Wydawnictwo UR 2021
ISSN 2544-1361 (online); ISSN 2544-2406
doi: 10.15584/ejcem.2021.1.8

http://www.ejcem.ur.edu.pl/en/
European Journal of Clinical and Experimental Medicine
Eur J Clin Exp Med 2021; 19 (1): 52–58

REVIEW PAPER

Kusum Ghosh [1(ABG,)], Diptendu Chatterjee [1(AFG)], Abhisikta Ghosh Roy [2(BG)],
Arup Ratan Bandyopadhyay [1(ABCDFGH)]

Socio-economic status, iron deficiency anemia and COVID-19 disease burden – an appraisal

[1] Department of Anthropology, University of Calcutta, Kolkata, India
[2] Anthropological Survey of India, Central Region, India

ABSTRACT

Introduction. Severe Acute Respiratory Syndrome-2, possesses varying degrees of susceptibility and lethality worldwide and WHO declared this as a pandemic of this century.

Aim. In this background, the aim of this present narrative is to provide a complementary overview of how low iron stores and mild anemia offers protection from infectious diseases like COVID-19 by restricting the viral replication and also to suggest some potential adjuvant therapeutic interventions.

Material and methods. Therefore, we performed a literature search reviewing pertinent articles and documents. PubMed, Google Scholar, Chemrxiv, MedRxiv, BioRxiv, Preprints and ResearchGate were investigated.

Analysis of the literature. Recent studies reported drastic systemic events taking place that contribute to the severe clinical outcomes such as decreased hemoglobin indicating anemia, hypoxia, altered iron metabolism, hypercoagulability, oxidative stress, cytokine storm, hyper-ferritinemia and thus Multi Organ Failure, reportedly hailed as the hallmark of the COVID-19 hyper-inflammatory state. Interestingly it is globally observed that, countries with higher Socio-economic status (SES) have considerably lower prevalence of Iron Deficiency Anemia (IDA) but higher Case Fatality Rate (CFR) rate due to COVID-19 while, low SES countries characterized by the higher prevalence of IDA, are less affected to COVID-19 infection and found to have less CFR, which is almost half to that of the higher SES counterpart.

Conclusion. Present review presumed that,low iron stores and mild anemia may play a beneficial role in some cases by offering protection from infectious diseases as low iron restricts the viral replication.Thus, suggested iron chelation or iron sequestration as an alternative beneficial adjuvant in treating COVID-19 infection.

Keywords. COVID-19, iron deficiency anemia, socio-economic status

Corresponding author: Arup Ratan Bandyopadhyay, e-mail: abanthro@caluniv.ac.in

Participation of co-authors: A – Author of the concept and objectives of paper; B – collection of data; C – implementation of research; D – elaborate, analysis and interpretation of data; E – statistical analysis; F – preparation of a manuscript; G – working out the literature; H – obtaining funds

Received: 4.09.2020 | Accepted: 9.01.2021
Publication date: March 2020

Ghosh K, Chatterjee D, Ghosh Roy A, Bandyopadhyay AR. *Socio-economic status, iron deficiency anemia and COVID-19 disease burden – an appraisal*. Eur J Clin Exp Med. 2021;19(1):52–58. doi: 10.15584/ejcem.2021.1.8

Introduction

COVID-19 is a novel infectious disease, caused by SARS-CoV-2 which belongs to the family Coronaviride.[1] SARS-CoV-2, is a severe, complex, and multifactorial diseaseand driven by a combination of genetic and epigenetic factors.[2]This disease endangers disproportionately the elderly especially those with pre-existing co-morbidities.[3]From the large family of Coronaviruses, three have been known to cause severe pneumonia such as Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) and Middle East Respiratory Syndrome Coronavirus (MERS-CoV) and recently recognized Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), possesses varying degrees of susceptibility and lethality worldwide.[4-7] Researches demonstrated that SARS-CoV-2 enters the human body through Angiotensin Converting Enzyme 2 (ACE2) receptor, present in the lung epithelial cell and develops a typical form of the acute respiratory distress syndrome (ARDS).[8,9] Current management system of COVID-19 is aptly focused on the fact that ARDS is the leading cause of fatalities.[10] Nevertheless with massive global research efforts and contemporary data and perceptive, continues to generate surge of information on COVID-19 pathogenesis. Consecutive studies reported drastic systemic events taking place that contribute to the severe clinical outcomes such as; decreased hemoglobin i.e. anemia, hypoxia,altered iron metabolism, hypercoagulability, oxidative stress, cytokine storm, hyper-ferritinemia and multi-organ-failure (MOF) which are reportedly hailed as the hallmark of the COVID-19 hyper-inflammatory state.[11-14] Evidences shows that these complications are inevitably associated at a systemic level, and suggests some other pathogenic mechanisms which remains largely un-elucidated.[15]

