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Iron Deficiency Anemia and COVID-19

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ABSTRACT

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a significant health and financial issue in the current century. Despite significant attempts to manage the illness, the transmission routes of the virus and its widespread genomic mutations have led to an increasing number of new infections and mortality rates. In the absence of specific treatment for this new virus, identifying and managing factors affecting the prognosis of the disease is one of the critical strategies to reduce disease mortality. Patients with iron deficiency anemia (IDA), who account for an estimated half a billion people globally, are more prone to infections due to immune system disorders. Since they visit hospitals more frequently for follow-up care and diagnosis, they are more susceptible to becoming infected with SARS-CoV-2. Once infected with SARS-CoV-2, low hemoglobin (Hb) levels and compromised immune systems disrupt the restriction of infection in these individuals, ultimately leading to severe complications of COVID-19.

INTRODUCTION

Emerging and reemerging infectious diseases are global challenges to public health [1]. The highly contagious respiratory infectious disease COVID-19 is caused by a novel beta-corona virus called SARS-CoV-2, initially discovered as the source of a cluster of unexplained pneumonia in Wuhan, China, in late 2019 [2]. Due to the widespread and rapid prevalence of COVID-19 all over the world [3], the World Health Organization (WHO) announced COVID-19 as a public health emergency of international concern on January 30, 2020, and on March 11, 2020, declared it as a global pandemic [4]. SARS-CoV-2 transmits by multiple modes, including direct/indirect contact and airborne transmission; however, it mainly spreads among people with close contact by droplets created by cough and sneezing [5] and causes mild to severe cardiovascular complications and even death [6].

So it is necessary to identify the risk factors for COVID-19 [7] as early warning indicators of its severity and mortality rate to re-optimize hospital resources and reduce the severe forms leading to death [8]. Anemia which is declared as a decrease in the number of red blood cells (RBC) or a decrease in Hb concentration to less than 13 g/dL in men and 12 g/dL in women by WHO [9], can exacerbate cardiovascular and liver diseases [10]. In addition, because anemia is so prevalent and accounts for about one-third of the world's population [11], it is essential to investigate its association with COVID-19. The most common cause of anemia is nutrient deficiencies, and in about half of anemic cases, iron deficiency(ID) is the chief cause [11]. IDA is mainly caused by a physiological rise in iron requirements, chronic blood loss, nutrient ID or malabsorption, and genetic problems [12]. As iron plays a central role in

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various biochemical processes, including Hb production reactions, oxygen transport, growth regulation, and immune cell differentiation [13], its deficiency leads to a range of adverse consequences, including hypoxia, immune system dysfunction, gastrointestinal, cardiovascular, neurological disorders and even migraine attacks [14]. Due to the importance of iron-dependent mechanisms, such as oxygen transport in COVID-19 severity [15], in this study, we reviewed the association between IDA and COVID-19 to help make preventive decisions to reduce COVID-19 mortality.

Characteristics and pathogenesis of SARS-CoV-2 and COVID-19 complications

SARS-CoV-2, the causative agent of COVID-19 pandemic, is a new strain of the coronavirus family [2]. Coronaviruses (CoVs) are respiratory viruses that three stains of them, including severe acute respiratory syndrome coronavirus (SARS-CoV-1), Middle East respiratory syndrome coronavirus (MERS-CoV), and SARS-CoV-2, have initiated three outbreaks in this century leading to lower respiratory tract infection, pneumonia and acute respiratory distress syndrome (ARDS) [16]. SARS-CoV-2 is structurally a crowned-shaped spherical and enveloped virus containing a positive sense single-stranded RNA of 29.8 kb length as a genome. According to phylogenetic studies, the viral genome is 87.9% similar to the bat coronavirus strain bat SARS-like coronavirus zc45 (bat-SL-covzc45). So it appears that the primary host of the new coronavirus is bats, which was subsequently transmitted to humans after infecting the intermediate hosts [17] and transmitted mainly through respiratory droplets among humans [5]. Viral nucleic acid contains several gene regions from which structural and nonstructural proteins are transcribed [17].

