RESEARCH

Effect of Altered Iron Metabolism on Hyperinflammation and Coagulopathy in Patients with Critical COVID-19: A Retrospective Study

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Abstract: A novel coronavirus disease 2019 (COVID-19) outbreak has started in Wuhan, China, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The relationship between altered iron homeostasis and hyperinflammation may be hallmarks of COVID-19 disease. We aimed to compare some iron (ferritin and iron), inflammation (C-reactive protein [CRP], hemoglobin, lactate dehydrogenase [LDH], neutrophil) and coagulation (prothrombin time [PT], activated partial thromboplastin time [APTT], D-dimer, platelet) marker results of critical COVID-19 patients with healthy controls results. In this single center retrospective study, 50 critical patients diagnosed with COVID-19 were included, demographic, clinical characteristics, severity of disease and laboratory test results were elicited from electronic medical records and compared to 50 healthy people. A statistically significant increase in CRP, LDH, neutrophil, PT, APTT, D-dimer ferritin levels was observed in critical COVID-19 patients compared with healthy people while a statistically significant decrease was observed in hemoglobin and iron levels. In addition, no statistically significant change in platelet levels was observed. Ferroptosis may be a significant cause of multiple organ failure in critical COVID-19 patients. Ferroptosis inhibitors might have potential to combat ferroptosis in COVID-19. Therefore, larger studies are needed to ferroptosis in COVID-19 *in vivo* and *in vitro.*

INTRODUCTION

A novel coronavirus disease, recently known as coronavirus disease 2019 (COVID-19) or severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), broke out in Wuhan, China and rapidly radiate to whole China and then to the world[1]. Due to the high affinity of the spike protein of the SARS -CoV-2 virus to angiotensin converting enzyme II (ACE2), multiple systems and organs can be infected. ACE2 protein, which is a functional receptor, is plentiful expressed in the tissues of the lung and small intestinal epithelium[2]. Therefore, the clinical spectrum (fever, mild upper respiratory tract disease, cough, shortness of breath, and severe viral pneumonia) of SARS-CoV-2 infection is wide[3]. In severe cases, system or organ damage may occur, leading to acute respiratory distress syndrome (ARDS), acute cardiac injury, shock, and death[4]. Studies have linked the hyper-inflammation associated with COVID-19 with a number of systemic alterations, including hypercoagulation problems, altered iron homeostasis, and oxidative stress injuries. These events are particularly associated with the pathogenesis of severe and critical COVID-19 patients[5-7]. Hyper-ferritinemia, which is particularly observed in COVID-19 patients, may develop in response to inflammation. But the role of hyper-ferritinemia on the prognosis of COVID-19 disease is not yet clear. According to certain information, hyper-inflammation associated with altered iron homeostasis in viral infections may play a critical role in disease pathogenesis. For this reason, the parameters of iron metabolism in COVID-19 patients; it is very important to investigate transferrin saturation, plasma iron levels, non-transferrin iron (NTBI) and hepcidin[8]. In this study we planned, we aimed to compare some iron (ferritin and iron), inflammation (C-reactive protein [CRP], hemoglobin, lactate dehydrogenase [LDH], neutrophil), and coagulation markers (activated partial thromboplastin time [APTT], prothrombin time [PT], platelet, D-dimer) results of COVID-19 patients admitted to the Intensive Care Unit of Malatya Turgut Ozal University Training and Research Hospital from March 15th, 2020 to March 15th, 2021 with healthy controls results.

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MATERIAL and METHODS

Study plan and participants

The planned single center retrospective study was conducted in Malatya Turgut Ozal University Training and Research Hospital, Malatya, Turkey. All patients were treated by an intensive care specialist in a 12-bed tertiary intensive care unit. In the retrospective analysis of data in electronic medical records between 15.03.2020 and 15.03.2021, a total of 35269 cases identified as positive for real-time polymerase chain reaction (RT-PCR) were detected. 50 critical patients who had all the biochemical parameters specified in this study in electronic records and met all criteria were included in the study. A control group was formed by selecting 50 healthy people with a similar profile with the COVID-19 group (age, gender) applied to the same hospital from their electronic medical records. The comorbidity of interest that was recorded was diabetes mellitus (DM), cardiovascular disease (CVD), hypertension (HT), chronic obstructive pulmonary disease (COPD), cerebrovascular disease (CVD) and chronic kidney disease (CKD).