Data suggests SARS-CoV-2 can form a secreted protein encoded by ORF8 and a novel short protein encoded by ORF3b, which play a role in the viral pathogenicity.[16] Recently, an innovative pathophysiological hypotheses based on *in silico* demonstration proposed that a number of transcribed non-structural proteins (ORF1ab, ORF10, ORF3a and ORF8) coordinately attack the heme on the 1-beta chain of hemoglobin and inhibited the heme anabolic pathway which in turn increases the level of free floating irons.[17] Subsequent in vitro immuno-electron microscopic studies, provided evidences on the possible virus spike (S) protein interaction with hemoglobin (Hb) in red blood cells and with iron metabolism using the CD147 and/or CD26 receptors, other than ACE2.[18,19] Due to the wide expression in erythrocytes these receptors are proven to be deeply implicated in extensive pathologies associated with oxidative hemolysis, like decreased Hb level, hypoxia, thrombosis, objectively related to the clinical symptoms highlighted in course of COVID-19 infection.[20-23] Iron containing protein Hb is a functional unit of Red Blood Cell (RBC). Being an essential component of RBC's Production i.e. erythropoiesis, iron is also important for proper functioning of the host immune system and regulating many physiological process.[24,25] Furthermore, for proper functioning of host immune system body have to maintain iron homeostasis, a balance between iron absorption, transportation, storage and utilization.[26,27] The interaction of the peptide hormone, hepcidin and iron exporter ferroportin, interplays central role in establishing this delicate balance.[28-30] But interruption of this balance results in impaired iron homeostasis, can lead to both iron deficiency and iron excess which have detrimental effects.[31] Hyper-ferritinemia is a response of excess iron load, characterizes with several autoimmune diseases, and evince pathogenic role on the ground of its immunomodulatory properties, which has already been described as a cardinal feature of COVID-19.[12,13,32,33]Low iron concentration on the other hand restricts iron uptake by erythrocyte precursors, limits hemoglobin synthesis and causes anemia in which Hb concentration drops below the normal level (Male: >13.0 f/dl; Female: >12.0 g/dl) and become incapable to meet an individual's physiological requirements.[34,35]Anemia has multiple etiologies including nutrient deficiencies, acute and chronic infections, and genetic hemoglobinopathies.[36,37] Iron deficiency is often considered as the primary and commonest cause of anemia globally.[37]The onset of iron deficiency anemia (IDA) is influenced by various host factors such as age, sex, physiological, pathological, dietary and socio-economic status (SES).[38] Iron exists in twoforms, heme iron (rich in meat) and non-heme iron (rich in whole grains, nuts, seeds, legumes).[39] Although the intake of non-heme iron rich foods did not differ across different SES strata but study reported heme iron uptake increased as household income rose.[40] Studies also reported significant association between low SES and higher prevalence of anemia which in turn related to the severity of several communicable and infectious disease.[44-46] Higher SES (defined by the countries' GDP per capita) seems to have a protective effect on anemia and its related health complications.[40]

But in case of COVID-19, interestingly it is observed from the world COVID-19 tracker that, countries with higher SES (United States, Canada, Europe, Australia) have considerably lower prevalence of IDA, but accounts for higher CFR rate due to COVID-19.[47,48] On the other hand, low SES countries for example Africa (poorest continent of the planet) and Indiacharacterized by the higher prevalence of IDA, are less affected to COVID-19 infection and possesses less CFR due to COVID-19, which is almost half to that of the higher SES counterpart (Fig. 1).[47-49]

Hence, developed countries denoted by higher SES condition and normal hemoglobin level possibly

