Diagnosis of Coronavirus Disease 2019 by Potential Laboratory Factors

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ABSTRACT

Aims COVID-19 is associated with infection and high death rate. The unresolved questions about the fatality rate of COVID-19 is most probably related to cytokine storm syndrome. There is currently no specific medication. Understanding the laboratory diagnostic tests will lead to the production of treatment and decreases of death rate. The aim of this study was to investigate the changes of peripheral blood parameters (Interleukin-6, Ferritin and hematological parameters) in COVID-19 patients

Materials & Methods There were no significant differences in the age and sex ratio between two groups. The mean IL-6 and Ferritin levels and hematological parameters between COVID-19 and non-COVID-19 patients were significantly different (p=0.001).

Findings Suctioning with catheters 10 and 12 at pressures of 100 and 150 increased the hemodynamic parameters immediately after endotracheal suction. These increases was significant in systolic blood pressure (p=0.004) and mean arterial blood pressure (p=0.01). This test showed a statistically significant difference between intervention and intra-intervention in mean arterial oxygen saturation at post-suction time (p=0.001).

Conclusion The coronavirus affects the inflammatory markers specifically IL-6 and Ferritin and hematological parameters (WBC, Lymphocytes, Neutrophils, Platelet and Hb).

Keywords COVID-19; Infection; Proinflammatory Cytokines; Interleukin-6; Ferritin

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Introduction

Coronavirus disease 2019 (COVID-19) or the severe acute respiratory syndrome corona virus 2 (SARS-CoV-2), was first reported in December 2019 in Wuhan City, China [1]. COVID-19 is an infectious disease with typical symptoms including dry cough, muscle aches or fatigue, high fever and shortness of breath with severe acute respiratory syndrome (ARDS) on CT scans [2-4]. In general, COVID-19 in infected people of all ages can be implications on different organs as lungs, brain and nervous system and eventually, may lead to death [5].

The chest CT scan and RT-PCR were recommended for diagnosis of covid-19 patients [6]. According to the latest guidelines released by the Chinese government, chest CT scan is a common imaging tool for pneumonia diagnosis, and the key indicator for the confirmation of the diagnosis of COVID-19 is based on RT-PCR or sequencing of the gene for respiratory or blood specimens [6, 7]. However, a rate of 10-40% RT-PCR false-negative results made this technique insufficient for proper detection [7, 8].

COVID-19 binds to the angiotensin-converting enzyme-2 (ACE2) which is present on respiratory, endothelial and immune cells such as alveolar monocytes/macrophages [9]. ACE2 can induce endogenous stress signals or mutations in the host genome and recruitment of inflammatory cells [10]. In the defensive line, innate immunity senses microorganisms and release of cytokines, chemokines and inflammatory mediators by immune cells, and epithelial cells in pathological conditions [11]. The increase in specific cytokine production can be linked to an activation cascade and uncontrolled cytokine release, the cytokine storm [12]. Although cytokines expression is strictly controlled by transcriptional and posttranscriptional mechanisms, but high-level concentrations of cytokines for a long time leads to chronic inflammatory diseases and widespread tissue damage including ARDS [13, 14].

During a virus infection, the plasma concentration Interleukin (IL)-6, IL-1 and IL-10 were increased [15], especially, IL-6, which promptly stimulate the production of acute phase proteins in response to infections and tissue injuries [11]. IL-6 alterations reflect the presence and severity of inflammation, and they have long been used as a clinical Guideline for diagnosis and management of diseases [15, 16].

High levels of lactate dehydrogenase and ferritin are suggestive due to the cytokine storm in Laboratory findings. Also, elevated Ferritin levels due to cytokine storm syndrome have been reported in COVID-19 patients [17]. In hospitalized patients, serum ferritin test-which is widely available and affordable-is a good qualified screening tool for informing physicians of cytokine storm syndrome for COVID-19 patients [18]. Therefore, the enigma regarding the high mortally rate associated with COVID-19 is most probably explained by a cytokine storm and infection. Understanding this pathogenetic pathway may lead to better therapy and better survival rates.

To date, there is no specific treatment for COVID-19 and few data on the predictive variables of COVID-19 were obtained [19, 20]. Therefore, diagnose of disease by measuring inflammatory mediators and hematological indices might help clinicians in identifying patients with poor prognosis at earlier stage [21]. Therefore, the present study was conducted to determine the changes of peripheral blood parameters (Interleukin-6, Ferritin and hematological parameters) in COVID-19 patients.

Materials and Methods

Samples Data collection

This is a descriptive-comparative study in which two groups including patients with COVID-19 disease and healthy people are compared in inflammatory mediators and hematological indices such as Ferritin, IL-6, WBC, Lymphocyte, Neutrophil, Platelet, and Hb. We collected data of 270 participants with total population sampling method in two groups according RT-PCR test results, including 133 patients with COVID-19 disease as case and 137 patients with non-COVID-19 diseases control, between March 20 and May 21, 2020. The clinical characteristics (demographic data, clinical symptoms, CT scanning, hematology test and other laboratory findings) and inflammatory indicators of patients which diagnosed by molecular test (RT-PCR) in Shahid Jalil hospital of Yasuj University of Medical Sciences, were collected from electronic Health Information Systems (HIS) using data collection forms.

