 December 2021; accepted: 9 May 2022

Introduction

Erythrocrine function is defined as the ability of erythrocytes to synthesis and releases of active signaling molecules. The capability of erythrocytes to liberate bioactive molecules such as ATP and nitric oxide (NO) seems to be an essential feature of their function. Thus, the erythrocrine function represents the exocrine function of erythrocytes that could play a potential role in the pathophysiology of different metabolic disorders.[1]

It has been shown by different in vitro studies that the erythrocyte nitric oxide synthase (NOS) regulates the erythrocrine function; for example, NOS inhibitors abolish

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erythrocyte-induced platelets aggregation.[2] Perfusion of isolated heart and lung with washed erythrocytes attenuates ischemic reperfusion injury (IRI) and pulmonary vasoconstriction.[3] Indeed, erythrocyte NO regulates its deformability and increases its perfusion and circulation to prevent tissue hypoxia.[4] Yang et al. observed that erythrocytes of diabetic patients have higher arginase activity with the production of reactive oxygen species (ROS) that increase the risk of myocardial infarction and exacerbate risk of IRI. Therefore, inhibitions of erythrocytes ROS may improve myocardial function through inhibition of myocardial IRI.[5]

Moreover, erythrocyte deformability triggers the release of ATP under the effect of NO in normoxic status and contributes to vasodilation and blood pressure control. Thus, erythrocytes NO participate in increasing of blood NO pool, which involved in the process of cardio-pulmonary protection. Fresh blood has high NO content than old blood, it has been reported that patients who received old blood transfusion for more than two weeks were more likely to die compared with that received fresh blood due to low erythrocyte NO content. Of note, low erythrocyte NO induces hemolysis, inflammation, and reduction capacity for oxygen transport.[6]

The erythrocytes also sense the reduction of oxygen saturation and oxyhemoglobin through erythrocyte oxygen sensing signaling. Hypoxemia activates the release of NO and ATP from erythrocytes that induces vasodilatation.[7] Crawford et al. revealed that hypoxic erythrocytes can induce vasodilation by reducing nitrite to NO and ATP release.[8] The nitrite reductase activity of hemoglobin is modulated and affected by heme redox potential and heme deoxygenation, suggesting that oxygen sensing by hemoglobin is associated with nitrite reduction and induction of vasodilation.[8] This finding proposed that nitrite reductase activity of erythrocytes hemoglobin is correlated with hypoxia to increase NO-dependent vasodilation and blood flow.[8]

On the other hand, the current coronavirus 2019 (COVID-19), which caused by a novel coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) leads to worldwide pandemic. In COVID-19, direct SARS-CoV-2 cytopathic injury and liberation of pro-inflammatory cytokines lead to the initiation of acute respiratory distress syndrome (ARDS).[9] In COVID-19, SARS-CoV-2 chiefly invades lung alveolar type II pneumocyte cells due to higher expression of angiotensin-converting enzyme 2 (ACE2), a receptor for entry of SARS-CoV-2. The majority of affected COVID-19 patients is asymptomatic or presented with mild respiratory symptoms. However, a small percentage of COVID-19 patients presented with severe forms of respiratory deterioration due to progression of acute lung injury (ALI), which may advance to ARDS.[10] Therefore, the aim of the present review was to find the association between erythrocrine function and COVID-19.

SARS-CoV-2 and erythrocrine function

Similarly, SARS-CoV-2 infection can activates erythrocyte protein kinase C alpha (PKC-α), causing significant changes in the erythrocyte functions. Therefore, inhibition of PKC-α by plant-derived molecule chelerythrine improves erythrocytes' biological function and vitality.[11,12] These findings indicate that the erythrocyte might be a target for SARS-CoV-2 in a patient with COVID-19.