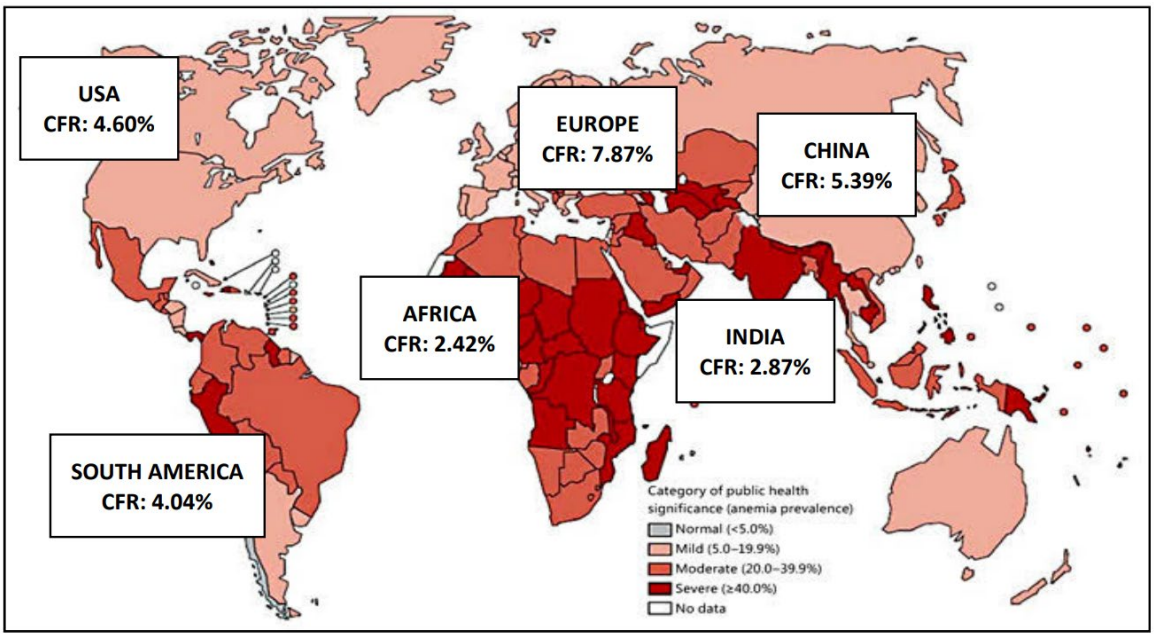

Fig. 1. Iron Deficient Anemia prone regions revealed low CFR by COVID-19, CFR: Case Fatality Rate (July, 2020 COVID tracker) Source: Pandey S, Singh V. Food Fortification to Combat Iron Deficiency Anaemia. International Journal of Advanced Nutritional and Health Science 2013;1(1): 39-47.

possesses greater severity of COVID-19 than the anemia endemic regions. While vaccines are yet to be approved, Remdesivir, an antiviral drug used for treating Ebola, SARS, MERS, has shown efficacy against SARS-CoV-2 infection.[50] Not only that, lopinavir/ritonavir, an approved anti HIV drug also has been recommended for treatment of SARS-CoV2 infection.[51] Most recently, high dose dexamethasone has shown efficacy in patients who are critically ill with COVID-19.[52] Although these drugs are showing a promising efficacy, but indeed, there is no specific drug against SARS-CoV-2. The drugs that are currently used for the treatment of COVID-19 are still assessed in clinical trials.[53] Therefore, it is urgently imperative to find out strategies for prevention and is urgently needed to recognize the possible factors causing variations in severity and fatality of the disease in different human populations.

Aim

In this background, the aim of this present narrative is to provide a complementary overview of how low iron stores and mild anemia offers protection from infectious diseases like COVID-19 by restricting the viral replication and also to suggest some potential adjuvant therapeutic interventions.

Material and methods

Therefore, we performed a literature search reviewing pertinent articles and documents. PubMed, Google Scholar, Chemrxiv, MedRxiv, BioRxiv, Preprints and ResearchGate were investigated, using the following headings and keywords, linked to the words COVID-19 or Sars-CoV-2: hemoglobin, heme, erythrocyte, hematopoiesis, erythroblast, hemolysis, hypoxia, hypoxemia, iron, hepcidin, ferroportin, ferritin, ferroptosis, hemochromatosis, iron chelation, translational medicine, oxidative stress, drugs, nutrition, food supplements, CD147, CD26, thromboembolism.