The general and specific biosafety guidelines for diagnosis of COVID-19 were accordance with the WHO guidance. A confirmed positive case for COVID-19 was assessed by real-time reverse transcriptase polymerase chain reaction (RT-PCR) test from the nasopharyngeal or oropharyngeal swabs specimens. Only RT-PCR positive for COVID-19 included in this study, while disease diagnosed based on clinical presentation and CT imaging findings without RT-PCR positive for COVID-19 were excluded.

ELISA Test

In this study, serum concentrations of IL-6 were measured in all COVID-19 and non-COVID-19 subjects by ELISA kit (MBL-Medical and Biological Laboratories; Japan) as per the manufacturer's instructions. Ferritin levels were assayed by using chemiluminescence assay (Roche Diagnostics; USA). CBC test was done by sysmex technique (XE-2100).

Statistical Analysis

Statistical analyses were done using SPSS 20 software (SPSS Inc.; USA). The distribution of data was examined using Kolmogorov-Smirnov test and non-parametric testes were applied due to the lack of normal distribution.

We made the following comparisons: the correlation

between of the laboratory findings in COVID-19 patients, demonstrated using Pearson correlation coefficients; differences in the laboratory findings of patients with COVID-19 and non- COVID-19 using Mann-Whitney tests. Chi-square were used to analyze the statistically significant relationship between demographic characteristics of participants.

Findings

Demographic and clinical characteristics

This study was conducted on COVID-19 patients consisted of 53.4% males and 46.6% females with the medium age of 45.56±18.55 years old and there were 50.04% males and 49.6% females with the medium age of 45.59±17.64 years old for non COVID-19 patients. There were no statistically significant differences in the ages and sex between two groups (Table 1).

Table 1) Frequency of demographic characteristics of participants

Parameter		COVID-19	Non-COVID-19	p Value (Chi-square test)
Sex	Male	71 (53.4)	69 (50.4)	0.628
	Female	62 (46.6)	68 (49.6)	
Age (years)	19>	2 (1.5)	9 (6.6)	0.429
	19-35	52 (39.1)	35 (25.5)	
	35-55	43 (32.3)	49 (35.8)	
	55<	36(27.1)	44(32.1)	

ELISA and Hematology Test

The results of this study showed that there were significant difference in the distribution (Mean Ranks) of IL-6, Ferritin and hematological indices between two groups of COVID-19 and non-COVID-19 at the level of 0.05%. All findings between two groups were significant at p<0.05 (Table 2).

Table 2) Comparison of the laboratory findings between COVID-19 and non-COVID-19 patients (All were recognized significant at 0.001 by Mann-Whitney test)

Parameter	Mean Rank COVID-19	Mean Rank non-COVID-19
Ferritin (pg/ml)	199.68	73.19
IL-6 (pg/ml)	184.05	88.37
WBC (×1000 UL)	185.40	87.06
Lymphocyte (%)	152.79	118.71
Neutrophil (%)	178.44	93.81
Platelet (×1000 UL)	102.34	167.69
Hb (mg/dL)	169.51	102.49

Data analysis revealed that there was a strong positive correlation between the serum levels of IL-6 with Ferritin (r=0.554; p=0.0001) and identified correlation between IL-6 with WBC (r=0.5; p=0.0001), Neutrophil (r=0.441; p=0.0001), Lymphocyte (r=0.213; p=0.001), and Hb (r=0.387; p=0.0001), while it was an inverse correlation between both IL-6 and platelet (r=-0.365; p=0.0001; Table 3).

Table 3) The Correlation between IL-6 and Ferritin and hematological parameters in COVID-19 patients

Parameter	7	6	5	4	3	2	1
1- Ferritin	0.278**	-0.41**	0.449**	0.131*	0.456**	0.554**	1
2- IL-6	0.387**	-0.365**	0.441**	0.213**	0.5**	1	
3- WBC	0.374**	-0.355**	0.522**	0.148*	1		
4- Lymphocyte	0.248**	-0.319**	-0.014	1			
5- Neutrophil	0.244**	-0.319**	1				
6- Platelet	-0.257**	1					
7- Hb	1						

*p<0.05; **p<0.01

Based on our assessment of whether the laboratory values are interrelated, an identified correlation was identified between the serum levels of Ferritin and the following parameters: strong direct correlation with WBC, Neutrophil and Hb, weakly correlation with Lymphocyte and strong negative correlation with Platelet. There was a significant correlation between Hematological indices, except for Lymphocyte with Neutrophil.

Discussion

The present study demonstrated comprehensive data on the clinical and laboratory features of patients with non-COVID-19 and COVID-19 in Kohgiluyeh and Boyer Ahmad (K&B) province in Iran. The results of this study showed that there was significant difference in the distribution of IL-6, Ferritin and hematological indices between two groups of COVID-19 and non-COVID-19.