An open reading frame (ORF1) gene located at the 5 'end of the genome is the largest region comprising two-thirds of the entire viral genome. It encodes large polyproteins synthesizing nonstructural proteins, including RNA polymerase, which plays a vital role in the process of transcription and replication of the virus genome in the host cells [2]. On the other hand, the remaining third of the viral genome at the '3 end, encodes four structural proteins, including spike (S), membrane (M) envelope (E), nucleocapsid (N), and eight sub-proteins including *3a*, *3b*, *p6*,*7a*, *7b*, *8b*, *9b*, *Orf14* [18]. Virus structural proteins play an essential role in maintaining and establishing the morphology and immuno-pathogenesis of the virus [17]. For instance, spike protein plays a role in the coronal appearance of the virus and also enables the virus to attach to angiotensin-converting enzyme 2 (ACE2) receptor-expressing cells in various tissues, including the alveolar epithelial cells (type 2Pneumocytes) of the lung [19]. Spike protein also assists viral entrance by membrane fusion after attachment [20]. After the virus entry into the host cell and the uncoating process, the viral genome is released into the cell cytoplasm, allowing the SARS-CoV-2 genome to replicate and translate [21]. The rapid intracellular proliferation of the virus, along with an increased response of pro-inflammatory cytokines such as IFN-γ, induces apoptosis through mechanisms such as Fas- L (Fas ligand) interaction in infected cells such as lung epithelial cells. As a result of the apoptosis of lung epithelial cells, the probability of pulmonary edema and, consequently, hypoxia increases [22].

Although COVID-19 is known to be a disease with a wide range of mild to severe symptoms that primarily affects the lungs, it can damage other organs, such as the cardiovascular system (cardiac tamponade), hematological system, and increase the risk of long-term health problems even in mild forms of the disease [23]. In 5% of cases, the patient's condition worsens and is associated with ARDS, infectious shock, and multiple organ failure (MOF) [24]. In most severe cases, underlying health conditions increase the risk of COVID-19 and exacerbation the disease. Identifying the risk factors involved in the severity of the disease is essential [25].

IDA and its effect on the body

Anemia is characterized by a slight decrease in the number of RBCs and the Hb concentration lower than their reference ranges [9]. Anemia affects one-third of the global population and is one of the most common clinical manifestations of an underlying fundamental pathological process [11]. IDA is the primary cause of anemia [26], classified into two types: absolute or functional ID. Functional iron deficiency (FID) refers to the condition in which there is inadequate iron incorporation for erythropoiesis in the face of seemingly sufficient body iron stores. In this condition, a partial block in iron transport to the erythroid marrow occurs in individuals with high hepcidin levels due to infectious and inflammatory diseases [27].

On the other hand, absolute iron deficiency, which refers to the low iron content in the body’s iron stores, has different causes based on age and sex status and may result from cow's milk feeding instead of breastfeeding in neonates or increased systemic requirements for iron in pregnant women and children or chronic blood loss in adult men [28]. Of course, other factors such as nutritional deficiencies, gastrointestinal malabsorption, parasitic infections, and genetic factors generate this type of ID. This ID can lead to anemia in three stages [12]: the first stage refers to the depletion of storage with no effect on Hb synthesis, the second to a lower concentration of serum iron and transferrin saturation, and the third to the development of microcytic hypochromic IDA with reduced serum iron and transferrin saturation hemoglobin and hematocrit levels. IDA may be identified by testing the indices mentioned above, including serum iron,

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ferritin, hemoglobin, and total iron binding capacity (TIBC) (Table 1) [29].

Table 1. Stages of iron deficiency

Stages		Characteristics of each stage
IDWA	**Pre-latent stage**	Depletion of iron stores, with normal serum iron concentrations, hemoglobin, and hematocrit concentrations, just reduced serum ferritin.
	Latent stage	Depleted iron stores with normal hemoglobin and hematocrit levels and reduced serum iron concentration and transferrin saturation.
IDA	**Marked IDA**	Depleted iron stores with reduced serum iron and transferrin saturation hemoglobin and hematocrit levels. (microcytic hypochromic RBC*s)

IDWA: iron deficiency without anemia, **IDA:** iron deficiency anemia, **RBCs**: red blood cells

If the anemia is mild or develops gradually, it will have no symptoms, but as the anemia worsens, the symptoms will become apparent. Since most of the body's iron is used to produce hemoglobin in red blood cells, the most apparent sign of ID is anemia with general symptoms including fatigue, lack of energy, headache, shortness of breath or chest pain, and rapid heartbeat, and specific symptoms of glossitis, koilonychia and pica [11]. In addition to making red blood cell hemoglobin, iron plays a central role in most biochemical processes, and its deficiency can lead to a wide range of adverse outcomes [14].