Analysis of the literature

Although there is fewer information about anemia or iron regulations in SARS-CoV-2 patients, some clues could be observed based on previous viral infections such as SARS,MARS, HIV-1.[54-57] Iron is crucial for both the host and the pathogen.[57,58] For the host, iron is essential for appropriate physiological process.[25]Likewise, several pathogens including virus, bacteria, fungi, and protozoa uses iron (host-cell elements) as niches for their survival.[29]Many Viruses, most likely including HCoVs rely on iron for their protein synthesis and genome replication in host cells. In the context of HIV-1 infection, iron is involved in several key steps of virus replication.[57,59] In the reverse transcription of viral RNA into DNA, the required dNTPs are generated by RNRs whichare an iron-dependent proteins.[54] NF-κB, contributes to the activation of HIV-1 promoter can be activated by iron and IκB kinase activation.[60-62] Nuclear export of new transcribed viral RNA is also iron dependent.[63] Finally, iron-binding ATPase, involved in the assembly of the gag capsid proteins into mature HIV-1 virions.[64] ATP hydrolysis is necessary for the unwinding activity of helicases of SARS-CoV and MERS-CoV during the viral replication.[55,56] Virus also use intracellular iron for their propagation beside heme iron.[57] Increased iron

storage in Macrophages also facilitates its replication which are presumed to be infected by SARS-CoV-2.[8] Thus, it is likely that SARS-CoV-2 requires iron for viral replication and for its functions.

Furthermore, studies reported many virusesincluding SARS-CoV-2disrupts iron homeostasis (induced by hemolysis) and increases the intercellular iron load, leads to the faster viral replication and ultimately the severity of the disease.[18,57,59] This iron overload in turn leads to significantly higher Ferritin level i.e. hyperferritinemia.[65] Ferritin, serves to bind iron molecules and to store iron in a biologically available form for vital cellular processes but moderate levels of hyper-ferritinemia are associated with autoimmune diseases, including systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), multiple sclerosis and antiphospholipid syndrome (APS) whereas, typically elevated levels are associated with other conditions including macrophage activation syndrome (MAS), adult-onset Still's disease (AOSD), catastrophic APS (cAPS) and septic shock.[66,67] Iron dependence of viral replication and modulation of host iron metabolism by viruses, signifies the importance of adequate iron supply for the completion of these replication process.[68] Butgrowing pile of clinical evidences reported that low iron stores and mild anemia may be beneficial in some cases by offering protection from infectious diseases as low iron restricts the viral replication.[29,58,59,65,69-71] Nevertheless, clinical data also indicated that poor prognosis is related to the condition of iron overload observed in patients with infection of hepatitis B/C (HBV/ HCV) virusesand iron depletion have a marked anti-HIV effect.[72-74]

As a consequence of above mentioned pathogenic scenario linking iron, ferritin and infection, it could be presumed that the potential of iron chelation or iron sequestration as an alternative beneficial adjuvant in treating SARS-CoV-2 infectionbecause of its ability to make a complex by binding with the iron and excrete from the circulation without any organ damage (Fig. 2) and also denying iron to invading microorganisms andprotecting the host tissues from hyper-ferretinemia related consequences.[57,65,75,76]

This diagram depicts COVID-19 leads to inflammation and during a heightened inflammatory state, cytokines, particularly IL-6, altered iron homeostasis and stimulate ferritin and hepcidin synthesis. Hepcidin, the key iron regulatory hormone, sequesters iron in the enterocytes and macrophages, leading to intracellular iron overload. Hyper-ferritinemia is associated with a state of iron overload. Excess intracellular iron enhances viral replication, interacts with molecular oxygen, generating reactive oxygen species (ROS) and also results in mitochondria dysfunction, microbiota dysbiosis (lungs and gut) and hyper coagulopathy. But, iron chelators may provide protective effects by inhibiting intracellular iron.