In the present study, the data reported that IL-6 cytokine rank was positively associated with the COVID-19 disease. In accordance with present study, Coomes *et al.* suggested that in patients with COVID-19, IL-6 levels are significantly elevated and associated with noxious clinical subsequences including: ICU admission, asthma, and death [22]. In the analysis by Zhang *et al.* IL-6 level in patients with COVID-19 have dramatically enhanced [23]. Similarly, in research by Ruan *et al.* reported higher levels of IL-6 in COVID-19 patients compared to non-patients [24]. Overall, elevations in IL-6 levels between patients with COVID-19 were identified in all previous studies [17, 25-27], this suggests that dynamic changes in level of IL-6 can be used as a predictive factor in diagnosis of patients with virus infections and also, on the other hand, the progression of COVID-19 to complexed disease may be the result of an over-response of the immune system to IL-6 inflammatory mediator [28]. IL-6 has anti-inflammatory properties and modulates

several aspects of the immune system including hematopoiesis, accumulation of neutrophils, expression of chemokines and their receptors [28]. Although, studies that presented here suggested that IL-6 signaling has clear effects in regulating the neutrophil trafficking during acute inflammation [29]. In the present study, strong correlation between serum ferritin and IL-6 marker were registered in COVID-19 patient. Similar studies have shown this parameter to be involved in parallel to the ferritin being increased during the acute stage of the inflammation [27, 30, 31]. In Yehuda *et al.* study, high levels of ferritin (hyper ferritinemia) have been associated with increased illness severity and adverse outcomes, including COVID-19 [32]. Moreover, in the study by Guan *et al.*, ferritin was significantly elevated in more cases of COVID-19 Compared with control group [33]. Accordance with retrospective cohort study by Zhou *et al.*, serum ferritin levels have been increased in non-survivors' patients with COVID-19 from Wuhan as compared with survivors [34]. However, Wu *et al.* reported that higher serum ferritin was related with ARDS development and was able to predict an increased risk of COVID-19 illness [30]. Recently together with this study, Ruscitti *et al.* have found the role of the H-chain of the ferritin in activating macrophages to increase the secretion of inflammatory cytokines [33]. Thus, the circle is completed on our understanding of the pathogenesis of the ferritin in the infection with Covid-19 [31]. Overall, in accordance with previous studies, it turns out that elevated ferritin concentrations play a critical role in innate immunity and associated with an increase in production of special signaling molecules of the body [17]. These studies may contribute clinicians to apply more aggressive treatment for those patients.

In the present study, COVID-19 cases had elevated levels of hematological indices (except for Platelet), compared with non- COVID-19 cases. The results showed, the COVID-19 can cause some hematological indices changes between cases. Several studies have shown the common presenting hematological manifestations of COVID-19. Wu *et al.* retrospectively demonstrated risk factors for the clinical outcomes of COVID-19 pneumonia and death in China patients. The study showed that several factors related to the development of disease which included neutrophils, lymphocyte and etc. [26]. Similar to the results of the present study, Guan *et al.* found that lymphocyte had significantly increased in most patients of COVID-19, while platelets had decreased [33]. Moreover, In Huang *et al.* study, COVID-19 infection is associated with alterations in the WBC and lymphocyte count [35]. In Dawei *et al.* study, Compared COVID-19 patients received ICU care with non-ICU patients who had significantly elevated neutrophil, WBC count and as well as lymphocyte were significantly increased [36]. However, like to the present study, Hu Yun *et al.* indicated that among Covid-19 Positive Patients, the number of platelets was reported to be significantly reduced in COVID-19 patients [37]. Similarity, Lippi *et al.* was showed that a low platelet count correlated with higher disease severity. Low platelet count has been associated with damaged lung tissue and pulmonary endothelial cells may activate platelets in the lungs, resulting in the aggregation and formation of microthrombi, thereby increasing platelet consumption [38, 39].

Although, inflammation markers including IL-6, serum ferritin, WBC count, and neutrophil in COVID-19 patients can be used as simple, cheap and easily available biomarkers for early diagnosis and identification of patients [25], but these parameters may not be specific for covid-19 in general population. We have some limitations in this study. There were not complete clinical information (Referral time, Severity of illness, Clinical symptoms and etc.) for all clients including healthy people, patients with COVID-19 or non covid-19 that referred to Jalil hospital during the study term. However, the study was conducted with limited sample size, therefore, we were unable to do a multivariate analysis and generalize the results. There may also be a selection bias when identify factors that influence the clinical outcomes.

We have an opinion that the findings of this epidemiological study, in a region in southeast of Iran with a high number of COVID-19 cases, was one of the strengths of the present study. The Results of this study reported the changes in hematological markers in covid-19 patients might help to developed the pathophysiology Knowledge of this disease and provide early guides to diagnosis of coronavirus based on routine laboratory tests.

Conclusion

In conclusion, inflammatory markers especially IL-6 and Ferritin and hematological parameters (WBC, Lymphocyte, Neutrophil, Platelet and Hb) were positively correlated with COVID-19.so, Measurement of IL-6, Ferritin and hematological indices may lead to a better therapeutic measurements which may entail also anti cytokinic therapy as well as workable tests to diagnosis, monitoring and prognosis of patients with COVID-19.

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