Human erythrocyte has impressive anti-inflammatory and immune-modulatory effects in different viral infections. The erythrocyte activates the proliferation of $CD8^+$ with the reduction of infected $CD4^+$ in the human immune deficiency virus (HIV).[13] Human erythrocytes have specific receptors such as sialoglycoprotein A (GPA) and gangliosides that bind circulating viral molecules by reducing viral load and infectivity since each GPA molecule binds a large number of viral molecules.[14] Therefore, the erythrocytes may have the ability to bind SARS-CoV-2 and its active particles with subsequent delivery of virus to liver and spleen macrophages; thus, the erythrocytes act as elimination for SARS-CoV-2 in COVID-19 through macrophage of reticuloendothelial system.[15] Besides, erythrocyte expresses complement receptors that enhance phagocytosis of infected erythrocytes by the reticuloendothelial system.[15]

Moreover, the erythrocyte stores and releases sphingosine-1 phosphate (S1P), which exerts a nephroprotective effect, improves endothelial function, and regulates lymphocyte functions.[15] S1P, a metabolic end-product of sphingomyelinase activity, is a robust immune-modulator molecule that might be synthesized within endothelial cells and platelets and stored in the erythrocytes.[16] S1P type 1 receptor (S1PR1) is highly expressed on dendritic cells, lymphocytes and endothelial cells.[15,16] Zhao and colleagues reported that S1PR1 agonists are regarded as a potential therapy against HIN1-induced ALI and cytokine storm through inhibition expression of chemokines, cytokines, and macrophages, neutrophils, and natural killer cells that limit immune exaggeration and progression of cytokine storm.[17] Marfia et al. revealed that serum S1P level and its transporter (albumin and apolipoprotein M) are reduced in COVID-19 patients and negatively correlated with COVID-19 severity.[18] The underlying mechanisms of low S1P in COVID-19 are related to induction of pro-inflammatory cytokines and cytokine storm that cause anemia (decrease S1P store) and endothelial dysfunction (decrease production of S1P) with significant reduction of S1P transporters (albumin and apolipoprotein M).[18] S1P has a bidirectional effect; the local interstitial S1P augment the inflammatory reactions, while the circulating S1P has an anti-inflammatory effect. Therefore, the beneficial effect

of glucocorticoid in Covid-19 might be through inhibition of local S1P.[19]

Moreover, human erythrocytes have anti-inflammatory and immunomodulatory effects through heme-containing molecules which bind and downregulate the expression of pro-inflammatory cytokines, including IL-6, IL-8, and IL-36.[20] The erythrocytes bind and inactivate different chemokines and dendritic cells, preventing excessive abnormal inflammatory interactions.[20] Therefore, human erythrocytes may reduce the inflammatory burden during SARS-CoV-2 infection through binding and attenuation activity of pro-inflammatory cytokines.[21]

Indeed, complement receptor 1 (CR1) binds human erythrocytes, which activated by complement classical and lectin pathways during SARS-CoV-2 infection, leading to the elimination of viral particles before transmitting to the immune cells.[22] However, this interaction alters erythrocyte rheology and increases intravascular thrombosis risk in Covid-19.[22]

Similarly, erythrocyte hemoglobin might be a potential target for SARS-CoV-2 through CD147, CD26, and ACE2 receptors located on the erythrocytes. SARS-CoV-2 ORF8 protein binds the porphyrin part of hemoglobin heme at the β1 chain, causing hemolysis and dysfunctional hemoglobin to reduce the oxygen-carrying capacity.[21] However, in a retrospective study, DeMartino et al. observed no evidence of hemoglobin injury and hemolysis during SARS-CoV-2 infection.[23] Moreover, SARS-CoV-2 entry to the erythrocytes is also mediated by G-protein coupled receptor 78 (GRP78) receptor. Thus, downregulation of these receptors in patients with β-thalassemia might be a protective mechanism against SARS-CoV-2 infection.[24,25] Moreover, GRP78 serum level is increased in COVID-19 patients, and GRP78 inhibitor imatinib could be a therapeutic strategy against COVID-19.[26] Therefore, GRP78 inhibitors may interfere with SARS-CoV-2 infection-induced erythrocrine dysfunction.

As well, SARS-CoV-2 infection induces anemia through hepcidin mimetic action with subsequent hyperferritinemia.[27] These changes lead to significant modifications in the volume and heterogeneity of circulating erythrocytes measured by red blood cell distribution width, which correlate with COVID-19 severity.[28] Lippi and colleagues illustrated that red blood cell distribution width is regarded as significant predictor of COVID-19 severity, and can be used for assessing the risk of critical outcomes in COVID-19 patients.[29]

These observations suggest that direct and indirect effects of SARS-CoV-2 infection on erythrocytes may induce functional and structural changes which affect the erythrocrine functions.

