EVALUATION OF IRON STATUS IN COVID-19 PNEUMONIA

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ABSTRACT

Introduction*: In late 2019, a new coronavirus disease was detected in Wuhan, China and called COVID-19. 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 changes in traditional biochemical iron status indicators during COVID-19 pneumonia.*

Materials and methods*: A case-control study. Case group was defined as COVID-19 pneumonia with polymerase chain reaction (PCR)-confirmed and the control group consisted of patients with non-COVID-19 pneumonia with culture confirmed. Biomarkers of anemia and iron metabolism, C-reactive protein (CRP), procalcitonin were analyzed. Demographic features, thorax tomography findings, oxygen saturation, development of acute respiratory distress syndrome (ARDS), intensive care unit 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. Hemoglobin (Hb), reticulocyte hemoglobin equivalent (RET-He), iron, transferin saturation (TSAT), CRP, procalcitonin (PCT) and oxygen saturation (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.*

Conclusions*: The patients with COVID-19 pneumonia had lower iron parameters even they were young. Low RET-He, iron, TSAT may effect the lung aeration loss related to paranchimal infiltrations and mortality of the patients with COVID-19 pneumonia. Our data indicates that iron deficiency parameters associated with longer hospital stays, lower oxygenation, higher CRP and procalsitonin.*

Keywords: *COVID-19, pneumonia, iron, hemoglobin, RET-He.*

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Introduction

In late 2019, a new coronavirus with acute respiratory disease was detected in Wuhan, China and called Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-COV-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, acute respiratory distress syndrome (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 research evidence on COVID-19 evaluating the biological roles of some proteins of the novel coronavirus, Liu et al.[3] put forward hypotheses about direct viral interaction with the heme group of hemoglobin. 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. This leads to the production of large amounts of serum ferritin to bind these free irons in order to reduce tissue damage. However, the methods used by Lui et al. have very recently been criticised[4]. It is unclear what testable physiological consequences might arise from an interaction between viral proteins and Hb but these are presumed to include a generalised loss of hemoglobin and/or a change in oxygen affinity. While mild anaemia and decreased Hb content have been reported, the effect of COVID-19 on O2 affinity has not been investigated. Recently, a review has highlighted the role of hemoglobin denaturation, iron dysmetabolism/tissue overload and hypoxia in COVID-19[5].

Various biochemical parameters are used to diagnose iron deficiency anemia (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[6]. Cellular iron status can be determined by the method of measuring the reticulocyte hemoglobin equivalent (RET-He)[7]. RET-He reflects a 'shortterm' indication concerning the status of reticulocytes hemoglobinization[8].

Serum ferritin is an important parameter in determining iron deficiency anemia. Serum ferritin concentration generally correlates with total body iron storage. However, liver parenchymal diseases, chronic inflammatory diseases, some infections and storage diseases can effect serum ferritin[9].

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 (10).

In this study; we assessed changes in spesific biochemical iron status indicators during COVID-19 infection.

Materials and methods

Patients with pneumonia who needed hospitalization at Mugla Sitki Kocman University Education and Training Hospital were analyzed retrospectively.

Adult patients (age≥18) who are hospitalized with the diagnosis of community-acquired pneumonia and COVID-19 pneumonia in the first 3 months of pandemic in our country (15 March-1 July 2020) were evaluated. A case-control study was planned. The case group was defined as pneumonia with PCR confirmed SARS-CoV-2 and the control group consisted of patients with culture confirmed bacterial pneumonia. The patients with previously diagnosed anemia, chronic renal failure, chronic obstructive pulmonary disease, liver parenchymal diseases, malignancies, chronic gastrointestinal inflammation and pregnant women were excluded since they might already had iron deficiency. 205 patients were included in the study.

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 on the first day of hospitalization.

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

CT findings of the patients with 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% sodium hypochlorite. 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 volumetric voxel 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.

Ethical statement

The study conformed to the principles of the Declaration of Helsinki and was approved by the ethics committee of Mugla Sitki Kocman University (200103-60).

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. The compatibility of quantitative variables to normal distribution was tested. 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 Spearman correlation tests. Variables were entered into a multivariate logistic regression model to evaluate the risk factors related to mortality and dyspnea.

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 50.1±1.8 years (60 men and 46 women). 99 of the patients had bacterial pneumonia with a mean age of 59.4±2.1 (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 66.3±12.1 and it was significantly higher (p<0.001). Mean duration of hospitalization was similar in both groups. Comorbidity frequency (diabetes mellitus and cardiovascular disease) in patients with COVID-19 was significantly higher than patients with bacterial pneumonia. Cigarette smoking ratio was significantly lower in COVID-19 group. Demographic characteristics of patients were summerized in table 1.