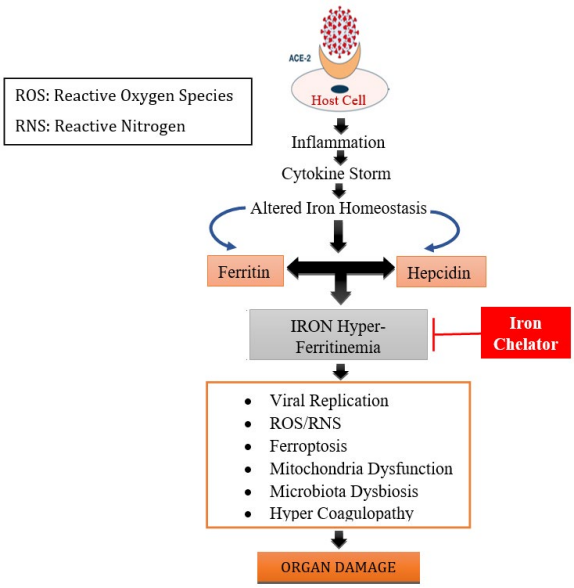

Fig. 2. Cycle of COVID-19 pathogenesis and the role of iron chelation

There are several iron chelators have been designed to excrete tissue iron through urine or feces. Each of these chelators has their own advantages and disadvantages. So while choosing iron chelation therapy one has to select very carefully according to the levels of deposited iron and clinical symptoms of the afflicted patients and the disease itself.[74] Beside this modulation of hepcidin and ferroportin expression during infection and inflammation increases iron metabolism as a host defense mechanism and decreases iron availability to invading pathogens.[29] This lead to the concept of nutritional immunity, as a whole of constitutive and inducible mechanisms that regulate the iron availability to pathogens and thus limit their capacity to infect the hostby disturbing the viral metal dependence which would presumably exhibit antiviral effects.[76,77]

Limitations

This review is mainly based on theoretical modeling, and on limited evidence. A number of scientific researches in this regard are needed in the next future. Data on COVID-19 case fatality rate (CFR) are taken using world COVID-19 tracker which might be biased by testing only symptomatic individuals, and not asymptomatic individuals for some countries. The speculative reasoning provided in this review may contribute to stimulate future studies, to corroborate or disprove our elaboration.

Conclusion

Present review presumed the potential of iron chelation or iron sequestration as an alternative beneficial adjuvant in treating COVID-19 infection due to its dual function of denying iron to invading microorganisms and protecting the host tissues from oxidative stress.