SARS-CoV-2 and erythrocyte nitric oxide

NO is important for the vascular system by controlling blood flow and vascular tone by activating the soluble guanylate cyclase of vascular smooth muscles. NO controls mitochondrial function by suppression of cytochrome c oxidase.[30] The erythrocytes metabolize endothelial-derived NO, limiting circulating NO; however, erythrocytes are regarded as a source of NO and ATP. NO within the erythrocyte is derived from the exterior by binding to β-chain of hemoglobin, from nitrite entering erythrocyte and from intracellular NO production within the erythrocytes.[31] Hypoxemia, acidosis, and stress activate NO production from erythrocytes leading to vasodilatation and cardio-protection under hypoxic status.[32]

Recently, there is a connotation between SARS-CoV-2 infection and erythrocrine function due to alteration in the release of NO and ATP from the erythrocytes.[33] Cosic et al. illustrated that the spike protein of SARS-CoV-2 binds erythrocyte band3 protein, which has a similar characteristic of angiotensin-converting enzyme 2 (ACE2), leading to alteration of erythrocyte physiology for oxygen transport with development of tissue hypoxia.[33] Tissue hypoxia is a condition in which the body or part of the body has inadequate oxygen supply at tissue level, it may be localized or generalized affecting the whole body.[34] Tissue hypoxia is occurs in severe anemia and methemoglobinemia in which ferric atom of hemoglobin has high affinity for oxygen and impair it delivery to the tissues.[35] However, hypoxemia refers to state of low arterial oxygen supply due to ventilation disorders as in ALI/ARDS which refer to lung alveolar hypoxia.[34] In SARS-CoV-2 infection, erythrocyte NO is increased that enable the release of oxygen into hypoxic tissues.[36] Prolonged hypoxia and associated acidosis trigger the erythrocytes to activate platelet aggregation and thrombosis through direct interaction with the platelets or indirectly through releasing chemical signaling.[37] Therefore, high erythrocyte NO in SARS-CoV-2 infection might be a compensatory mechanism against hypoxia and may involve the progression of silent hypoxemia in COVID-19 patients.[38]

Into the bargain, released NO from the erythrocytes has an antiviral effect by inhibition of SARS-CoV-2 3CL protease.[39] NO blocks the interaction between SARS-CoV-2 and ACE2 with inhibition of transmembrane serine protease 2 (TMPRSS2), which facilitate binding of SARS-CoV-2 to the ACE2 by trimming of the spike protein. Therefore, dietary inorganic nitrate improves endothelial and pulmonary vascular by restoration of NO.[40]

Siroka et al. observed that the erythrocytes have a higher expression of nuclear factor kappa B (NF-κB), mainly in obese patients that contribute to inflammation and oxidative stress.[41] The NF-κB pathway is engaged with the development of pro-inflammatory cytokine and ALI. Thus, obese subjects are at higher risk of developing COVID-19 complications due to underlying inflammatory and oxidative stress disorders.[42] Thus, SARS-CoV-2-induced NF-

κB activation could be the possible mechanism for erythrocrine dysfunction in COVID-19.

Moreover, activation of erythrocyte adenosine receptor type 2B is involved in the activation of erythrocyte mitogen-activated protein kinase (MAPK) under the effect of high circulating angiotensin II (AngII) during hypoxia.[43] In COVID-19, MAPK is highly activated by SARS-CoV-2 and pro-inflammatory cytokines leading to endothelial dysfunction and thrombosis.[44] Similarly, high AngII in COVID-19 due to downregulation of ACE2 also activates MAPK leading to severe complications.[45] Taken together, high AngII and activated MAPK may interfere with the erythrocrine function of erythrocyte anti-inflammatory actions with reduction of erythrocyte NO and subsequent endothelial dysfunction. These changes induce abnormal erythrocyte function with the development of extracellular vesicles, which stimulate MAPK and NF-κB with subsequent development of cytokine storm.[46] As well abnormal erythrocrine function in Covid-19 with abnormal accumulation of porphyrin is due to oxidative stress and mitochondrial dysfunction that affecting heme biosynthesis.[47]

These findings reveal that SARS-CoV-2 infection induces erythrocrine dysfunction through inhibition of NO, S1P, and heme biosynthesis. Both SARS-CoV-2 and associated pro-inflammatory changes participate together in the modulation of erythrocrine function (Figure 1).

