

Impact of Anaemia and Dysregulated Iron Metabolism on COVID-19 Clinical Outcome – Review Article

Matea Bogović¹, Robert Rončević², Stjepan Grga Milanković^{*3}

¹ Department of Radiology, National Memorial Hospital Vukovar, Vukovar, Croatia

² Department of Diagnostic and Interventional Radiology, Clinical Hospital Centre Osijek, Osijek, Croatia

³ Department of Otorhinolaryngology and Head and Neck Surgery, Clinical Hospital Centre Osijek, Osijek, Croatia

*Corresponding author: Stjepan Grga Milanković, stjegan.grga.milankovic@gmail.com

Abstract

Coronavirus disease-19 (COVID-19) is a disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that can manifest in a wide range of forms, but the most common symptoms are fever, headache, fatigue, respiratory problems, lost sense of smell and taste, sore throat, muscle pain and malaise.

In patients with COVID-19, the inflammatory response of the organism affects iron homeostasis. Severe COVID-19 infections may lead to a hyperinflammatory condition, characterised by elevated ferritin levels that correlate with the severity of the clinical course, prolonged intensive care unit (ICU) stay, development of acute respiratory distress syndrome and a fatal outcome. As a result of iron metabolism disorders in inflammation, decreased erythropoiesis and reduced biological activity of erythropoietin, the erythrocyte half-life is shortened, leading to anaemia of chronic inflammation. Cytokine IL-6 plays the most crucial role in regulating iron concentration. It affects iron metabolism by producing hepcidin via STAT 3. Hepcidin produces regulatory effects on iron by binding with ferroportin, the only known transmembrane iron exporter.

Anaemia has long been characterised as a significant risk factor contributing to increased mortality and poorer clinical outcomes for various infections. The most severe forms of COVID-19 infection result in pneumonia, causing a reduced supply of oxygen to the circulation, ultimately leading to ischemia of vital organs. Anaemia of chronic disease is more common in COVID-19 positive patients and is associated with a poorer clinical outcome. A higher ferritin/transferrin ratio indicates an advanced inflammatory condition and may be a predictive factor of ICU admission.

(Bogović M, Rončević R, Milanković SG. Impact of Anaemia and Dysregulated Iron Metabolism on COVID-19 Clinical Outcome – Review Article. SEEMEDJ 2021; 5(2); 9-17)

Received: Aug 25, 2021; revised version accepted: Nov 8, 2021; published: Nov 26, 2021

KEYWORDS: COVID-19, anaemia, iron metabolism, SARS-CoV-2

Introduction

In the Hubei Province of the People's Republic of China, in December 2019, a new type of virus emerged – severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The world faced a new global issue, the pandemic of the coronavirus disease 2019 (COVID-19). Currently, there have been over 200,000,000 coronavirus cases recorded and most patients have presented with mild clinical symptoms (with over 180,000,000 patients recovered). However, 4,000,000 deaths from COVID-19 have been recorded up to this moment (1).

This pandemic has affected many aspects of our everyday life, from health to economy. In order to provide optimal treatment to patients, it is vital to identify the risk factors contributing to the development of severe forms of the disease so as to effectively use the limited resources available in the fight against the virus. Despite the progress that has been made, such as the development of the vaccine, the scientific community is still trying to understand the impact of the virus and its new variants on the clinical outcomes of patients with COVID-19. Infection with the SARS-CoV-2 virus can manifest itself in a wide range of clinical presentations: from asymptomatic vectors and milder forms to more severe ones, which require hospital care and respirators, and finally those ending in death. The infection affects various systems and the clinical presentation differs from patient to patient, but the most common symptoms include fever, headache, fatigue, respiratory problems, lost sense of smell and taste, sore throat, muscle pain and malaise (2).

A combination of symptoms, medical history information, epidemiological data, polymerase chain reaction (PCR) testing, serological testing, laboratory findings, chest X-ray or computed tomography (CT) findings results in a clinical diagnosis (3). Many agents are used in the treatment of COVID-19: antiviral drugs, corticosteroids, various antibiotics, anti-inflammatory drugs or immunomodulators. Over time, the scientific community has discovered alternative forms of treatment and prevention of

the disease. At the moment, the best form of protection against infection and the development of more severe forms of the disease is vaccination, which is the most effective weapon in the fight against viruses.

In patients with COVID-19, the inflammatory response of the organism affects iron homeostasis and leads to a reduction in iron absorption in the intestine, which further reduces the availability of iron for erythropoiesis and haemoglobin production (4).