Definition

COVID-19 pneumonia was described with the clinical symptoms, SARS-CoV-2 positive real-time RT-PCR and radiological results (computed tomography and/or chest radiography) according to the national guideline of COVID-19 in China. The clinical classification of COVID-19 patients can be summarized as follows:

(1) mild type: Patients with mild clinical symptoms and no signs of pneumonia on radiological examination
(2) common type: Patients with fever and respiratory symptoms and also pneumonia
(3) severe type: mean oxygen saturation 93%, respiratory distress during rest, respiratory frequency 30 beats/min or partial arterial oxygen partial pressure to inhaled oxygen fraction (PaO_2: FiO_2)>300 mmHg (1 mmHg = 0.133 kPa)
(4) critical type: experiencing respiratory failure, needing mechanical ventilation, development of organ dysfunction, shock and meeting the criteria for admission to intensive care[9].

In the study we planned, we defined the critical type patients under the COVID-19 patient group.

Data sources

Clinical characteristics, demographic data, laboratory tests and data about the severity of the disease of the patients were obtained from the medical registry system of Malatya Turgut Ozal University Training and Research Hospital and recorded. Laboratory data of patients within the first 8 hours after admission to the intensive care unit were evaluated.

Data collection

Analyses of the markers in the study were performed on biochemistry (Abbott Architect c16000, Illinois, United States of America), hemogram (Sysmex Corporation XN-10, Kobe, Japan), coagulation, (Diagon Coag XL, Budapest, Hungary) and hormone (Roche Diagnostics Cobas E601, Tokyo, Japan) devices.

Statistical analysis

Statistical analysis of the data was performed using the Statistical Package for the Social Sciences (Version 22.0, NY, USA) software. The compatibility of the data with the normal distribution was evaluated using the Kolmogorov-Smirnov test. The data obtained were presented in the form of median (interquartile range-IQR) for variables with non-parametric distribution. For the variables with non-parametric distribution, Mann Whitney U test was used for the differences between the two groups. Values of $p<0.05$ were considered significant.

RESULTS

Demographic characteristics and laboratory markers of critical COVID-19 patients and healthy controls

Of the 50 patients with COVID-19, the median age was 68,12 years (interquartile range [IQR], 31–89). The number of women was 25 (50 %), and the number of men was 25 (50 %). Of the 50 healthy controls, the median age was 68,04 years (IQR, 31–88). The number of women was 25 (50 %), and the number of men was 25 (50 %).

Ferritin (715,5 IQR, [405,6-2000]), iron (25,9 IQR, [5-58,8]), CRP (7,63 IQR, [0,61- 28,39]), hemoglobin (11,95 IQR , [8,1-14,9]), LDH (418 IQR, [281-1008]), neutrophil (8,425 IQR, [0,76-33,89]), PT (13,85 IQR, [10,2-35,4]), APTT (27,5 IQR [19,2-103,3]), D-dimer (0,8725 IQR), [0,22-8,24]), platelet (205 IQR, [70-439]) levels were determined in COVID-19 patients.

Ferritin (106,85 IQR, [9,78-463,2]), iron (85,95 IQR, [37,4-162,6]), CRP (0,1650 IQR, [0,02-1,70]), hemoglobin (13,75 IQR , [10,3-18,1]), LDH (205,5 IQR, [96-304]), neutrophil (4,13 IQR, [1,59 -7,98]), PT (11,25 IQR, [8,8-14,2]), APTT (24,9 IQR [19,1-34,4]), D-dimer (0,2915 IQR), [0,001-1,7]), and platelet (225 IQR, [143-380]) levels were determined in healthy sample of people.

All results are shown in Table 1.

Comparison of inflammation marker values of critical COVID-19 patients with healthy controls

A statistically significant increase was observed in CRP, LDH, neutrophil levels in COVID-19 patients compared to the healthy control group (p=0.0001, p=0.01 and p=0.0001, in order of) while a statistically significant decrease was observed in hemoglobin levels (p=0.0001).