Erythrocyte deformability in SARS-CoV-2 infection

Erythrocyte deformability represents the normal function of erythrocytes to facilitate blood flow in the narrow area of circulation. Therefore, is essential for the normal circulation and survival of erythrocytes. Erythrocyte deformability is affected by erythrocyte mean cell volume and mean cell hemoglobin which affect erythrocyte cytoplasmic viscosity.[48] Improvement of erythrocyte deformability by vinpocetin and pyritinol reduce risk of cerebrovascular

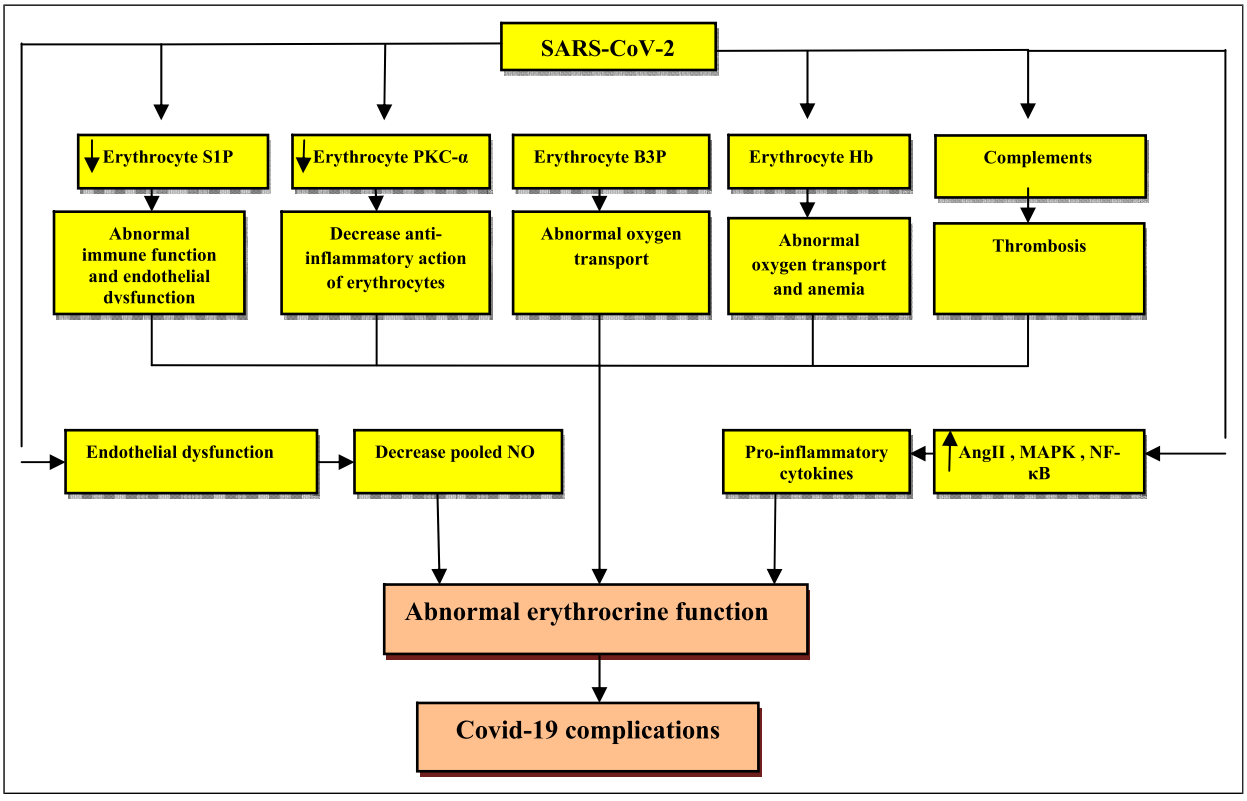

Figure 1. Abnormal erythrocrine function in COVID-19: SARS-CoV-2 inhibits sphingosine-1 phosphate (S1P) and protein kinase C alpha (PKC-α), leading to abnormal immune function and endothelial dysfunction, decreased anti-inflammatory action of erythrocytes, respectively. SARS-CoV-2 activates erythrocyte band3 protein (B3P) and erythrocyte complement, leading to abnormal oxygen transport and thrombosis, respectively. As well, SARS-CoV-2 erythrocyte hemoglobin (Hb) leading to abnormal oxygen transport and anemia. In addition, SARS-CoV-2 causes endothelial dysfunction with a reduction release of nitric oxide (NO). SARS-CoV-2, through activation of mitogen-activated protein kinase (MAPK) and nuclear factor kappa B (NF-κB) with high angiotensin II (AngII), induces the release of pro-inflammatory cytokines. These changes are causing abnormal erythrocrine function, which increases COVID-19 complications.

disorders.[49] Moreover, erythrocyte deformability is regarded as a partner of inflammatory response in different inflammatory disorders.[50] Silva-Herdade et al. observed that erythrocyte deformability is impaired during acute inflammation due to changes in blood viscosity and reduction of content of erythrocytes NO.[50] Likewise, systemic inflammation increases eryptosis (erythrocyte programmed cell death), platelet reactivity, and thrombotic activation that affect hemorheological properties of erythrocytes.[51] Beside, oxidative stress reduces erythrocyte deformability and increases sensitivity for high shear-mediated injury.[52] Of note, reduction of erythrocyte deformability is also linked with human immune deficiency virus 1 (HIV-1) and disease severity.[53]