Iron is an important redox catalyst in several reactions. Due to the fact that a variety of pathogens need iron, one of many defence mechanisms is to limit the availability of iron to infectious agents. For example, iron is mostly found within cells, bound to haemoglobin in erythrocytes. Bacteria and viruses have developed mechanisms to steal iron from their hosts (5).

The aim of this review is to present the current knowledge from available papers and literature on the complex relationship between iron metabolism, anaemia and COVID-19 that affects the clinical course of the disease.

Regulation of iron metabolism

Maintenance of iron homeostasis is a complex process involving the regulation of (A) iron in duodenal enterocytes, (B) use in erythroblasts, (C) storage in hepatocytes and (D) macrophage recycling in the spleen. After being reduced with ascorbic acid and duodenal cytochrome b (DCYTB) on the apical membrane of enterocytes, iron is absorbed by divalent metal transporter 1 (DMT1) and transferred to the basolateral membrane, where it exits the cells with the help of ferroportin into the circulation, where it binds to transferrin (holo-Tf). Erythrocytes, the cells that require the most iron, bind holo-Tf to the transferrin receptor TfR1. After endocytosis, iron is used in the mitochondria to synthesise haem, which will be incorporated into haemoglobin. If the body absorbs more iron than it needs, it is stored in 6 ferritins, mostly in hepatocytes. The largest

source of iron are macrophages, which phagocytose stale erythrocytes and release iron from haem via haem oxygenase 1 (HO1). These processes are regulated by hepcidin, which binds to ferroportin and promotes its internalisation and degradation. In this way, it

prevents the absorption of iron and the release of iron stored in hepatocytes and recycled in macrophages. (6) (Figure 1).