	COVID-19 pneumonia (n=106)	Bacterial pneumonia (n=99)	P value
Age (years)	50.1±1.8	59.4±2.1	**0.001**
Gender (female (n)/male (n))	46/60	33/66	0.153
Comorbidity (yes/no)	66/40	40/59	**0.000**
HT (yes/no)	46/60	23/76	0.153
CVD (yes/no)	16/90	5/94	**0.047**
DM (yes/no)	23/83	14/85	**0.016**
Smoking (yes/no)	50/56	68/31	**0.001**
Hospitalization day	7.8±5.0	7.2±5.2	0.178
ICU admission (yes/no)	23/83	14/85	**0.016**
Discharge status (death/survival)	13/93	10/89	0.591

Table 1: Demographic characteristics.
HT. Hypertension; CVD: Cardiovascolar disease; DM: Diabetes mellitus; ICU: Intensive care unit

	COVID-19 pneumonia (n=106)	Bacterial pneumonia (n=99)	P value
Fever (yes/no)	66/40	77/22	**0.016**
Cough (yes/no)	64/42	76/23	**0.012**
Dyspnea (yes/no)	45/61	51/48	0.194
Myalgia (yes/no)	62/44	18/81	**0.000**
Diarrhea (yes/no)	8/98	6/93	0.673
Anosmia (yes/no)	6/100	0/99	**0.016**
Thoracic CT (unilateral/bilateral)	15/71	37/62	**0.003**
Thoracic CT (lober/multilober)	15/71	24/75	0.258
Lung aeration loss (%)	31.33±15.14	29.20±15.23	0.369

Table 2: Symptoms and thoracic CT findings.
CT. Computed tomography

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. Mean lung aeration losses of the patients with COVID-19 pneumonia and the control group were similar (Table 2). Hemoglobin, RET-He, iron, TSAT, CRP, PCT and SpO2 of patients with COVID-19 pneumonia were significantly lower than the control group (Table 3).

	COVID-19 pneumonia (n=106)	Bacterial pneumonia (n=99)	P value
Hemoglobin (g/dl)	12.84 ±2.34	14.66±2.93	**0.000**
MCV (fL)	84.37±6.36	84.79±9.60	0.587
MCH (pg)	28.34±2.88	28.44±2.79	0.861
RDW (fL)	42.65±7.15	44.49±6.87	**0.003**
RET-He (pg)	25.88±4.10	27.16±4.60	**0.031**
Iron (µg/dL)	50,62±42.41	61.05±28.53	**0.001**
Ferritin (ng/mL)	448.38±877.31	423.77±985.12	0.930
TIBC (µg/dL)	297.79±88.91	290.70±63.92	0.511
TSAT (%)	17.63±9.27	21.85±9.17	**0.003**
CRP (mg/L)	49.54±81.76	77.59±107.75	**0.036**
PCT (µg/L)	0.23±0.08	0.68±4.19	**0.021**
SpO2 (%)	93.06±5.64	94.28±4.75	**0.016**

Table 3: Laboratory findings.
MCV. Mean corpuscolar volume; MCH: Mean corpuscolar hemoglobin; RDW. Red blood cell distribution width; RET-He: Reticulocyte hemoglobin equivalent; TIBC: Total Iron binding capacity; TSAT: Serum transferrin saturation; CRP: C-reactive protein; PCT: Procalcitonin; Spo2: Oxygen saturation

The mean values of hemoglobin, RET-He, iron, TSAT, SpO2 were significantly low where as the

mean RDW, CRP and PCT were significantly higher in critically ill COVID-19 patients. Laboratory findings of patients with COVID-19 pneumonia were summerized in table 4.