In COVID-19, both inflammatory disorders and oxidative stress are augmented and may cause impairment of erythrocyte deformability with subsequent reduction of capillary blood flow and oxygen transport.[54] Reduced erythrocyte deformability leads to failure of microcirculation and tissue hypoxia with reduction of drug concentration in the affected organs. Therefore, alteration of erythrocyte deformability is linked with COVID-19 severity.[55] A prospective study involved seven hospitalized COVID-19 patients compared with seven patients with sepsis and seven healthy controls illustrated that erythrocyte aggregations were increased in both Covid-19 and sepsis compared to the controls.[55] Changes in erythrocyte membrane lipid composition and protein fragmentations could be the proposed mechanism for erythrocyte aggregations and erythrocyte deformability in COVID-19 patients.[55]

Indeed, reduction of erythrocyte deformability is correlated with chronic obstructive pulmonary diseases promotes development of hyperviscosity syndrome with induction of coagulation system and thrombotic disorders.[56] Therefore, patients with chronic obstructive pulmonary diseases are at high risk for development of systemic complication during SARS-CoV-2 infection.[56]

These verdicts suggest that erythrocyte deformability is reduced in viral infections including SARS-CoV-2 infection due to inflammatory and oxidative stress disorders with induction of COVID-19 complications.

Limitations of the present review were paucity of clinical studies concerning erythrocrine function in COVID-19 and most of studies were speculative in the effect of SARS-CoV-2 on the erythrocytes. In addition, most of the studies elucidate effect of COVID-19 on RBCs NO and ignored other potential functions of erythrocytes. However, in the present review whole erythrocrine functions were reviewed and how these functions are affected. This review opens a new window to study the mechanism of erythrocrine dysfunction in COVID-19.

Conclusion

SARS-CoV-2 infection and associated pro-inflammatory disorders lead to abnormal erythrocrine function with subsequent inflammatory complications and endothelial dysfunction due to deficient protective released molecules (NO, S1P, and ATP) from functional erythrocytes. In vitro, preclinical, and clinical studies are mandatory in this regard.

Authors Contributions

HMA, HO, AIA, and GEB conceived and designed research. HMA, AIA, HO, and GEB conducted the review experiments. HMA, HO, AIA, and GEB analysed the graphical illustrations data. HMA, HO, AIA, and GEB wrote the article. All authors read and approved the article and all data were generated in-house and that no paper mill was used.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Consent to Publish

All the authors have read and agreed to the final copy of the finding as contained in the article.