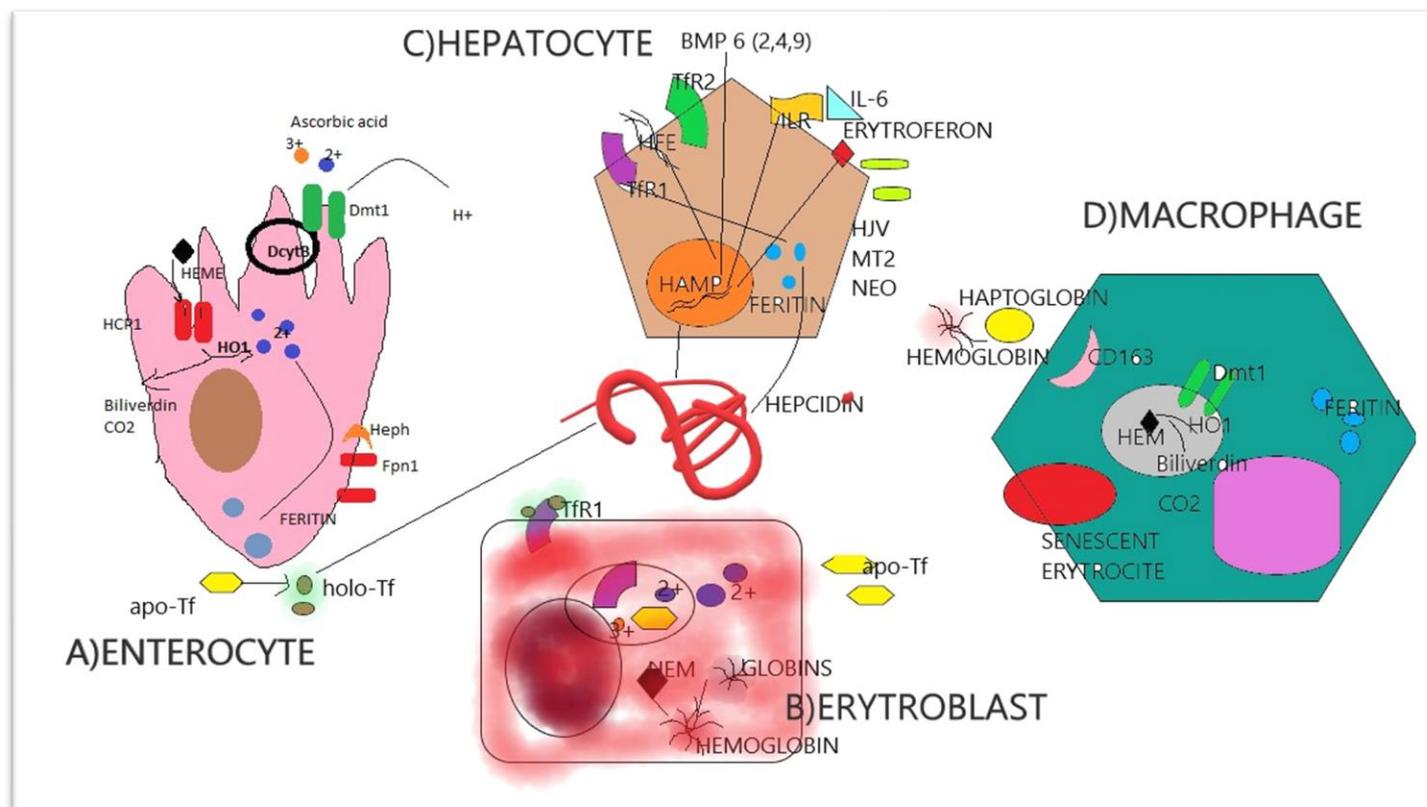


Figure 1. Maintenance of iron homeostasis

Inflammation leads to disbalanced iron homeostasis

Various comorbidities, such as obesity, hypertension, cardiovascular disease, hypercholesterolemia, chronic kidney disease and metabolic syndrome, as well as old age, are associated with higher mortality and poorer treatment outcomes of COVID-19 (7). Patients suffering from a more severe form of the disease, among other laboratory findings, had leukocytosis with low lymphocyte and platelet count. Inflammatory markers, such as C-reactive protein (CRP), interleukin 6 (IL-6) and ferritin were elevated (8). Viral infections, including SARS-CoV-2 infections, affect the haemoglobin molecule through ACE2, CD147, CD26 and other

receptors on erythrocytes and/or blood cell precursors. Viral endocytosis can cause hemoglobinopathy through the connection between spike proteins and cellular receptors. ORF8 protein and surface glycoproteins on the virus can bind to porphyrin, attacking haem on the 1- β chain of haemoglobin. Consequently, SARS-CoV-2 promotes haemolysis and/or creates a haem release complex, forming dysfunctional haemoglobin with a reduced oxygen concentration and CO₂ transport (9). More severe forms of COVID-19 are characterised by an excessive inflammatory response in the form of a cytokine storm, which is characterised by IL-6 hyper-expression and hyperferritinemia (Figure 2). IL-6 also affects iron metabolism by inducing the production of

hepcidin via STAT 3 (10), which is important in the regulation of iron homeostasis. According to the research published so far, cytokine IL-6 plays the most crucial role in regulating iron concentration, at least in humans and animals (11). Other cytokines, such as interleukin-1 and activin B, are also involved in regulating iron production, but their role has not been investigated sufficiently (12). Heparin produces its regulatory effects on iron by binding to ferroportin, the only known transmembrane iron exporter (13).

Increased hepcidin concentrations inhibit iron absorption in the duodenum, where ferroportin delivers the absorbed iron into the circulation. They also act on macrophages by blocking the release of iron recycled from older erythrocytes into plasma (14). Recent research suggests that in higher concentrations, hepcidin can directly block iron exports by occluding ferroportin, a mechanism that may be important in limiting the release of iron from endocytic-deficient cells machines (erythrocytes) or in conditions where endocytosis is slow (15). This mechanism leads to elevated intracellular ferritin. Excess intracellular iron reacts with free oxygen radicals, creating oxidative stress. The intracellular iron excess leads to ferroptosis, programmed cell death. Excess iron is also thought to cause mitochondrial dysfunction, microbiome diversity and hypercoagulability (16). New evidence suggests that IL-6 may have a secondary suppressive effect on erythroid precursors (17). In addition, loss of IL-6 and hepcidin results in milder anaemia and faster haemoglobin recovery in a well-established mouse model (18). IL-6 knockout animals showed faster bone marrow recovery compared to hepcidin knockout animals. Heparin downregulates the release of iron into plasma by binding to and functionally lowering ferroportin 1, the sole iron exporter (13,19). Persons with high iron levels are at an increased risk of developing various infections. Evidence suggests that better control of patients' iron levels could be a protective factor in the fight against the virus (20). It is still debatable whether an iron metabolism disorder is a result of a physiological response within an infectious

disease or it leads to a worse disease outcome. However, recent research has shown that cell damage and inadequate immune response lead to iron disbalance. Therefore, we can conclude that iron metabolism disorders significantly contribute to the course of COVID-19 (4).

