Evaluation of Iron Deficiency in COVID-19 Pneumonia

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Abstract

Background: Inlate 2019, a new coronavirus disease was detected in Wuhan, China and called COVID-19. There are so many unknown factors about the virus. Iron metabolism is one of the topics have to be investigated for the development of therapeutic strategies for COVID-19. The aim of this study is to assess sequential changes in traditional biochemical iron status indicators during COVID-19 pneumonia. Methods: A case-control study. Case group was defined as pneumonia with PCR-confirmed SARS-CoV-2 and the control group consisted of patients with non-COVID-19 pneumonia. Biomarkers of anemia and iron metabolism, CRP, procalcitonin were analyzed. Demographic features, CT findings, SpO2, development of ARDS, ICU admission, duration of hospitalization, discharge status (event free survival or death) were evaluated. Results: 205 hospitalized patients with pneumonia were analyzed retrospectively. COVID-19 group was significantly younger than control group. 23 of 106 patients had critical COVID-19 infection. Comorbidity frequency and mortality rate of patients with COVID-19 pneumonia were significantly higher. Hb, RET-He, iron, TSAT, CRP, PCT and SpO2 were significantly lower. Hb, RET-He, iron, TSAT levels significantly correlated to lung aeration loss, hospitalization day and inflamatory markers in COVID-19 pneumonia. Conclusion: The patients with COVID-19 pneumonia had iron deficiency anemia even they were young. Iron deficiency may effect the lung aeration loss related to paranchimal infiltrations of COVID-19 and mortality of the patients with COVID-19 pneumonia. Our data indicates that iron deficiency is associated with longer hospital stays, lower oxygenation, higher CRP and procalsitonin.

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Results: 205 hospitalized patients with pneumonia were analyzed retrospectively. COVID-19 group was significantly younger than control group. 23 of 106 patients had critical COVID-19 infection. Comorbidity frequency and mortality rate of patients with COVID-19 pneumonia were significantly higher. Hb, RET-He, iron, TSAT, CRP, PCT and SpO2 were significantly lower. Hb, RET-He, iron, TSAT levels significantly correlated to lung aeration loss, hospitalization day and inflamatory markers in COVID-19 pneumonia.

Conclusion: The patients with COVID-19 pneumonia had iron deficiency anemia even they were young. Iron deficiency may effect the lung aeration loss related to paranchimal infiltrations of COVID-19 and mortality of the patients with COVID-19 pneumonia. Our data indicates that iron deficiency is associated with longer hospital stays, lower oxygenation, higher CRP and procalsitonin.

Keywods: COVID-19, pneumonia, iron, hemoglobin, anemia

Introduction Inlate 2019, a new coronavirus with acute respiratory disease was detected in Wuhan, China and called SARS-COV-2 (Severe Acute Respiratory Syndrome Coronavirus-2) (1). The name of the disease has been determined as Coronavirus disease 2019 (COVID-19) by the World Health Organization.

The diagnosis includes the presence of contact, findings compatible with viral pneumonia in lung imaging, and laboratory findings not specific to COVID-19 (such as lymphopenia, d-dimer, ferritin elevation, etc.). Although reverse transcription polymerase chain reaction (RT-PCR) for SARS-COV-2 is the gold standard in diagnosis, errors in sampling result in false negativity in the period of the disease.

The most common symptoms are fever, cough, and dyspnea. Pneumonia, severe acute respiratory tract infection, renal failure, sepsis/septic shock, ARDS, and multiorgan failure or even death may develop in more severe cases (2).

Since the life cycle of SARS-COV-2 has not been fully revealed, there are still unknown points about the disease. Diagnosis, follow-up and treatment algorithms are tried to be explained.