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References

1. Carelli-Alinovi C and Misiti F. (2017) Erythrocytes as potential link between diabetes and Alzheimer's disease. *Frontiers in aging neuroscience* 9: 276.
2. Buko V, Zavodnik I, Kanuka O, et al. (2018) Antidiabetic effects and erythrocyte stabilisation by red cabbage extract in streptozotocin-treated rats. *Food & function* 9(3): 1850–1863.
3. Davidson SM, Andreadou I, Barile L, et al. (2019) Circulating blood cells and extracellular vesicles in acute cardioprotection. *Cardiovascular research* 115(7): 1156–1166.
4. Richardson KJ, Kuck L and Simmonds MJ. (2020) Beyond oxygen transport: Active role of erythrocytes in the regulation of blood flow. *American Journal of Physiology-Heart and Circulatory Physiology* 319(4): H866–H872.
5. Yang J, Zheng X, Mahdi A, et al. (2018) Red blood cells in type 2 diabetes impair cardiac post-ischemic recovery through an arginase-dependent modulation of nitric oxide

synthase and reactive oxygen species. *JACC: Basic to Translational Science* 3(4): 450–463.
6. Cortese-Krott MM and Kelm M. (2014) Endothelial nitric oxide synthase in red blood cells: key to a new erythrocrine function? *Redox biology* 2: 251–258.
7. González-Alonso J, Olsen DB and Saltin B. (2002) Erythrocyte and the regulation of human skeletal muscle blood flow and oxygen delivery: role of circulating ATP. *Circulation research* 91(11): 1046–1055.
8. Crawford JH, Isbell TS, Huang Z, et al. (2006) Hypoxia, red blood cells, and nitrite regulate NO-dependent hypoxic vasodilation. *Blood* 107(2): 566–574.
9. Al-Kuraishy HM, Al-Gareeb AI, Alblihed M, et al. (2021) COVID-19 and risk of acute ischemic stroke and acute lung injury in patients with type ii diabetes mellitus: the anti-inflammatory role of metformin. *Frontiers in Medicine* 8: 110.
10. Al-Kuraishy HM, Hussien NR, Al-Naimi MS, et al. (2020) Renin–Angiotensin system and fibrinolytic pathway in COVID-19: One-way skepticism. *Biomedical and Biotechnology Research Journal (BBRJ)* 4(5): 33.
11. Khawaja UA, Shamsoddin E, Desideri, et al. (2021) Infection of red blood cells by SARS-CoV-2: new evidence. *Einstein (São Paulo)* 19: eCE6285.
12. Valipour M, Zarghi A, Ebrahimzadeh, et al. (2021) Therapeutic potential of chelerythrine as a multi-purpose adjuvant for the treatment of COVID-19. *Cell Cycle* 20(22): 2321–2336.
13. Kim A, Dadgostar H, Holland GN, et al. (2006) Hemorheologic abnormalities associated with HIV infection: altered erythrocyte aggregation and deformability. *Investigative Opthalmology & Visual Science* 47(9): 3927–3932.
14. Costafreda MI, Ribes E, Franch À, et al. (2012) A single mutation in the glycophorin A binding site of hepatitis A virus enhances virus clearance from the blood and results in a lower fitness variant. *Journal of virology* 86(15): 7887–7895.
15. Al-Kuraishy HM, Al-Gareeb AI, Alzahrani KJ, et al. (2021) The potential role of neopterin in Covid-19: a new perspective. *Molecular and Cellular Biochemistry* 476(11): 4161–4166.
16. Winkler MS, Claus RA, Schilder M, et al. (2021) Erythrocytes increase endogenous sphingosine 1-phosphate levels as an adaptive response to SARS-CoV-2 infection. *Clinical science (London, England : 1979)* 135(24): 2781–2791.