Impact of impaired iron metabolism on anaemia

Anaemia has long been characterised as a significant risk factor contributing to increased mortality and poorer clinical outcomes for various infections. It is well known that anaemia exacerbates the severity of respiratory problems, since various diseases and previous studies have shown a high prevalence of anaemia in patients with community-acquired pneumonia (21). Although it has not been documented explicitly, the underlying causes and patterns of inflammation, genetic composition and the patient's pre-disease condition, including iron concentration and erythropoietic capacity, could contribute to each pathophysiological pathway of inflammatory anaemia (22). Initially, systemic immune activation leads to significant changes in iron transport, causing iron retention in macrophages and reduced absorption of iron from food. Iron sequestration in macrophages is far more critical because 90% of daily iron requirements for haemoglobin (Hb) synthesis and erythropoiesis come from recycled iron originating from aged erythrocytes. Iron stores in tissues and in the circulation stimulate the expression of hepcidin (11,23) and inflammatory cytokines, hypoxia (12), iron deficiency and ineffective erythropoiesis. Inflammation adversely affects erythropoiesis by separating iron from erythroid precursors, thus causing iron-restricted erythropoiesis (24). Inflammatory anaemia, a condition involving elevated hepcidin levels, can conceptually be called functional iron deficiency. Due to this iron-restricted erythropoiesis, erythroferrone (ERFE) increases and is likely to provide some counter-regulation of elevated hepcidin. ERFE knockout mice treated with heat-killed *Brucella abortus*, a well-accepted model of inflammatory anaemia, showed delayed haemoglobin recovery because of inadequate hepcidin suppression

(25). Thus, suppressed erythropoiesis in inflammatory anaemia may allow a further increase in hepcidin expression.

Most COVID-19 infections have a milder clinical course and up to 20% of patients require hospital care, most often because of pneumonia, with admission to the ICU and a need for mechanical ventilation (26,27). The most severe forms of COVID-19 infection result in pneumonia, which leads to diffuse alveolar damage and gas exchange disorders (28). As a result, arterial oxygenation becomes impaired. Oxygen saturation depends on the concentration of haemoglobin, which is why reduced haemoglobin levels cause a decrease in the oxygen transfer capacity and oxygen saturation of arterial blood (29). Anaemia, as a separate condition, can cause ischemia of vital organs (30). The incidence of anaemia in patients hospitalised in the ICU is about 95% (31), while haemoglobin levels are lower in COVID-19 positive patients admitted to the ICU compared to hospitalised COVID-19 positive patients with a milder clinical presentation (32).

Increased levels of ferritin and hepcidin may be a predictive factor of a poorer clinical outcome. Severe COVID-19 infections are characterised by a hyper inflammatory condition, including elevated ferritin levels that correlate with the severity of the clinical presentation, prolonged ICU stay, development of acute respiratory distress syndrome and a fatal outcome. As a result of iron metabolism disorders in inflammation, decreased erythropoiesis and reduced biological activity of erythropoietin, the erythrocyte half-life is shortened, leading to anaemia of chronic inflammation (33). A clinical study conducted in China has found that patients with a severe clinical course of COVID-19 infection had higher levels of hepcidin and ferritin compared to patients with a milder clinical course. It was concluded that hepcidin and ferritin could be predictive factors of the clinical outcome of coronavirus infection (34). Also, an elevated ferritin/transferrin ratio is a predictive factor of a worsening clinical condition and longer stay in the ICU (31) (Figure 2)..

