



REVIEW PAPER

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

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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

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Introduction

COVID-19 is a novel infectious disease, caused by SARS-CoV-2 which belongs to the family Coronaviridae.¹ SARS-CoV-2, is a severe, complex, and multifactorial disease and 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 g/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 two forms, 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 India characterized 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

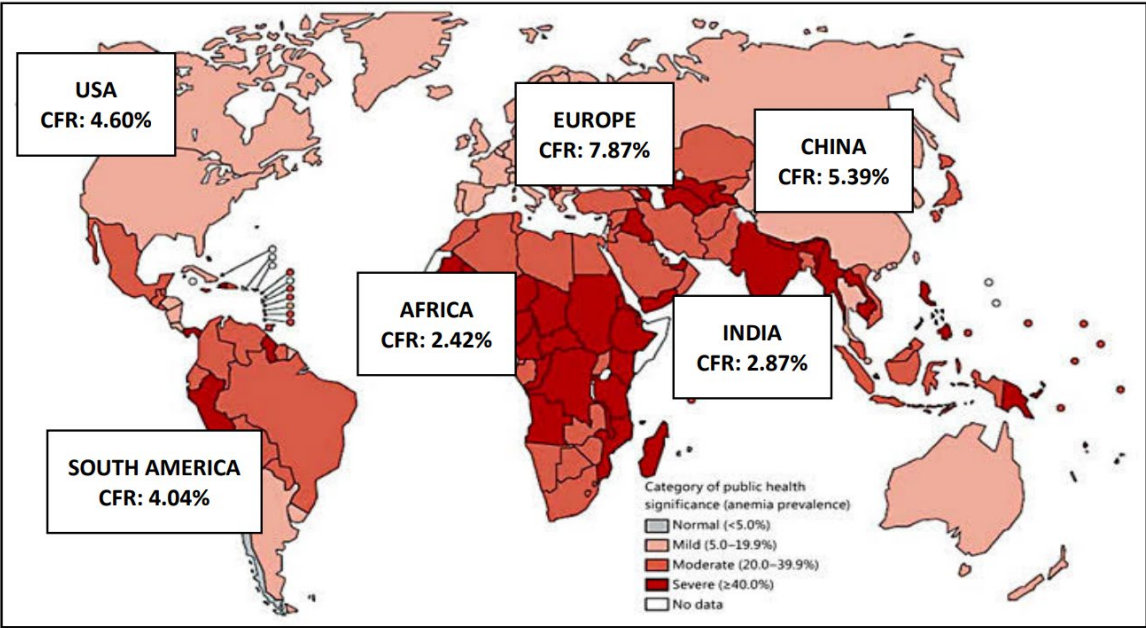


Fig. 1. Iron Deficient Anemia prone regions revealed low CFR by COVID-19, CFR: Case Fatality Rate (July, 2020 COVID tracker)
Source: Pandey S, Singh V. Food Fortification to Combat Iron Deficiency Anaemia. International Journal of Advanced Nutritional and Health Science 2013;1(1): 39-47.

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 which are 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 viruses including SARS-CoV-2 disrupts 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 But growing 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) viruses and 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 infection because 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 and protecting the host tissues from hyper-ferritinemia 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.

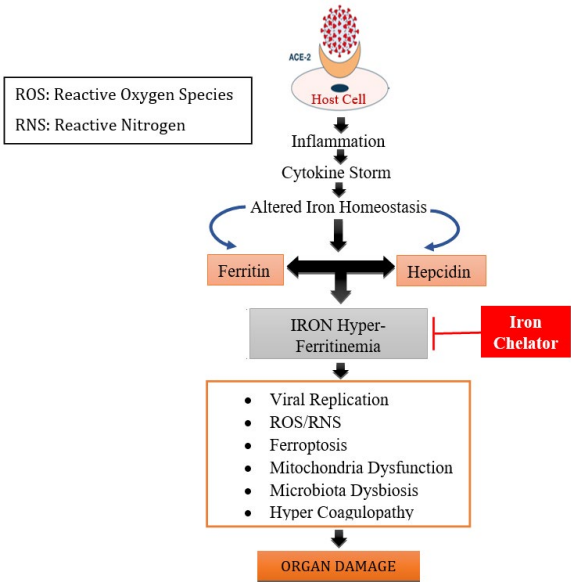


Fig. 2. Cycle of COVID-19 pathogenesis and the role of iron chelation

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 host by 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.

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