IDA, immune system, and their association with COVID-19

Iron is essential for cell proliferation and immune system pathways [30]. It affects the proliferation and differentiation of immune cells and the production of cytokines [31]. Likewise, one of the main effects of ID is the reduction of peripheral T cells and subsequent disruption of the cell-mediated immune response [32]. ID arrests T lymphocytes proliferation like other cells, apparently because it is required by ribonucleotide reductase, an enzyme involved in the biosynthesis of deoxyribonucleotides and cell division [30]. On the other hand, due to malnutrition, such as ID and lack of activity of enzymes involved in cell proliferation, the thymus, the primary site of T lymphocyte maturation, loses its thymic epithelial space and causes atrophy. In particular, it causes a decrease in the number of circulating T lymphocytes and leukopenia [33 34]. Thymic atrophy reduces the production and migration of efficient naïve T cells into the peripheral circulation. Hence, the risk of opportunistic infections, autoimmunity, and cancer increases, and the possibility of restoring immune function after chemotherapies and infections decreases [35]. In addition to affecting the number of T lymphocytes, ID also affects the cell's function and differentiation potency [36]. Low levels of interleukin-2 (IL-2) secreted from active T cells in children with ID [37] indicate the effect of ID on the immune function of helper1 T cells [38].

On the other hand, improvement of cell-mediated immune function and a significant increase in lymphocytes with positive natural killer receptors, an important subset of localized immune responses, evidenced by ID treatment approves that hypothesis [36]. In addition to affecting cell mediated immunity, ID is also associated with innate immune system disorders [38]. ID disperses (thins) and disrupts the defense mechanisms of the airway [39], and reduces the phagocytic capacity of monocytes and polymorphonuclear [40]. Also, iron is a component of myeloperoxidase, which is the enzyme responsible for producing reactive oxygen species to kill intracellular pathogens, and its deficiency causes neutrophil dysfunction and defects in infection restriction [38]. As a result, although anemia does not often cause death [41], while it plays an essential regulatory role in the immune system function, its deficiency can predispose the body to recurrent or severe viral infections and inflammation [42], especially in the upper respiratory tract and comes with the brain, cardiovascular, and developmental problems in children and adolescents [43]. In COVID-19, and other viral infections, T cells are crucial in killing virus-infected cells and clearing viruses [44]. Decreasing the number of T lymphocytes reduces the function of the immune system against the virus and increases the possibility of severe complications of the disease [45]. The presence and function of these cells are so crucial that identifying the factors affecting their number is important for treatment and the goal of most efforts to produce a specific SARS-CoV-2 vaccine is to stimulate the body's cellular immune system and produce memory T lymphocytes [46].

IDA, respiratory system, and their association with COVID-19

According to the findings, ID is associated with asthma, increased sensitivity to airway receptors, and unexplained and chronic cough in women [47 48]. Having ID without anemia (IDWA), associated with a reduced capacity for activity and a shorter life span, is common in patients with idiopathic pulmonary arterial hypertension [49]. In a study using a rat model feeding on an iron-free diet, it was discovered that ID reduced mitochondrial function by altering hemodynamics and causing pre-inflammatory conditions that resulted in the induction of apoptosis-resistant cells, and the development of pulmonary arterial pressure (PAP), pulmonary vascular resistance, and right ventricular hypertrophy [50]. The patient's ability to respond to the oxygen demand of peripheral tissues determines how well they will deal with COVID-19, and

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poor performance might result in hypoxia and ischemia even in settings with excessive ventilation [51]. By decreasing the synthesis of pulmonary enzymes [52] and hemoglobin, a protein crucial to oxygen transport to tissues, iron deficiency may contribute significantly to the failure of several organs [28], which in turn may lead to ARDS [53]. ARDS is a potentially life-threatening clinical syndrome characterized by lung inflammation, aspiration, and inhalational lung injury with severe shortness of breath, rapid decrease in blood oxygen levels, and fluid accumulation in the lungs. These patients have an oxygen in arterial blood (PaO2) to the fraction of the oxygen in the inspired air (FiO2) (PaO2/FiO2) ratio of less than 300 which is also one of COVID-19's severity markers [54]. Also, patients with severe COVID-19 who died during hospitalization had significantly lower serum iron levels than those who survived indicating that low serum iron level is an independent severity marker for death in COVID-19 patients [55].