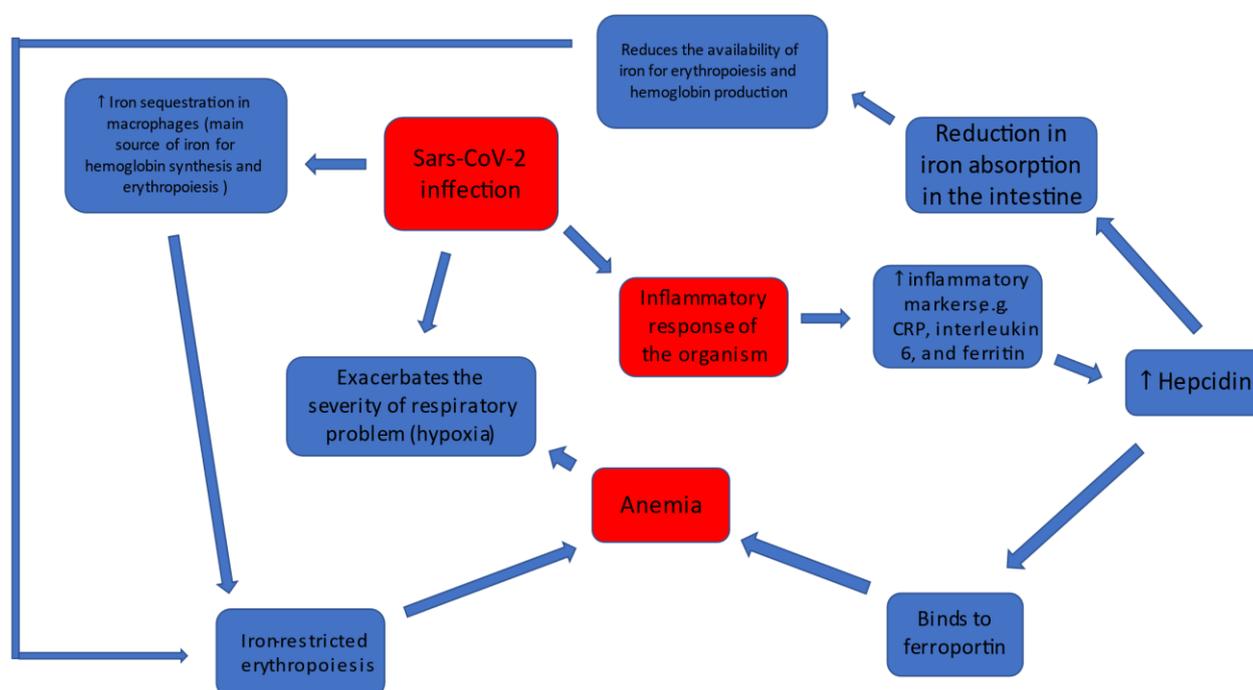


Figure 2. Increased levels of ferritin and hepcidin may be a predictive factor of a poorer clinical outcome

A review of the literature, including prospective studies monitoring the impact of anaemia on the clinical outcome of COVID-19 infections, shows that, of the total number of patients hospitalised due to COVID-19 infection, the proportion of patients with anaemia ranges between 25% and 65% (33,35,36). Studying the difference in the clinical outcome of COVID-19 infection in patients with and without anaemia, Tao, Z. et al. found that patients suffering from anaemia were older and more often had chronic kidney disease. The Chinese scientists classified patients with anaemia into three groups according to haemoglobin levels. Patients with severe anaemia (Hb < 80 g/L) had a higher incidence of dyspnoea and lower levels of O₂ partial pressure and O₂ saturation compared to patients with mild anaemia (Hb between 110 and 119 g/L for women and Hb between 110 and 129 g/L for men) and with moderate anaemia (Hb between 80 and 110 g/L) (35). Patients with severe anaemia were more likely to have coagulation disorders (elevated D-dimers) and increased inflammatory parameters compared to mild-to-moderate anaemia (35). A prospective study conducted in Iran by Dinevari et al. showed a high prevalence of COVID-19 infected patients with anaemia at admission to the hospital as well as an increased risk of admission to ICU, need for mechanical ventilation and mortality rates compared to COVID-19 positive patients without anaemia. It should also be emphasised that patients with anaemia were older and had more comorbidities, which also increased the risk of a poorer clinical outcome (36). In a study comparing hospitalised COVID-19 positive patients with other patients exhibiting the same symptoms, a higher prevalence of anaemia was found among COVID-19 positive patients, mainly due to inflammation with elevated ferritin levels and decreased saturated transferrin levels. Despite the higher prevalence, no statistically significant higher mortality was observed in anaemic patients compared to COVID-19 positive patients without anaemia (37). Elevated iron and ferritin levels in the circulation and in the lungs increase the risk of injury to the lung parenchyma (38). Severe forms of COVID-

19 have been associated with disseminated intravascular coagulation and thrombosis, but the mechanism of thrombosis is unknown. Patients infected with COVID-19 have elevated transferrin levels, which may be associated with a hypercoagulable condition (39). It has long been known that transferrin is not only an iron transporter, but it also inhibits antithrombin and promotes the effect of thrombin and coagulation factor XIIIa (40). The tendency to develop thrombosis is one of the most dangerous complications of COVID-19 infection. In order to protect the lungs from excessive free iron, treatment of COVID-19 positive patients with lactoferrin and iron chelators has been proposed to reduce circulating free iron (41). However, no clinical study has been published to date to show the effectiveness of this method. Regarding COVID-19 positive paediatric patients, no significant number of cases involving patients with anaemia have been reported, nor have they had a significantly worse clinical outcome (42).

Conclusion

In conclusion, anaemia of chronic disease is more common in COVID-19 positive patients and it is associated with a poorer clinical outcome. A higher ferritin/transferrin ratio reflects an advanced inflammatory condition and may be a predictive factor of ICU admission and the need for mechanical ventilation. Given the important role of iron metabolism in COVID-19 infection, future studies should evaluate the efficacy of treatment with iron chelators and lactoferrin and their impact on the clinical outcome of these diseases.