Comparison of coagulation marker values of COVID-19 patients with healthy controls

There was a statistically significant increase in PT, APTT, D-dimer levels in COVID-19 patients compared to the healthy control group (p=0.0001, p=0.004, p=0.0001 respectively), but no statistically significant change was observed in platelet levels (p=0.062).

Comparison of iron metabolism marker values of critical COVID-19 patients with healthy controls

A statistically significant increase in ferritin levels was observed in COVID-19 patients compared to the healthy control group (p=0.0001), while a statistically significant decrease was observed in iron levels (p=0.0001).

DISCUSSION

COVID-19 disease caused by the SARS-CoV-2 virus is much more than a respiratory disease that affects the immune system at multiple levels[10]. It has become clear that the mortality rate associated with COVID-19, especially in older people or patients with other illnesses is due to the inability of inflammatory responses to resolve the infection[11]. In severe and critical cases of COVID-19, hyper-inflammation caused by SARS-CoV-2 triggers an excessive immune response known as cytokine storm. Cytokine storm is a potentially fatal immune response by increasing the immune cell's production of large inflammatory cytokines and chemical mediators that activate highly[12]. Hyper-inflammation associated with COVID-19 is linked to hypercoagulation, oxidative stress, and altered iron metabolism[5-7]. In our study, we investigated the status of iron metabolism in critical patients. We found a significant association

Table 1. Laboratory marker values of critical COVID-19 patients and healthy controls

	Control (F+M) (n=50)	COVID-19 Patients (F+M) (n=50)	
Parameters	Median (IQR)	Median (IQR)	p value
Iron Metabolism			
Iron (µg/dL)	85,95 (37,4-162,6)	25,9 (5-58,8)	0,0001
Ferritin (ng/mL)	106,85 (9,78-463,2)	715,5 (405,6- 2000)	0,0001
Inflammation			
CRP (mg/dL)	0,1650 (0,02-1,70)	7,63 (0,61- 28,39)	0,0001
LDH (U/L)	205,5 (96-304)	418 (281-1008)	0,01
Neutrophil (10^3/µL)	4,13 (1,59-7,98)	8,4250 (0,76-33,89)	0,0001
Haemoglobin (g/dL)	14,83 (12,3- 18,1)	11,95 (8,1-14,9)	0,0001
Coagulation			
Prothrombin Time (sec)	11,25 (8,8-14,2)	13,85 (10,2-35,4)	0,0001
APTT (sec)	24,9 (19,1-34,4)	27,5 (19,2-103,3)	0,004
D-Dimer (µg FEU/mL)	0,2915 (0,001-1,7)	0,8725 (0,22-8,24)	0,0001
Platelet (10^3/µL)	225 (143-380)	205 (70-439)	0,062

Values are expressed as median (IQR).
Abbreviations: F+M: Female+male; IQR: Interquartile range; CRP: C-reactive protein; LDH: Lactate dehydrogenase; PT: Prothrombin Time; APTT: Activated partial thromboplastin time.
$p<0.05$ were regarded as statistically significant.

between disturbances in iron metabolism and COVID-19 disease, and therefore impaired iron homeostasis is thought to have various adverse consequences in patients. Critical COVID-19 patients have been associated with increased serum ferritin levels and decreased serum iron levels, and these patients in particular may be prone to more severe organ damage.

Recent studies have shown that several hematological parameters change clearly in COVID-19 patients[13]. In particular, the increase in CRP and LDH values may be an indicator of lung damage and may reflect respiratory distress due to hyperinflammation in critical COVID-19 patients[14]. We observed that CRP, LDH, neutrophils, and hemoglobin were significantly different between the two groups (Table 1). These results were parallel to the studies by Fan et al. (LDH, neutrophils and hemoglobin)[13], Poggiali et al. (LDH, CRP and neutrophils)[14], Ferrari et al. (CRP, LDH and neutrophils)[15], Mardani et al. (CRP, LDH and neutrophils)[16], and Wang et al. (LDH and neutrophils)[17].