Exacerbation of anemia due to COVID-19

Along with the exacerbation of inflammatory diseases through IDA, COVID-19 can worsen anemia by affecting iron metabolism [51]. Changes in iron homeostasis and anemia are frequent findings in acute COVID-19 and post-acute COVID-19 follow-ups [56]. There are two hypotheses for the aggravation of anemia by the SARS-CoV-2 virus. According to the first theory, SARS-CoV-2 can interact with hemoglobin molecules in red blood cells through receptors like ACE2, a cluster of differentiation-147 (CD-147), and CD-26, degrade the beta-globin chain of hemoglobin, and cause hemolysis [57]. The second hypothesis also states that cytokines such as IL-6 increase due to inflammation in SARS-CoV-2 infection. Increased pro-inflammatory cytokines can cause increased synthesis and secretion of hepcidin by liver cells [52]. Augmented hepcidin level reduces the digestive absorption of iron and its release from reserves, resulting in FID and COVID-19 exacerbation [27].

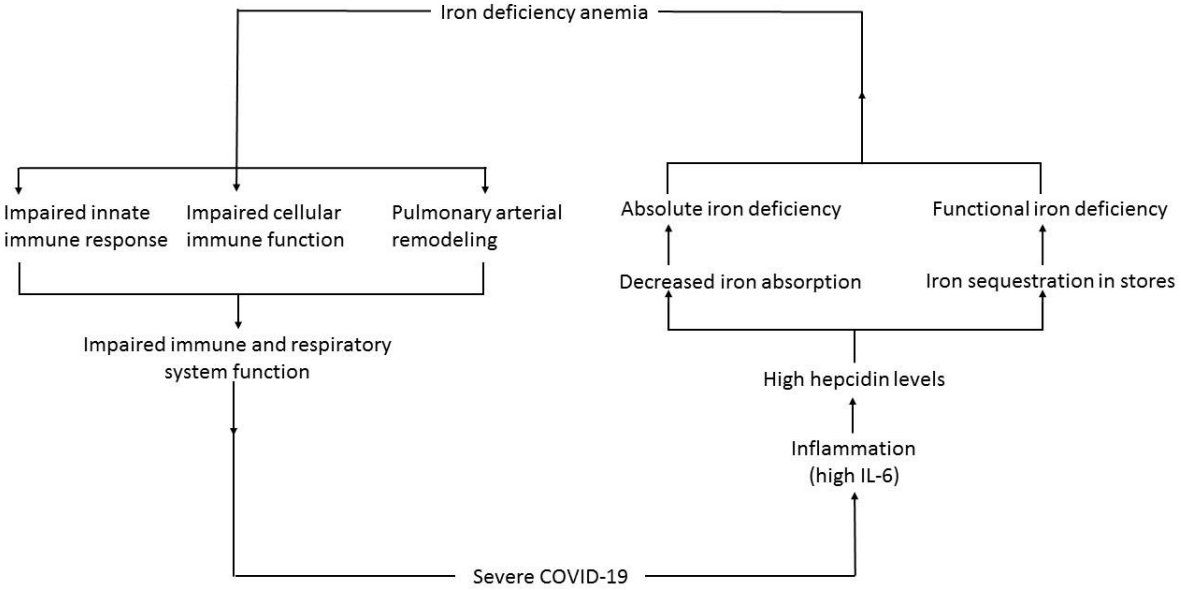

Fig. 1. The relation between Iron deficiency anemia and COVID-19.

DISCUSSION

Patients with IDA go to medical centers to diagnose their disorders and receive treatments. These centers are high-risk places due to the referral of COVID-19 patients for diagnosis [58] and make anemic patients to a high rate of exposure to the virus and prone them to COVID-19 complications due to impaired immune function. In anemic patients, there is a lack of hemoglobin, a decrease in oxygen supply to vital organs, lymphopenia, and a malfunction of the immune system; all of these have a poor prognosis for COVID-19 [56]. Therefore, appropriate planning should be adopted to diagnose and follow up the treatment of patients with iron deficiency so that they become less exposed to the virus while receiving and following their treatments. There is also a need for appropriate indicators of iron deficiency in anemic patients with COVID-19. According to a study, high zinc protoporphyrin (ZnPP) levels are accurate predictors of IDA in COVID-19 patients, and the ratio of ZnPP to lymphocytes (ZnPP/L) may be able to indicate the severity of COVID-19 [59].

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CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest associated with this manuscript.

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