17. Zhao J, Zhu M, Jiang H, et al. (2019) Combination of sphingosine-1-phosphate receptor 1 (S1PR1) agonist and antiviral drug: a potential therapy against pathogenic influenza virus. *Scientific reports* 9(1): 5272–5281.
18. Marfia G, Navone S, Guarnaccia L, et al. (2021) Decreased serum level of sphingosine-1-phosphate: a novel predictor of clinical severity in COVID-19. *EMBO molecular medicine* 13(1): e13424.
19. Taboada M, Caruezo V, Naveira A, et al. (2020) Corticosteroids and the hyper-inflammatory phase of the COVID-19 disease. *Journal of clinical anesthesia* 66: 109926.
20. Wißbrock A, Goradia NB, Kumar A, et al. (2019) Structural insights into heme binding to IL-36α proinflammatory cytokine. *Scientific reports* 9(1): 16893–16894.
21. Comentale G, Manzo R and Pilato E. (2020) Sars-Cov-2 interference in HEME production: is it the time for an early predictive biomarker? *Journal of Molecular Medicine* 98(8): 1053–1054.
22. Lam LM, Reilly JP, Rux AH, et al. (2021) Erythrocytes identify complement activation in patients with COVID-19. *American Journal of Physiology-Lung Cellular and Molecular Physiology* 321(2): L485–L489.
23. DeMartino AW, Rose JJ, Amdahl MB, et al. (2020) No evidence of hemoglobin damage by SARS-CoV-2 infection. *Haematologica* 105(12): 2769–2773.
24. Allam L, Ghrifi F, Mohammed H, et al. (2020) Targeting the GRP78-dependant SARS-CoV-2 cell entry by peptides and small molecules. *Bioinformatics and Biology Insights* 14: 1177932220965505.
25. Lithanatudom P, Leecharoenkiat A, Wannatung T, et al. (2010) A mechanism of ineffective erythropoiesis in β-thalassemia/Hb E disease. *Haematologica* 95(5): 716–723.
26. Sabirli R, Koseler A, Goren T, et al. (2021) High GRP78 levels in Covid-19 infection: A case-control study. *Life Sci* 265: 118781.
27. Ehsani S. (2020) Distant sequence similarity between hepcidin and the novel coronavirus spike glycoprotein: a potential hint at the possibility of local iron dysregulation in COVID-19. arXiv preprint arXiv:2003.12191.
28. Henry BM, Benoit JL, Benoit S, et al. (2020) Red blood cell distribution width (RDW) Predicts COVID-19 severity: a prospective, observational study from the cincinnati SARS-CoV-2 emergency department cohort. *Diagnostics* 10(9): 618.
29. Lippi G, Henry BM and Sanchis-Gomar F. (2021) Red blood cell distribution is a significant predictor of severe illness in coronavirus disease 2019. *Acta Haematol* 144(4): 360–364.
30. Cinelli MA, Do HT, Miley GP, et al. (2020) Inducible nitric oxide synthase: Regulation, structure, and inhibition. *Medicinal research reviews* 40(1): 158–189.
31. Grivennikov SI, Tumanov AV, Liepinsh DJ, et al. (2005) Distinct and nonredundant in vivo functions of TNF produced by t cells and macrophages/neutrophils: protective and deleterious effects. *Immunity* 22(1): 93–104.
32. Ulker P, Gunduz F, Meiselman HJ, et al. (2013) Nitric oxide generated by red blood cells following exposure to shear stress dilates isolated small mesenteric arteries under hypoxic conditions. *Clinical hemorheology and microcirculation* 54(4): 357–369.
33. Cosic I, Cosic D and Loncarevic I. (2020) RRM prediction of erythrocyte Band3 protein as alternative receptor for SARS-CoV-2 virus. *Applied Sciences* 10(11): 4053.
34. Iguchi N, Lankadeva YR, Mori TA, et al. (2019) Furosemide reverses medullary tissue hypoxia in ovine septic acute kidney injury. *Am J Physiol Regul Integr Comp Physiol* 317(2): R232–R239.