	COVID-19 pneumonia (n=83)	Critical COVID-19 pneumonia (n=23)	P value
Hemoglobin (g/dl)	13.45±1,94	11.41±2.82	**0.001**
MCV (fL)	84.49±6,26	83.89±6.94	0.846
MCH (pg)	28.56±2,78	27.39±3.18	0.135
RDW (fL)	41.23±5,79	48.73±9.22	**0.000**
RET-He (pg)	28.35±3,44	26.24±5.32	**0.030**
Iron (µg/dL)	52.66±29,37	42.95±23.62	0.159
Ferritin (ng/mL)	198.19±184,22	1393.75±1997.64	**0.000**
TIBC (µg/dL)	289.00±92.29	291.05±56.06	0.907
TSAT (%)	17.99±9.05	14.75±9.74	**0.001**
CRP (mg/L)	28.68±46.61	139.23±129.56	**0.000**
PCT (µg/dL)	0.15±0.29	1.50±2.13	**0.000**
SpO2 (%)	96.31±1.79	85.55±3.37	**0.000**

Table 4: Laboratory findings of patients with CIVID-19 pneumonia.
MCV. Mean corpuscolar volume; MCH: Mean corpuscolar hemoglobin; RDW. Red blood cell distribution width; RET-He: Reticulocyte hemoglobin equivalent; TIBC: Total Iron binding capacity; TSAT: Serum transferrin saturation; CRP: C-reactive protein; PCT: Procalcitonin; Spo2: Oxygen saturation

Hb, RET-He, iron, TSAT levels significantly correlated to lung aeration loss, hospitalization day and inflamatory markers (CRP, PCT) in COVID-19 pneumonia (Table 5). We could not find any significant association between iron deficiency parameters and mortality in patients with COVID-19 pneumonia.

			Hospitalization day	Lung aeration loss	CRP	PCT	SpO2
Spearman's rho	Hb	r	-.196	-.254	-.398	-.218	.323
		p	**0.045**	**0.004**	**0.000**	**0.026**	**0.001**
	RDW	r	-.410	.	.526	507	-.488
		p	**0.000**	.	**0.000**	**0.000**	**0.000**
	RET-He	r	-.144	-.227	-.215	-.143	.
		p	**0.041**	**0.035**	**0.027**	**0.045**	.
	Iron	r	-.126	-.332	-.218	.	.212
		p	**0.048**	**0.000**	**0.025**	.	**0.030**
	TSAT	r	-.170	-.278	-.147	-.115	.436
		p	**0.041**	**0.002**	**0.033**	**0.043**	**0.000**
	Ferritin	r	.267	.297*	.465	.475	-.256
		p	**0.000**	**0.001**	**0.001**	**0.000**	**0.000**

Table 5: Correlation between some iron deficiency parameters in COVID-19 pneumonia.
Hb hemoglobin; RDW: Red blood cell distribution width; RET-He: Reticulocyte hemoglobin equivalent; CRP: C-reactive protein; PCT: Procalcitonin; Spo2: Oxygen saturation

Discussion

Our results show that patients with COVID-19 pneumonia had lower RET-He and TSAT. And we speculate that these parameters may effect the lung aeration loss related to paranchimal infiltrations of COVID-19. Our data indicates that RET-He and TSAT may be associated with longer hospitalization stay, lower oxygenation, higher CRP and procalcitonin. Pre-existing impaired iron metabolism may be a risk factor for COVID-19 pneumonia and it's severity.

Bellmann-Weiler et al.[11] 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. Our results support this claim. Systemic inflammations are associated with increased serum ferritin levels. Serum iron and TSAT decrease early after infections, inhibiting iron availability to the pathogens[12,13].

Edeas M et al.[14] 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[15]. Hyper-ferritinemia may be associated with iron toxicity from damaged tissue releasing free iron. There is no consensus to exclude this possibility. This may be the reason of high ferritin levels in our patients.

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 to 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[16].

Huang et al.[17] 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 suffer 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 bacterial pneumonia.

Alipour R et al.[18] 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.[5] 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.[19] ferritin was significantly higher in severe patients. Shah et al.[20] 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 bacterial pneumonia but the ferritin level of severe COVID-19 pneumonia was higher. This may be related to inflammation 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.

The study of Peerschke et al.[21] supports the use of RET-He to rule out iron deficiency, defined by traditional serum biochemical parameters, in a complex patient population with cancer, during routine automated CBC and reticulocyte analysis. In this unselected patient population with cancer, a high negative predictive value for ruling out iron deficiency was achieved using an RET-He cutoff of 31 to 32 pg, when iron deficiency was defined by serum iron and transferrin saturation, with or without ferritin. The mean RET-He values of patients in both of the groups in our study were under this value.

Our results might be limited by the small sample size. Also, it is difficult to verify whether that SARS-CoV-2 has a direct effect in iron metabolism because we had no information on the haemoglobin levels before the infection.

Conclusion

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? Our study is close to the side of iron replacement but this subject is still controversial and has to be determined in future studies.

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