Acknowledgement. None.

Disclosure

Funding. No specific funding was received for this study.

Competing interests. None to declare

References

- Ge H, Wang X, Yuan X, Xiao G, Wang C, Deng T, Yuan Q, Xiao X. The epidemiology and clinical information about COVID-19. *European journal of clinical microbiology & infectious diseases*. European Society of Clinical Microbiology. 2020; 39(6):1011-9. DOI: 10.1007/s10096-020-03874-z.
- Booth A, Reed AB, Ponzo S, Yassaee A, Aral M, Plans D, Labrique A, Mohan D. Population risk factors for severe disease and mortality in COVID-19: A global systematic review and meta-analysis. *PLoS One*. 2021;16(3):e0247461. DOI: 10.1371/journal.pone.0247461
- Yüce M, Filiztekin E, Özkaya KG. COVID-19 diagnosis -A review of current methods. *Biosens Bioelectron*. 2021; 172:112752. DOI: 10.1016/j.bios.2020.112752
- Cavezzi A, Troiani E, Corrao S. COVID-19: hemoglobin, iron, and hypoxia beyond inflammation. A narrative review. *Clin Pract*. 2020; 10(2):1271. DOI: 10.4081/cp.2020.1271
- Cassat JE, Skaar EP. Iron in infection and immunity. *Cell Host Microbe*. 2013; 13(5):509-19.
- Silva B, Faustino P. An overview of molecular basis of iron metabolism regulation and the associated pathologies. *Biochim Biophys Acta*. 2015; 1852(7):1347-59. DOI: 10.1016/j.bbadis.2015.03.011
- Parohan M, Yaghoubi S, Seraji A, Javanbakht MH, Sarraf P, Djalali M. Risk factors for mortality in patients with Coronavirus disease 2019 (COVID-19) infection: a systematic review and meta-analysis of observational studies. *Aging Male*. 2020; 23(5):1416-1424. DOI: 10.1080/13685538.2020.1774748
- Hong KH, Lee SW, Kim TS, Huh HJ, Lee J, Kim SY, Park J-S, Kim GJ, Sung H, Roh KH, Kim J-S, Kim HS, Lee, S-T, Seong M-V, Ryoo N, Lee H, Kwon KC, Yoo CK. On behalf of Korean Society for Laboratory Medicine, COVID-19 Task Force and the Center for Laboratory Control of Infectious Diseases, the Korea Centers for Disease Control and Prevention Guidelines for Laboratory Diagnosis of Coronavirus Disease 2019 (COVID-19) in Korea. *Ann Lab Med*. 2020; 40(5):351-60. <https://doi.org/10.3343/alm.2020.40.5.351>
- Cavezzi A, Troiani E, Corrao S. COVID-19: Hemoglobin, Iron, and Hypoxia beyond Inflammation. A Narrative Review. *Clinics and Practice*. 2020; 10(2):24-30. <https://doi.org/10.4081/cp.2020.1271>
- Muckenthaler MU, Rivella S, Hentze MW, Galy B. A red carpet for iron metabolism. *Cell*. 2017;168(3):344-361. DOI: 10.1016/j.cell.2016.12.034
- Nemeth E, Rivera S, Gabayan V, Keller C, Taudorf, Pedersen BK, Tomas Ganz. IL-6 mediates hypoferremia of inflammation by inducing the synthesis of the iron regulatory hormone hepcidin. *J Clin Invest*. 2004; 113(9):1271-1276. DOI: 10.1172/JCI20945
- Nicolas G, Chauvet C, Viatte L, Danan JL, Bigard X, Devaux I, Beaumont C, Kahn A, Vaulont S. The gene encoding the iron regulatory peptide hepcidin is regulated by anemia, hypoxia, and inflammation. *J Clin Invest*. 2002; 110:1037-1044. DOI: 10.1172/JCI15686
- Nemeth E, Tuttle MS, Powelson J, Vaughn MB, Donovan A, McVey Ward D, Ganz T, Kaplan J. Hepcidin regulates cellular iron efflux by binding to ferroportin and inducing its internalization. *Science*. 2004; 306(5704): 2090-2093. DOI: 10.1126/science.1104742
- Ganz T, Nemeth E. Hepcidin and iron homeostasis. *Biochim Biophys Acta*. 2012; 1823(9):1434-1443. DOI: 10.1016/j.bbamcr.2012.01.014
- Aschemeyer S, Qiao B, Stefanova D, Valore EV, Sek AC, Ruwe TA, Vieth KR, Jung G, Casu C, Rivella S, Jormakka M, Mackenzie B, Ganz T, Nemeth E. Structure-function analysis of ferroportin defines the binding site and an alternative mechanism of action of hepcidin. *Blood*. 2018; 131(8):899-910. DOI: 10.1182/blood-2017-05-786590
- Saleh J, Peyssonnaud C, Singh K, Edeas M. Mitochondria and microbiota dysfunction in COVID-19 pathogenesis. *Mitochondrion*. 2020; 54:1-7. DOI: 10.1016/j.mito.2020.06.008.
- McCranor BJ, Kim MJ, Cruz NM, Xue X-L, Berger AE, Walston JD, Civin CI, Roy CN. Interleukin-6 directly impairs the erythroid development of human TF-1 erythroleukemic cells. *Blood Cells Mol Dis*. 2014; 52:126-133. DOI: 10.1016/j.bcmd.2013.09.004
- Gardenghi S, Renaud TM, Meloni A, Casu C, Crielgaard BJ, Bystrom LM, Greenberg-Kushnir N, Sasu BJ, Cooke KS, Rivella S. Distinct roles for hepcidin and interleukin-6 in the recovery from anemia in mice injected with heat-killed *Brucella abortus*. *Blood*. 2014; 123:1137-1145. DOI: 10.1182/blood-2013-08-521625.
- Donovan A, Lima CA, Pinkus JL, Pinkus GS, Zon LI, Robine S, Andrews NC. The iron exporter