35. Sahu KK and Mishra A. (2019) Methemoglobinemia: challenges in diagnosis and management. *J Assoc Physicians India* 67(8): 94.
36. Swenson KE, Ruoss SJ and Swenson ER. (2021) The pathophysiology and dangers of silent hypoxemia in COVID-19 lung injury. *Annals of the American Thoracic Society* 18: 1098–1105.
37. Weisel JW and Litvinov RI. (2019) Red blood cells: the forgotten player in hemostasis and thrombosis. *J Thromb Haemostasis* 17(2): 271–282.
38. Mortaz E, Malkmohammad M, Jamaati H, et al. (2020) Silent hypoxia: higher NO in red blood cells of COVID-19 patients. *BMC Pulm Med* 20(1): 269–276.
39. Akaberi D, Krambrich J, Ling J, et al. (2020) Mitigation of the replication of SARS-CoV-2 by nitric oxide in vitro. *Redox biology* 37: 101734.
40. Green SJ. (2020) Covid-19 accelerates endothelial dysfunction and nitric oxide deficiency. *Microb Infect* 22(4): 149–150.
41. Široká M, Franco C, Guľašová Z, et al. (2020) Nuclear factor-kB and nitric oxide synthases in red blood cells: good or bad in obesity? A preliminary study. *Eur J Histochem: EJH* 64(1): 3081.
42. Camp OG, Bai D, Gonullu DC, et al. (2021) Melatonin interferes with COVID-19 at several distinct ROS-related steps. *J Inorg Biochem* 223: 111546.
43. Peng Z, Luo R, Xie T, et al. (2019) Erythrocyte adenosine A2B receptor-mediated AMPK activation: a missing component counteracting CKD by promoting oxygen delivery. *J Am Soc Nephrol* 30(8): 1413–1424.
44. Al-Kuraishy HM, Al-Gareeb AI, Al-Hussaniy HA, et al. (2022) Neutrophil Extracellular Traps (NETs) and Covid-19: A new frontiers for therapeutic modality. *Int Immunopharm* 104: 108516.
45. Al-Kuraishy HM, Al-Gareeb AI, Butnariu M, et al. (2022) The crucial role of prolactin-lactogenic hormone in Covid-19. *Molecular and Cellular Biochemistry*: 1–2.
46. Al-Kuraishy HM, Al-Gareeb AI and Batiha GE. (2022) The possible role of Ursolic acid in Covid-19: A real game changer. *Clinical Nutrition ESPEN* 47: 414–417.
47. San Juan I, Bruzzone C, Bizkarguenaga M, et al. (2020) Abnormal concentration of porphyrins in serum from COVID-19 patients. *Br J Haematol* 190(5): e265.
48. Stuart J. (2019) Erythrocyte deformability. *Clinical Blood Rheology* 38: 965–977, CRC Press.
49. Alkuraishy HM, Al-Gareeb AI and Albuhadilly AK. (2014) Vinpocetine and pyritinol: a new model for blood rheological modulation in cerebrovascular disorders—a randomized controlled clinical study. *BioMed Res Int* 2014: 324307–324308.
50. Silva-Herdade AS, Andolina G, Faggio C, et al. (2016) Erythrocyte deformability—A partner of the inflammatory response. *Microvascular research* 107: 34–38.
51. Pretorius E. (2018) Erythrocyte deformability and eryptosis during inflammation, and impaired blood rheology. *Clinical hemorheology and microcirculation* 69(4): 545–550.
52. McNamee AP, Horobin JT, Tansley GD, et al. (2018) Oxidative Stress Increases Erythrocyte Sensitivity to Shear-Mediated Damage. *Artif Organs* 42(2): 184–192.
53. Kim A, Dadgostar H, Holland GN, et al. (2006) Hemorheologic abnormalities associated with HIV infection: altered erythrocyte aggregation and deformability. *Investigative Opthalmology & Visual Science* 47(9): 3927–3932.
54. Goud PT, Bai D and Abu-Soud HM. (2021) A multiple-hit hypothesis involving reactive oxygen species and myeloperoxidase explains clinical deterioration and fatality in COVID-19. *Int J Biol Sci* 17(1): 62–72.
55. Farber PL. (2021) Can erythrocytes behavior in microcirculation help the understanding the physiopathology and improve prevention and treatment for covid-19? *Clin Hemorheol Microcirc* 78: 41–47.
56. Todoriko L, Gumeniuk M, Semianiv I, et al. (2021) Functional state of erythrocytes in chronic obstructive pulmonary disease on the background of COVID-19, ways of correction. *European Respiratory Journal* 58: PA872.