It has been reported that excessive inflammation may play a critical role in disease pathogenesis by altering serum iron balance, including viral infections. The excessive increase in ferritin levels observed in critical COVID-19 patients is induced by hyper-ferritinemia, inflammation. Thus, cytokine storm also stimulates ferritin synthesis. But the role of iron metabolism in the prognosis of COVID-19 disease is not yet clear[18-20]. In our study, we found that ferritin levels increased significantly in patients with COVID-19 compared to the healthy control group (Table 1). Consistent with our findings, Dahan et al.[21], Ruan et al.[22] and Chen et al.[23] found a significant increase in ferritin levels in severe patients diagnosed with COVID-19. Ferritin is regulated by the amount of free iron as well as by inflammation[19,24]. Further studies have shown that iron is linked to the severity of inflammation and redox biology. Raised ferritin levels due to infection deprive bacteria of iron, preventing them from reproducing. Thus, it represents a significant defensive mechanism that protects human immunity. In addition, it can be protective by restricting the production of free radicals or mediating the regulation of the immune response. Furthermore, hyper-ferritinemia in high-risk patients is an important acute phase reactant used by clinicians as a signal for therapeutical intervention aimed at organizing inflammation. A different viewpoint is that hyper-ferritinemia is a harmless biomarker of uncontrolled inflammation that can be used to evaluate effect of disease. Consistent with the above that induction of ferritin could be a defensive effect for patients. Others claim that ferritin have an important role for immunosuppressive and pro-inflammatory effects in excessive hyper-ferritinemia. Because of these different ideas, there is a frankly need for further studies of the role of ferritin in excess inflammatory conditions[25].

Cecchini et al. talked about a vicious circle that locks the immune system of the SARS-CoV-2 virus and causes a cytokine storm. According to this cycle, after the virus reaches the airways of the host, the natural immune response comes into play. This response activates macrophage and dendritic cells and enable to production of inflammatory cytokines and reactive oxygen species (ROS). Inflammatory cytokines and ROS spread into the blood disrupt the structure of the erythrocytes and cause the release of hemoglobin from the erythrocytes. The hemoglobin molecule dissociates into free iron ion (Fe^{2+}) and heme molecules in the blood. Superoxide radicals (O_2^-) formed by activated macrophages and neutrophils react with Fe^{2+} released from the hemoglobin molecule and form the hydroxyl radical by Haber-Weiss and Fenton reactions and cause the increase of ROS. Oxidative stress and/or free iron provide the conversion of soluble plasma fibrinogen to fibrin clots. This transformation causes to form of fibrin deposits, leading to microthrombosis in the vascular system and the pulmonary microcirculation[26]. Although the same markers were used, different results were obtained in studies of coagulation markers. Spiezia et al. found that D-dimer increased significantly in COVID-19 patients compared with healthy people. However, they did not find a significant difference for APTT, PT and platelets between the two groups[27]. Han et al. found that D-dimer increased significantly in COVID-19 patients compared with healthy people. But they did not find significant difference for APTT and PT between the two groups[28]. Yin et al. found that platelets increased significantly in COVID-19 patients compared with healthy people. However, they did not find significant differences for D-dimer and APTT between the two groups[29]. In our study, we found that D-dimer, APTT and PT levels increased significantly in patients with critical COVID-19 compared with healthy people. But we did not find a significant difference between the two groups for platelets. Different results may be due to different profiles of control groups. However, as the severity of COVID-19 disease increases, plasma oxidative stress and free iron ion levels increase. Hence, increased oxidative stress and free iron ion may affect coagulation state. This situation may alter the levels of measured parameters related to coagulation.

Some viruses (hepatitis B virus, human immunodeficiency virus, cytomegalic virus, and vaccinia virus etc.) need to iron for replication