- ferroportin/Slc40a1 is essential for iron homeostasis. *Cell Metab.* 2005; 1:191-200. DOI: 10.1016/j.cmet.2005.01.003.
20. Khan FA, Fisher MA, Khakoo RA. Association of hemochromatosis with infectious diseases: expanding spectrum. *Int J Infect Dis.* 2007; 11(6):482-7. DOI: 10.1016/j.ijid.2007.04.007.
21. Hariyanto TI, Kurniawan A. Anemia is associated with severe coronavirus disease 2019 (COVID-19) infection. *Transfus Apher Sci.* 2020; 59(6):102926. DOI: 10.1016/j.transci.2020.102926
22. Weiss G, Ganz T, Goodnough LT. Anemia of inflammation. *Blood.* 2019; 133(1):40-50. DOI: 10.1182/blood-2018-06-856500
23. Pigeon C, Ilyin G, Courselaud B, Leroyer P, Turlin B, Brissot P, Loréal OA. new mouse liver-specific gene, encoding a protein homologous to human antimicrobial peptide hepcidin, is overexpressed during iron overload. *J Biol Chem.* 2001; 276: 7811-7819. DOI: 10.1074/jbc.M008923200.
24. Langer AL, Ginzburg YZ. Role of hepcidin-ferroportin axis in the pathophysiology, diagnosis, and treatment of anemia of chronic inflammation. *Hemodial Int.* 2017; 21 Suppl 1(Suppl 1):S37-S46. DOI: 10.1111/hdi.12543
25. Kautz L, Jung G, Nemeth E, Ganz T. Erythroferrone contributes to recovery from anemia of inflammation. *Blood.* 2014; 124:2569-2574. DOI: 10.1182/blood-2014-06-584607
26. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, Cheng Z, Xiong Y, Zhao Y, Li Y, Wang X, Peng Z. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA.* 2020; 323(11):1061-1069. DOI: 10.1001/jama.2020.1585
27. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, Wu Y, Zhang L, Yu Z, Fang M, Yu T, Wang Y, Pan S, Zou X, Yuan S, Shang Y. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med.* 2020; 8(5):475-481. DOI: 10.1016/S2213-2600(20)30079-5.
28. Carsana L, Sonzogni A, Nasr A, Rossi RS, Pellegrinelli A, Zerbi P, Rech R, Colombo R, Antinori S, Corbellino M, Galli M, Catena E, Tosoni A, Gianatti A, Nebuloni M. Pulmonary post-mortem findings in a series of COVID-19 cases from northern Italy: a two-centre descriptive study. *Lancet Infect Dis.* 2020; 20(10):1135-1140. DOI: 10.1016/S1473-3099(20)30434-5
29. Pittman R. Regulation of Tissue Oxygenation. *Colloquium Series on Integrated Systems Physiology: From Molecule to Function.* 2011; 3(3):1-100.,
30. Saaby L, Poulsen T, Hosbond S, Larsen T, Pyndt Diederichsen A, Hallas J, Thygesen K, Mickley H. Classification of Myocardial Infarction: Frequency and Features of Type 2 Myocardial Infarction. *The American Journal of Medicine.* 2013; 126(9):789-797. DOI: 10.1016/j.amjmed.2013.02.029
31. Prakash D. Anemia in the ICU. *Critical Care Clinics.* 2012; 28(3):333-343. DOI: 10.1016/j.ccc.2012.04.012
32. Lippi G, Mattiuzzi C. Hemoglobin value may be decreased in patients with severe coronavirus disease 2019. *Hematology, Transfusion and Cell Therapy.* 2020; 42(2):116-117. DOI: 10.1016/j.htct.2020.03.001
33. Bellmann-Weiler R, Lanser L, Barket R, Rangger L, Schapfl A, Schaber M, Fritsche G, Wöll E, Weiss G. Prevalence and Predictive Value of Anemia and Dysregulated Iron Homeostasis in Patients with COVID-19 Infection. *Journal of Clinical Medicine.* 2020; 9(8):2429. DOI: 10.3390/jcm9082429.
34. Zhou C, Chen Y, Ji Y, He X, Xue D. Increased Serum Levels of Hepcidin and Ferritin Are Associated with Severity of COVID-19. *Med Sci Monit.* 2020 Sep 26;26:e926178. DOI: 10.12659/MSM.926178.
35. Tao Z, Xu J, Chen W, Yang Z, Xu X, Liu L, Chen R, Xie J, Liu M, Wu J, Wang H, Liu J. Anemia is associated with severe illness in COVID-19: A retrospective cohort study. *Journal of Medical Virology.* 2020; 93(3):1478-1488. DOI: 10.1002/jmv.26444
36. Faghieh Dinevari M, Somi M, Sadeghi Majd E, Abbasalizad Farhangi M, Nikniaz Z. Anemia predicts poor outcomes of COVID-19 in hospitalized patients: a prospective study in Iran. *BMC Infectious Diseases.* 2021; 21(1):62. DOI: 10.1186/s12879-020-05746-5.
37. Bergamaschi G, Borrelli de Andreis F, Aronico N, Lenti M, Barteselli C, Merli S, Pellegrino I, Coppola L, Cremonese EM, Croce G, Mordà F, Lapia F, Ferrari S, Ballesio A, Parodi A, Calabretta F, Ferrari MG, Fumoso F, Gentile A, Melazzini F, Di Sabatino A; Internal Medicine Covid-19 Collaborators. Correction to: Anemia in patients with Covid-19: pathogenesis and clinical significance. *Clinical and Experimental Medicine.* 2021; 21(2):247-247. DOI: 10.1007/s10238-021-00699-8