References

1. Gorbalenya AE, Baker SC, Baric RS, et al. The species Severe Acute Respiratory Syndrome-related Coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. *Nat Microbiol.* 2020;5(4):536-544.
2. Gemmati D, Bramanti B, Serino ML, Secchiero P, Zauli G, Tisato V. COVID-19 and Individual Genetic Susceptibility/Receptivity: Role of ACE1/ACE2 Genes, Immunity, Inflammation and Coagulation. Might the Double X-Chromosome in Females Be Protective against SARS-CoV-2 Compared to the Single X-Chromosome in Males? *Int J Mol Sci.* 2020;21(10):3474.
3. Yang J, Zheng Y, Gou X, et al. Prevalence of comorbidities and its effects in coronavirus disease 2019 patients: A systematic review and meta-analysis. *Int J Infect Dis*. 2020;94:91-95.
4. Drosten C, Gunther S, Preiser W. Identification of a novel coronavirus in patients with severe acute respiratory syndrome. *N Engl J Med*. 2003; 348:1967-1976.
5. Zaki AM, Van BS,Bestebroer TM, OsterhausAD,Fouchier RA. Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. *N Engl J Med.* 2012;367(19): 1814-1820.
6. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet.* 2020;95:497-506.
7. Bandyopadhyay AR, Chatterjee D, Ghosh K, Sarkar P. COVID 19: An Epidemiological and Host Genetics Appraisal. *Asian J Med Sci*. 2020;11(3):71-76.
8. Wan Y, Shang J, Graham R, et al. Receptor recognition by novel coronavirus from Wuhan: an analysis based on decade-long structural studies of SARS. *J Virol.* 2020;94(7):1-9.
9. Gattinoni L, Coppola S, Cressoni M, Busana M, Rossi S, Chiumello D. Covid-19 Does Not Lead to a "Typical" Acute Respiratory Distress Syndrome. *Am J Respir Crit Care Med.* 2020;201(10):1299-1300.
10. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet.* 2020; 395:1054–1062.
11. Taneri PE, Gómez-Ochoa SA, Llanaj E, et al. Anemia and iron metabolism in COVID-19: a systematic review and meta-analysis. *Eur J Epidemiol*. 2020;35: 763–773.
12. Mehta D, McAuley DF, Brown M, et al. COVID-19: Consider cytokine storm syndromes and immunosuppression. *Lancet.* 2020; 395:1033-1034.
13. Phua J, Weng L, Ling L, et al. Intensive care management of coronavirus disease 2019 (COVID-19): Challenges and recommendations. *Lancet Respir Med*. 2020;8(5):506-517.
14. Zaim S, Chong JH, Sankaranarayanan V, Harky A. COVID-19 and multiorgan response. *Curr Probl Cardiol*. 2020;45(8):1-22.
15. Kernan KF, Carcillo JA, Coffman LG, et al. Hyperferritinemia and Inflammation. *Int Immunol.* 2017;29(9):401-409.
16. Chan JF, Kok KH, Zhu Z, et al. Genomic characterization of the 2019 novel human-pathogenic coronavirus isolated from a patient with atypical pneumonia after visiting Wuhan. *Emerg Microb Infect*. 2020;9:221-236.
17. 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.
18. Ulrich H, Pillat MM. CD147 as a Target for COVID-19 Treatment: Suggested Effects of Azithromycin and Stem Cell Engagement. *Stem Cell Rev Rep*. 2020;20:1–7.
19. Li Y, Zhang Z, Yang L, et al. The MERS-CoV receptor DPP4 as a candidate binding target of the SARS-CoV-2 spike. *iScience.* 2020;23(6):1-8.
20. Coste I, Gauchat JF, Wilson A, et al. Unavailability of CD147 leads to selective erythrocyte trapping in the spleen. *Blood*. 2001;97(12):3984–3988.
21. Lippi G, Mattiuzzi C. Hemoglobin value may be decreased in patients with severe coronavirus disease. *Hematol Transfuse Cell Ther.* 2020;42(2):116–117.
22. Xie J, Covassin N, Fan Z, et al. Association between hypoxemia and mortality in patients with COVID-19. *Mayo Clin Proc.* 2020; 95(6):1138-1147.
23. Cui S, Chen S, Li X, et al. Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia. *J Thromb Haemost.*2020;18(6):1421-1424.
24. Abbaspour N, Hurrell R, Kelishadi R. Review on iron and its importance for human health. *J Res Med Sci*. 2014;19(2):164-174.
25. Khodour Y, Kaguni LS, Stiban J. Iron-sulfur clusters in nucleic acid metabolism: varyingroles of ancient cofactors. *Enzymes*. 2019;45:225–256.
26. Lieu PT, Heiskala M, Peterson PA, Yang Y. The roles of iron in health and disease. *Mol Aspects Med*. 2001;2: 1-87.
27. Ganz T. Molecular control of iron transport. *J Am Soc Nephrol*. 2007;18(2):394–400.
28. Nemeth E, Tuttle MS, Powelson J, etal.Hepcidin Regulates Cellular iron Efflux by Binding to ferroportin and inducing its internalization. *Science.* 2004;306(5704):2090-2093.
29. Ganz T. Hepcidin and iron regulation, 10 years later. *Blood*. 2011;117:4425–4433.
30. Lavin Y, Mortha A, Rahman A, Merad M. Regulation of macrophage development and function in peripheral tissues. *Nat Rev Immunol*. 2015;15:731–744.
31. Ganz T, Nemeth E. Hepcidin and iron Homeostatis. *Biochim Biophys Acta*. 2012;1823(9):1434-1443.
32. Goddard GZ, Shoenfeld Y. Ferritin in autoimmune diseases. *Autoimmun Rev.* 2007;6(7):457-463.
33. Recalcati S, Invernizzi P, Arosio P, Cairo G. New functions for an iron storage protein: the role of ferritin in immunity and autoimmunity. *J Autoimmun*. 2008;30(1-2):84-89.
34. Chaparro CM, Suchdev PM. Anemia epidemiology, pathophysiology, and etiology in low-and middle-income countries. *Ann N Y Acad Sci*. 2019;1450(1):15-31.