A study evaluating the biological roles of some proteins of the novel coronavirus (3) showed the ORF8 and surface glycoprotein could bind to the porphyrin. The researchers speculated that orf1ab, ORF10, and ORF3a proteins could coordinate attack the heme on the 1-beta chain of hemoglobin to dissociate the iron to form the porphyrin. Thus, it has been claimed that hemoglobin, which can carry oxygen and carbondioxide, is reduced, lung cells are damaged due to the inadequate exchange of carbondioxide and oxygen, and groundglass densities appear in lung imaging due to inflammatory response.

Anaemia screening only based on hemoglobin measurements is inappropriate and inconclusive in many subjects. Iron deficiency anemia (IDA) is one of the most common form of anemia. Various biochemical parameters are used to diagnose IDA, including ferritin, transferin saturation (TSAT), serum iron, and mean corpuscular volume (MCV). However, measures of mature erythrocyte indices MCV, mean corpuscular hemoglobin (MCH), and red blood cell distribution width (RDW) cannot detect early iron-deficient erythropoiesis due to the slow turnover of erythrocytes in circulation (4). Cellular iron status can be determined by the method of measuring the reticulocyte hemoglobin equivalent (RET-He) (5). RET-He reflects a 'shortterm' indication concerning the status of reticulocytes hemoglobinization (6).

Serum ferritin is an important parameter in determining iron deficiency anemia. Serum ferritin concentration generally correlates with total body iron storage. However, despite the presence of iron deficiency in the course of liver parenchymal disease, chronic inflammatory diseases, some infections and storage diseases, normal serum ferritin level can be found, as well as in hypothyroidism, pregnancy and vitamin C deficiency, it may be low because ferritin synthesis is decreased (7).

Reticulocytes are the youngest erythrocytes released from bone marrow in to blood. The reticulocyte hemoglobin content (RET-He) indicates the amount of iron available in the bone marrow for hemoglobin production. Therefore, RET-He has been proposed as an indicator of iron status (8). In this study; we assessed sequential changes in traditional biochemical iron status indicators during Covid-19 infection.

Methodology

The study conformed to the principles of the Declaration of Helsinki and was approved by the ethics committee of Mugla Sitki Kocman University. Patients with pneumonia who needed hospitalization at Mugla Sitki Kocman University University Education and Training Hospital were analyzed retrospectively. Adult patients hospitalized with a diagnosis of pneumonia between March 15, 2020 and July 1, 2020 were evaluated.

The patients with previously diagnosed anemia, chronic renal failure, chronic obstructive pulmonary disease, liver parenchymal disease, malignancies and chronic gastrointestinal inflammation were excluded. The remaining 205 patients were included in the study. A case-control study was planned with the collected data. The case group was defined as pneumonia with PCR-confirmed SARS-CoV-2 and the control group consisted of patients with non-COVID-19 pneumonia.

Biomarkers of anemia and iron metabolism (hemoglobin, serum iron, ferritin, total iron-binding capacity (TIBC), transferrin saturation, MCV, MCH, RDW, RET-He, C-reactive protein (CRP), procalcitonin (PCT) were analyzed.

Demographic features, thoracic computed tomography (CT) findings, oxygen saturation (SpO2), respiratory symptoms, development of acute respiratory distress syndrome (ARDS), intensive care unit (ICU) admission, duration of hospitalization, discharge status (event free survival or death) were evaluated.

CT findings of the patients with COVID-19 pneumonia were analyzed advancedly. All thoracic CT scans were obtained without contrast agent injection, during deep inspiration, in the supine position and sometimes in

the prone position. Radiological images were obtained with 256-slice Toshiba-TCT-60 AX and 4-slice Siemens Somatom device localized in the emergency room for COVID-19 patients only.

The following technical parameters were used:

Tube voltage: 120 kV; tube current modulation 100-250 mAs; spiral pitch factor: 0.98; collimation width: 0.625.

The decontamination protocol for the chamber consisted of surface disinfection with 62-71% ethanol or 0.1% sodiumhypochlorite. Passive air exchange was performed for 40-60 minutes after chest CT examination in each patient.

CT images were transferred to the VIA port system in the workstation of our hospital and 3D reconstruction was performed. Images were evaluated on high resolution medical screen.