38. Kim J. The Role of Iron Metabolism in Lung Inflammation and Injury. *J Allergy Therapy*. 2012;3(Suppl 4):004. DOI: 10.4172/2155-6121.S4-004.

39. McLaughlin K, Bechtel M, Bojkova D, Münch C, Ciesek S, Wass M, Michaelis M, Cinatl Jr J. COVID-19-Related Coagulopathy—Is Transferrin a Missing Link? *Diagnostics*. 2020; 10(8):539. DOI: 10.3390/diagnostics10080539

40. Tang X, Zhang Z, Fang M, Han Y, Wang G, Wang S, Xue M, Li Y, Zhang L, Wu J, Yang B, Mwangi J, Lu Q, Du X, Lai R. Transferrin plays a central role in coagulation balance by interacting with clotting

factors. *Cell Research*. 2019; 30(2):119-132. DOI: 10.1038/s41422-019-0260-6

41. Habib H, Ibrahim S, Zaim A, Ibrahim W. The role of iron in the pathogenesis of COVID-19 and possible treatment with lactoferrin and other iron chelators. *Biomedicine Pharmacotherapy*. 2021; 136:111228. DOI: 10.1016/j.biopha.2021.111228

42. Kosmeri C, Koumpis E, Tsaouri S, Siomou E, Makis A. Hematological manifestations of SARS-CoV-2 in children. *Pediatric Blood Cancer*. 2020 Dec;67(12):e28745. DOI: 10.1002/psc.28745..

Conception and design: Bogović M, Rončević R, Milanković SG

Critical revision of the article for important intellectual content: Bogović M, Rončević R, Milanković SG

Drafting of the article: Bogović M, Rončević R, Milanković SG

Final approval of the article: Bogović M, Rončević R, Milanković SG

¹ **Author contribution.** Acquisition of data: Bogović M, Rončević R, Milanković SG
Administrative, technical or logistic support: Bogović M, Rončević R, Milanković SG