35. Beutler E, Waalen J. The definition of anemia: what is the lower limit of normal of the blood hemoglobin concentration? *Blood*. 2006;107(5):1747-1750.
36. Calis JC, Phiri KS, Faragher EB, et al. Severe anemia in Malawian children. *N Engl J Med*. 2008;358:888 –899.
37. WHO. Nutritional Anemia: tools for effective prevention. Geneva: World Health Organization, 2017.
38. World Health Organization. Iron Deficiency Anaemia: Assessment, Prevention And Control. A guide for programme managers. WHO: Geneva, 2001.
39. Conrad ME, Umbreit JN, Moore EG. Iron absorption and transport. *Am J Med Sci*. 1999; 318(4):213–229.
40. Kim JY, Shin S, Han K, et al. Relationship between socioeconomic status and anemia prevalence in adolescent girls based on the fourth and fifth Korea National Health and Nutrition Examination Surveys. *Eur J Clin Nutr*. 2014;68(2): 253–258.
41. Issaragrisil S, KaufmanDW, Anderson TE, et al. An association of aplastic anaemia in Thailand with low socioeconomic status. Aplastic Anemia Study Group. *Br J Haematol*. 1995;91(1):80–84.
42. Gompakis N, Economou M, Tsantali C, et al. The effect of dietary habits and socioeconomic status on the prevalence of iron deficiency in children of northern Greece. *Acta Haematol*. 2007;117(4):200–204.
43. Thankachan P, Muthayya S, Walczyk T, Kurpad AV, Hurrell RF. An analysis of the etiology of anemia and iron deficiency in young women of low socioeconomic status in Bangalore, India. *Food Nutr Bull*. 2007;28(3):328–336.
44. Animasahun BA, Temiye EO, Ogunkunle OO, Izuora AN, Njokanma OF. The influence of socioeconomic status on the hemoglobin level and anthropometry of sickle cell anemia patients in steady state at the Lagos University Teaching Hospital. *Niger J Clin Pract*. 2011;14(4):422–427.
45. Shilpa S, Biradar SPB, Alatagi AC, Wantamutte AS, Malur PR. Prevalence of anaemia among adolescent girls: a one year cross-sectional study. *J Clin Diag Res*. 2012;6(3): 372– 377.
46. Ifeanyi OE. International Journal of Advanced Multidisciplinary Research. *Int J Adv Multidiscip Res*. 2018;5(4):11-15.
47. COVID tracker (https://covid19.who.int/) Accessed 20 July, 2020.
48. https://howmuch.net/articles/gdp-per-capita-2018. International Monitory Fund-World Economic Outlook. Accesses on 13 July, 2020.
49. Benoist BD, McLean E, Egli I, Cogswell M. Worldwide prevalence of anemia 1993– 2005: WHO Global Database on Anemia. Geneva, Switzerland: World Health Organization; 2008.
50. Agostini ML, Andres EL, Sims AC, et al., Coronavirus susceptibility to the antiviral remdesivir (GS-5734) is mediated by the viral polymerase and the proofreading exoribonuclease. *mBio*. 2018;9(2):1-15.
51. Yao TT, Qian JD, Zhu WY, Wang Y, Wang GQ. A Systematic review of lopinavir therapy for SARS Coronavirus and MERS Coronavirus-a possible reference for Coronavirus Disease-19 treatment option. *J Med Virol*. 2020;92(6):556-563.
52. Lester M, Sahin A, Pasyar A. The use of Dexamethsone in the treatment of COVID-19. *Ann Med Surg (Lond)*. 2020;56:218-219.
53. Huang L, Chen Y, Xiao J, et al. Progress in the Research and Development of Anti-COVID-19 Drugs. *Front Public Health*. 2020;365(8):1-8
54. Romeo AM, Christen L, Niles EG, Kosman DJ. Intracellular chelation of Iron by bipyridyl inhibits DNA virus replication: ribonucleotide reductase maturation as a probe of intracellular iron pools. *J Biol Chem*. 2001;276(26):24301–24308.
55. Adedeji A, Lazarus H. Biochemical characterization of Middle East respiratory syndrome coronavirus helicase. *mSphere*. 2016;1(5):e00235–16.
56. Jia Z, Liming Y, Ren Z, et al. Delicate structural coordination of the severe acute respiratory syndrome coronavirus Nsp13 upon ATP hydrolysis. *Nucleic Acids Res*. 2019;47(12):6538-6550.
57. Liu W, Zhang S, Nekhai S, et al. Depriving Iron Supply to the Virus Represents a Promising Adjuvant Therapeutic Against Viral Survival. *Current Clinical Microbiology Reports*. 2020;7:13-19.
58. Cassat JE, Skaar EP. Iron in infection and immunity. *Cell Host Microbe*. 2013;13(5):509– 519.
59. Drakesmith H, Prentice A. Viral infection and iron metabolism. *Nat Rev Microbiol*. 2008;6(7):541–552.
60. Pereira LA, Bentley K, Peeters A, Churchill MJ, Deacon NJ. A compilation of cellular transcription factor interactions with the HIV-1 LTR promoter. *Nucleic Acids Res*. 2000;28(3):663–668.
61. Xiong S, She H, Takeuchi H, et al. Signaling role of intracellular Iron in NF-κB activation. *J Biol Chem*. 2003;278(20):17646–17654.
62. Xiong S, She H, Sung CK, Tsukamoto H. Iron-dependent activation of NF-kappaB in Kupffer cells: a priming mechanism for alcoholic liver disease. *Alcohol*. 2003;30(2):107–113.
63. Hoque M, Hanauske-Abel HM, Palumbo P, et al. InhibitionofHIV-1geneexpressionby Ciclopirox and Deferiprone, drugs that prevent hypusination of eukaryotic initiation factor 5A. *Retrovirology*. 2009;6:90.
64. Zimmerman C, Klein K, Kiser P, et al. Identification of a host protein essential for assembly of immature HIV-1 capsids. *Nature*. 2002;415(6867):88–92.
65. Perricone C, Bartoloni E, Bursi R, et al. COVID-19 as part of the hyperferritinemic syndromes: the role of iron depletion therapy. *Immunol Res*. 2020;68(4):213–224.
66. Zandman-Goddard G, Shoenfeld Y. Ferritin in autoimmune diseases. *Autoimmun Rev*. 2007;6(7):457–463.
67. Bennett TD, Hayward KN, Farris RW, Ringold S, Wallace CA, Brogan TV. Very high serum ferritin levels are asso-