Right lung 3 lobes left lung 2 lobes were examined separately. Each lobe was accepted as 20% and lobe volume was measured first. Then, the areas in the consolidated and groundglass area were calculated by calculating the volumetricv oxel on the computer, and they were calculated over the total volume. Total lung aeration loss was found by summing the percentage values of all lobes.

Statistical Analysis

Data was analyzed using IBM SPSS Statistics Version 23.0. All tests were two-tailed and p-value$<$0.05 was statistically significant. The descriptive statistics are presented as frequencies, percentage, mean, standard deviation (SD) values. Variables are depicted as n (%) or means. Student's t-test, Mann–Whitney-U test, or chi-square tests were performed to test for significant differences between groups. The relationships between variables were evaluated using the Pearson or Spearman correlation tests. Logistic regression analysis was performed to analyze the effects of risk factors.

Results

We retrospectively analyzed 205 hospitalized patients with pneumonia. 106 of the patients has been treated as PCR confirmed COVID-19 infection with a mean age of 50.12+-1.79 years: 60 men and 46 women. 99 of the patients had atypical pneumonia with a mean age of 59.38+-2.07: 66 men and 33 women. COVID-19 group was significantly younger than control group.

23 (19.9%) of 106 PCR posivite patients had critical COVID-19 infection with ARDS or ICU admission. The mean age of critical patients was 66.30+-12.13 and it was significantly higher (p=0.000). 14 (16.7%) of 99 patients with non-COVID-19 pneumonia were severe. Mean duration of hospitalization was 7.97+-5.03 days in COVID-19 infection while it was 7.20+-5.23 days in non-COVID-19 group. Comorbidity frequency (diabetes mellitus and cardiovascular disease) in patients with COVID-19 was significantly higher than patients with non-COVID-19 pneumonia. Mortality rate in COVID-19 group as 7.54%, and it was 10.10% in the control group. Cigarette smoking ratio was significantly lower in COVID-19 group. Mean SpO2 (%) of the patients with COVID-19 pneumonia were lower than the patients with severe non-COVID-19 pneumonia in both clinics and ICU. Demographic characteristics of patients were summerized in table 1.

Fever, cough, myalgia and anosmia were more common in the patients with COVID-19 pneumonia (Table 2). Bilateral infiltrations were more often in the thoracic CT scans of COVID-19 pneumonia group (Table 2). Hemoglobin, RET-He, iron, TSAT, CRP, PCT and SpO2 of patients with COVID-19 pneumonia were significantly lower than thec ontrol group (Table 3). Critical COVID-19 pneumonia group was significantly older than the patients with COVID-19 pneumonia those were treated in clinics. The comorbidity, smoking, mean lung aeration loss ratios were higher, the hospitalization time was longer in critically ill patients. As a result the mortality ratio was also significantly high in this group. Characteristics of patients with COVID-19 pneumonia were mentioned in table 4.

When we compared the COVID-19 pneumonia as critical and not critical; mean values of hemoglobin, RET-He, iron, TSAT, SpO2 were significantly low in critical group where as the mean RDW, CRP and PCT were

significantly higher. Laboratory findings of patients with COVID-19 pneumonia were summerized in table 5.

Mean lung aeration loss of the patients with COVID-19 pneumonia was 16.04+-12.23. Hb, RET-He, iron, TSAT levels significantly correlated to lung aeration loss, hospitalization day and inflamatory markers (CRP, PCT) in COVID-19 pneumonia (Table 6). We found a significant effect of iron deficiency parameters (RET-He, iron, ferritin, TSAT, Hb, RDW) on both mortality (p=0.001) and dyspnea (0.000).