process. For this reason, it is probably that more iron will be transported into the cell through transferrin receptors[30]. Sonnweber et al. found no association between serum iron levels in patients with severe COVID-19 and those in patients with mild and moderate COVID-19[31]. However, Zhao et al. found that serum iron levels in patients with severe COVID-19 were significantly lower than those in patients with mild COVID-19[32]. Consistent with Zhao et al.[32], we found that iron levels decreased significantly in patients with critical COVID-19 compared to control group (Table 1). It seems likely that iron enters in the cells and accumulates in there. This situation may cause lowering the serum iron levels. Accumulation of iron may trigger the increase in intracellular labile iron (Fe^{2+}) pool (LIP) and Fenton reaction, generating lipid ROS, and lead to ferroptosis[30]. Ferroptosis is a type of regulated cell death and discovered in 2012 and induced by intracellular phospholipid peroxidation and has morphologically, biologically, and genetically differences compared to other types of cell death[33]. During the infection, excessive of transferrin carry Fe^{3+} ion. The transferrin is recognized by transferrin receptors and enters the cells via these receptors. Thereafter, Fe^{3+} is converted to Fe^{2+} through the divalent metal transporter 1 (DMT1). Thus, the amount of iron (Fe^{2+}) increases in the cells. Excessive iron (Fe^{2+}) and hydrogen peroxide (H_2O_2) causes lipid peroxidation through the Fenton reaction and produces lipid ROS. This can be clear off by glutathione peroxidase 4 (GPX4) and its substrate glutathione (GSH). But, because of the iron overload, immense Fenton reactions produce numerous lipid ROS, reasoning cell membrane damage and finally cell death[30]. Also, it may be hyper-ferritinemia is related to a situation of iron toxicity which may arise from enhanced ferritin leaks from damaged tissue[8]. In the normal conditions, 95 % of cellular iron is securely bound to diverse proteins. Hemoglobin is the most iron-using protein in the body, and if hemoglobin is damaged in some way, a significant amount of iron is released into the environment. This situation causes hemoglobin related disorders. Ferritin is the main iron storage protein and can be thought of as an antioxidant. Because it securely stores surplus iron non-toxic form. In the normal conditions, only a small part of cellular iron exists in the LIP form. When the LIP increases in cells, there is the potential to generate ROS such as hydrogen peroxide, superoxide, and hydroxyl radicals in tissues with high oxygen concentration such as particularly in the lungs[34].

As discussed in this article, one of the most common conditions in COVID-19 is ARDS. In this case, the SARS-CoV-2 virus replicates its genomes in the host cells and spreads over the lung surface, causing pathologies such as inflammation and hypercoagulation. The pulmonary leanness observed in COVID-19 patients may have different causes as well as cell damage in the lungs. The SARS-CoV-2 virus can also attack the heme on the 1-beta chain of hemoglobin and destroy it. This causes iron to be released from the porphyrin ring. Thus, the amount of iron in the circulation increases excessively. Ferritin production is increased to reduce high systemic iron levels. The increased amount of serum ferritin may reason liver cell death inducing release of iron from ferritin, which leads to an increase in systemic iron levels. The excessive abundance of free iron can aggravate inflammatory state through ROS-induced oxidative injury and ferroptotic cell death. If this condition is left untreated, ferroptosis exacerbates the inflammation and may cause multiple organ failure and serious lung damage. Free iron also causes excess hydroxyl radical generation in severe COVID-19 patients. Hydroxyl radicals may contribute to hypercoagulation state by transforming fibrinogen into fibrin clots.

The present study has one limitation. The limitation is the lack of parameters of iron metabolism such as transferrin, transferrin saturation, hemosiderin etc. Since these parameters were measured very rarely in COVID-19 patients, we could not obtain the parameters from electronic medical records.

Conclusion

In response to the infection of SARS-CoV-2, iron metabolism dysfunction has been broadly documented in a great ratio of COVID-19 patients. We think that ferroptosis may play a vital role in the development of multiple organ involvement in critical COVID-19 patients. Ferroptosis inhibitors might have potential to combat ferroptosis in COVID-19. A better understanding of the role of ferroptosis in COVID-19 will open new horizons for diagnosis and therapeutic intervention. Therefore, we hope that studies on ferroptosis in COVID-19 will increase *in vivo* and *in vitro*.

Conflicts of interest statement

The authors declare no conflicts of interest.

Ethics committee approval

The requisite approval was obtained from the Malatya Turgut Ozal University, Clinical Research Ethical Committee (date: 09/04/2021, number: 2021/7). All procedures were carried out in accordance with the ethical standards of the institutional and/or national research committee and the 1964 Declaration of Helsinki. In addition, all patient privacy and data were respected and protected.

Informed consent

All patients had completed treatment at the beginning of the study, and the study did not interfere with diagnosis or treatment in any case. Therefore, the need for informed consent was waived by the Malatya Turgut Ozal University, Clinical Research Ethical Committee.

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