ciated with increased mortality and critical care in pediatric patients. *Pediatr Crit Care Med*. 2011;12(6):e233–236.
68. Arieh S, Laham-Karam N, Schechter C, et al. A single viral protein HCMV US2 affects antigen presentation and intracellular iron homeostasis by degradation of classical HLA class I and HFE molecules. *Blood*. 2003;101(7):2858–2864.
69. Hariyanto TI, Kurniawan A. Anemia is associated with severe coronavirus disease 2019 (COVID-19) infection. *Transfus Apher Sci*. 2020;59(6):102926.
70. Moalem S, Weinberg ED, Percy ME. Hemochromatosis and the enigma of misplaced iron: implications for infectious disease and survival. *Biometals*. 2004;17(2):135-139.
71. Scindia Y, Dey P, Thirunagari A, et al. Hepcidin mitigates renal ischemia-reperfusion injury by modulating systemic iron homeostasis. *J Am Soc Nephrol*. 2015;26(11):2800–2814.
72. Thursz M. Iron, hemochromatosis and thalassemia as risk factors for fibrosis in hepatitis C virus infection. *Gut*. 2007;56(5):613–614.
73. Galli A, Svegliati-Baroni G, Ceni E, et al. Oxidative stress stimulates proliferation and invasiveness of hepatic stellate cells via a MMP2-mediated mechanism. *Hepatology*. 2005;41(5):1074–1084.
74. Debebe Z, Ammosova T, Jerebtsova M, et al. Iron chelators ICL670 and 311 inhibit HIV-1 transcription. *Virology*. 2007;367(2):324–333.
75. Mobarra N, Shanaki M, Ehteram H, et al. A Review on Iron Chelators in Treatment of Iron Overload Syndromes. *Int J Hematol Oncol Stem Cell Res*. 2016;10(4):239–247.
76. Weinberg ED. Iron availability and infection. *Biochim Biophys Acta*. 2009;1790(7):600–605.
77. Ganz T, Nemeth E. Iron homeostasis in host defense and inflammation. *Nat Rev Immunol*. 2015;15(8):500–510.