Discussion

Our results show that patients with COVID-19 pneumonia had iron deficiency even they were young. And we speculate that iron deficiency effects the lung aeration loss related to paranchimal infiltrations of COVID-19. Our data indicates that iron deficiency is associated with longer hospitalization, lower oxygenation, higher CRP and procalsitonin. We found a significant effect of iron deficiency parameters on mortality of COVID-19 pneumonia. Pre-existing iron deficiency may be a risk factor for COVID-19 pneumonia and it's severity. Since COVID-19 patients in our study had a higher prevalence of comorbidities such as hypertension, cardiovascular disease and diabetes mellitus; reduced tissue oxygenation as a result of chronic inflammation may be the reason of iron deficiency.

Bellmann-Weiler et al. (9) claimed anemia, specifically anemia of inflammation is prevalent in patients with severe SARS-CoV-2 infection and that anemia is associated with longer hospital stays, poor clinical conditions and poor survival. Systemic inflammations are associated with increased serum ferritin levels. Serum iron and TSAT decrease early after infections, inhibiting iron availability to the pathogens (10,11).

Edeas M et al. (12) speculated that increased serum ferritin levels as a result of COVID-19 related hyper-inflammation and increased ferritin levels may lead to further tissue damage. It has been reported that hyper-inflammation in association with altered iron homeostasis may play a key role in pathogenesis of disease including viral infections (13). Hyper-ferritinemia may be associated with iron toxicity from damaged tissue releasing free iron. There is no consensus to exclude this possibility.

Iron metabolism and anemia may play an important role in multiple organ dysfunction syndrome in COVID-19. A meta-analysis suggested that hemoglobin and ferritin levels vary according tot the severity of COVID-19 as well as age, gender and presence of comorbidity. The mean diference in serum ferritin was higher in severe COVID-19 compared to moderate cases. From seven observational studies and 717 individuals, the mean difference in RBC count was lower, while RDW was higher in patients with severe COVID-19 (14).

Huang et al. (15) reported reduction in hemoglobin levels in 38.2% of hospitalized COVID-19 patients. Hemoglobin concentration is one of the most important determinants of the oxygen-carrying capacity of the blood. COVID-19 patients, could sufer from a decreased capability of hemoglobin to support the increased peripheral tissue demands for oxygen due to the hyper-metabolic states during infection. Our results supports this idea since hemoglobin of patients with COVID-19 was significantly lower than the patients with non-COVID-19 pneumonia.

Alipour R et al. (16) found out that serum iron levels were lower than normal range of patients with mild, modarate and severe COVID-19 infection. They claimed that serum iron levels of ICU admitted patients were significantly lower than others. Based on the results, they spaculated that the severity of respiratory symptoms might depend on low serum iron. Our results showed that dyspnea of patients with COVID-19 infection. In our study there was an inverse relation between iron deficiency parameters (RET-He, TSAT, iron) and radiological infiltrations, hosptalization days and inflamatory parameters (CRP, PCT) of COVID-19 patients. In the otherwise Cavezzi at al. (17) mentioned about the possible role of hemoglobin denaturation and tissue iron overload in COVID-19; potential adjuvant therapeutic interventions in a review article.

In a study by Li et al. (18) ferritin was significantly higher in severe patients. Shah et al. (19) reported no significant differences in serum ferritin levels and transferrin saturation between patients with non-severe and severe hypoxemia. They reported significantly lower levels of serum iron in patients with severe hypoxemia.

In our study, there was not a significant difference in ferritin levels between COVID-19 and non-COVID-19 pneumonia but the ferritin level of severe COVID-19 pneumonia was higher.

Virus-connected iron metabolism is one of the topics have to be investigated for the development of therapeutic strategies for COVID-19. Which one might be used to treat COVID-19 infections; iron replacement treatment or iron chelators? This subject is still controversial and has to be determined in future studies.

References

1. Chang D, Lin M, Wei L, Xie L, Zhu G, Dela Cruz CS, et al. Epidemiologic and clinical characteristics of novel coronavirus infections involving 13 patients outside Wuhan, China. JAMA 2020; 323,11:1092-1093.
2. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patientswith 2019 novel coronavirus–infected pneumonia in Wuhan, China. JAMA 2020; 323(11):1061-1069.
3. Wenzhong Liu, Hualan Li. COVID-19: Attacks the 1-Beta Chain of Hemoglobin and Captures the Porphyrin to Inhibit Human Heme Metabolism. DOI: 10.26434/chemrxiv.12120912.
4. Mast AE, Blinder MA, Dietzen DJ. Reticulocyte hemoglobin content. Am J Hematol. 2008; 83:307-310.
5. Eguchi A, Tsuchiya K, Tsukada M, Nitta K. Clinical usefulness of reticulocyte hemoglobin equivalent (RET-He) in patients at the pre-dialysis stage and in patients on peritoneal dialysis. Japanese Journal of Nephrology. 2010; 52(2):132-140**.**
6. Thomas C, Thomas L. Biochemical markers and hematologic indices in the diagnosis of functional iron deficiency. Clin Chem. 2002; 48:1066-1076.
7. Fairbanks VF, Beutler E. Iron Deficiency. In: Beutler E, Lichtman MA, Coller BS, et al. Editors. Williams Hematology, Sixth edition. New York: McGraw-Hill; 2001. Pp: 447-470.
8. Kim JM, Ihm CH, Kim HJ. Evaluation of reticulocyte haemoglobin content as marker of iron deficiency and predictor of response to intravenous iron in haemodialysis patients. Int J Lab Hematol. 2008; 30:46-52.
9. Bellmann-Weiler R, Lanser L, Barket R, Rangger L, Schapfl A, Schaber M, et al. Prevalence and Predictive Value of Anemia and Dysregulated Iron Homeostasis in Patients with COVID-19 Infection. J. Clin. Med. 2020; 9:2429: 1-11.
10. Eskeland B, Baerheim A, Ulvik R, Hunskaar S. Influence of mild infections on iron status parameters in women of reproductive age. Scand J Prim HealthCare. 2002; 20:50–56.
11. Punnonen K, Irjala K, Rajamaki A. Serum transferrin receptor and its ratio to serum ferritin in the diagnosis of iron deficiency. Blood. 1997; 89:1052–1057.
12. Edeas M, Saleh J, Peyssonnaux C. Iron: innocent by stander or vicious culprit in COVID-19 pathogenesis? Int J InfectDis. Int J InfectDis. 2020; 97: 303–305.
13. Drakesmith H, Prentice A. Viral infection and iron metabolism. Nat. Rev. Microbiol. 2008; 6:541-552.
14. Taneri PE, Gomez-Ochoa SA, Llanaj E, Raguindin PF, Rojas LZ, Roa-Diaz ZM, et al. Anemia and iron metabolism in COVID-19: a systematic review and meta-analysis. European Journal of Epidemiology. 202; 35: 763–773.
15. Huang Y, Tu M, Wang S, Chen S, Zhou W, Chen D, et al. Clinical characteristics of laboratory confirmed positive cases of SARS-CoV-2 infection in Wuhan, China: A retrospective single center analysis. Travel Medicine and Infectious Disease 36 (2020) 101606. https://doi.org/10.1016/j.tmaid.2020.101606.
16. Alipour R, Hashemi SH, Mikaeili F. Serum iron level in patients with COVID-19: a case report study. Int J Res Med Sci. 2020 Jul; 8(7): 2658-2662.
17. Cavezzi A, Troiani E, Corrao S. COVID-19: hemoglobin, iron, and hypoxia beyond inflammation. A narrative review. Clinics and Practice. 2020; 10:1271:24-30.
18. Li X, Xu S, Yu M, Wang K, Tao Y, Zhou Y, et al. Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan. J Allergy Clin Immunol. 2020; 146(1):110–8.
19. Shah A, Frost JN, Aaron L, Donovan K, Drakesmith H. Collaborators Systemic hypoferremia

and severity of hypoxemic respiratory failure in COVID-19. Crit Care. 2020;24(1):320. https ://doi.org/10.1186/s1305 4-020-03051-w.

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