Diagnosis of Coronavirus Disease 2019 by Potential Laboratory Factors

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ABSTRACT

Objectives: Coronavirus disease 2019 (COVID-19) associated by infection and high death rate. The unresolved questions about the fatality rate of COVID-19 are most probably related to cytokine storm syndrome. There is currently no specific medication. Understanding the pathogenic pathway of this disease will lead to production of treatment and decreases of death rate. The aim of this study is to investigate changes of peripheral blood parameters (Interleukin-6, Ferritin and hematological parameters) in COVID-19 patients, which may be beneficial in the management of patients.

Methods: In this comparative study, we collected data of 270 subjects in two groups according RT-PCR test results, including 133 patients with COVID-19 and 137 patients with non-COVID-19, between March 20 and May 21, 2020. After obtaining the ethics code from the ethics committee, the clinical characteristics and laboratory findings of patients were collected from electronic Health Information Systems using data collection forms in Shahid Jalil hospital of Yasuj university of medical sciences. The data were analyzed by SPSS software version 20. Descriptive statistics and chi-square, Mann-Whitney U, Kruskal-Wallis tests and Pearson's correlation coefficient were used to analyse the data.

Results: The enrolled COVID-19 patients consisted of 53.4% males and 46.6% females with the medium age of 45.56±18.55 years and there were 50.04% males and 49.6% females with the medium age of 45.59±17.0 years for non COVID-19 patients. There was no significant difference in the age and sex ratio between two populations under study.

The proportion interstitial abnormalities evidenced by CT imaging in COVID-19 patients was 91.0%, while, 4.4% abnormalities were found in non-COVID-19 patients.

The mean IL-6 and Ferritin levels and hematological parameters in two groups of patients with COVID-19 and non-COVID-19 were significantly different across all comparisons.

There was a direct positively correlated between serum level of IL-6, Ferritin levels and hematological parameters including WBC, Lymphocytes, Neutrophils and Hb, except for platelets (negatively correlate), with COVID-19.

Conclusion: In conclusion, inflammatory markers specifically IL-6 and Ferritin and hematological parameters (WBC, Lymphocytes, Neutrophils, Platelet and Hb) were correlated with the severity of COVID-19. Measurement of IL-6, Ferritin and hematological indices might be workable tests to diagnosis and prognosis of patients with COVID-19.

Keywords: COVID-19; Infection; Proinflammatory cytokines; Interleukin-6; Ferritin

INTRODUCTION

Coronavirus disease 2019 (COVID-19) or the severe acute respiratory syndrome corona virus 2 (SARS-CoV-2), it was first reported in December 2019 in Wuhan City, China [1]. COVID-19 is an infectious disease by typical symptoms include dry cough, muscle aches or fatigue, high fever and shortness of breath with

severe acute respiratory syndrome (ARDS) on CT scans [2-4].

COVID-19 binds to the angiotensin-converting enzyme-2 (ACE2) which is present on no immune cells, such as respiratory and endothelial cells and immune cells such as alveolar monocytes/macrophages [5], and can induce endogenous stress signals or mutations in the host genome and recruitment of inflammatory cells [6]. In the defensive line, innate immunity senses microorganisms and release of cytokines, Chemokines and inflammatory mediators by immune cells, epithelial cells and etc. in pathological conditions [7]. The increase in specific cytokine production can be linked to an activation cascade and uncontrolled cytokine release; the cytokine storm [8]. 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 [9,10].

During a virus infection, the plasma concentration Interleukin (IL)-6, IL-1 and IL-10 were increased [11], especially, IL-6, which promptly stimulate the production of acute phase proteins in response to infections and tissue injuries [7]. 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 [11,12].

Also, high levels of lactate dehydrogenase (LDH), and ferritin are suggestive due to the cytokine storm in Laboratory findings. Also, elevated Ferritin and Lactate dehydrogenase (LDH) levels due to cytokine storm syndrome have been reported in severe COVID-19 patients [13]. 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 [14].

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 [15]. Therefore, diagnose and treatment of cytokine storm and infection by measuring serum concentrations of IL-6 and blood ferritin has become an important part of rescuing severe patients.

MATERIAL AND METHODS

Sample's data collection

In this comparative study, we collected data of 270 subjects in two groups according RT-PCR test results, including 133 patients with COVID-19 disease and 137 patients with non-COVID-19 disease, between March 20 and May 21, 2020. After obtaining the ethics code from the ethics committee (IR.YUMS. REC.1399.003), the clinical characteristics (demographic data, clinical symptoms, CT scanning, hematology test and other laboratory findings) and inflammatory indicators of patioents 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.

In this study, general and specific biosafety guidelines for diagnosis of COVID-19 was 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. Lonely laboratory confirmed cases were contained in this study, while

disease diagnosed based on clinical presentation and CT imaging findings 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, Nagoya, Japan) as per the manufacturer's instructions. Ferritin levels were assayed by using chemiluminescence assay (Roche Diagnostics, Indianapolis, IN, USA).

Statistical analysis

Statistical analyses were done using SPSS-20 software (SPSS Inc. Chicago, IL, USA). The distribution of data was examined using Kolmogorov-Smirnov test and non-parametric testes were applied due to the lack of normal distribution. Descriptive statistics and chi-square, Mann-Whitney U, Kruskal-Wallis tests and Pearson's correlation coefficient were used to analyse the data. $p < 0.05$ was considered statistically significant.

Ethical considerations

Since, there was no threat for participants and its results were only used to improve diagnosis planning of covid19; so we obtained informed consent. It should also be noted that in this study, we avoided mentioning any names, titles or characteristics that cause the loss of privacy of the participants, and the participants were clearly informed of the possible uses of the results.

RESULTS AND DISCUSSION

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 statistical evidence for different association in the ages and sex between two groups (Table 1).

Table 1: Frequency of clinical characteristics of patients with COVID-19 and non- COVID-19.

Variables		COVID-19 n (%)	non-COVID-19 n (%)	p-Value
Sex	Male	71 (53.4)	69 (50.4)	0.628
	Female	62 (46.6)	68 (49.6)	
Age	19>yrs	2 (1.5)	9 (6.6)	0.429
	19-35 yrs	52 (39.1)	35 (25.5)	
	35-55yrs	43 (32.3)	49 (35.8)	
	55<yrs	36 (27.1)	44 (32.1)	
Mean ± SD		45.56 ± 18.55	45.5 9 ± 17.64	
CT	Positive	121 (91.0)	6 (4.4)	0.000
	Negative	12 (9.0)	131 (95.6)	

The percentage of lung abnormalities on CT imaging in COVID-19 patients was 91.0% (121), while, 4.4% (6) abnormalities was found in imaging of non-COVID-19 patients ($p < 0.05$) (Table 1).

ELISA and haematology test

The results of this study showed that there were significant difference in the distribution (Mean Ranks) of IL-6, Ferritin and haematological 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 level p<0.05 (Table 2).

Table 2: Comparison of the laboratory findings of patients with COVID-19 and non- COVID-19.

Variables	Mean Rank COVID-19	Mean Rank non-COVID-19	p-Value
Ferritin (pg/ml)	199.68	73.19	0.000
IL-6 (pg/ml)	184.05	88.37	0.000
WBC (×1000 UL)	185.40	87.06	0.001
Lymphocyte (%)	152.79	118.71	0.001
Neutrophil (%)	178.44	93.81	0.001
Platelet (×1000 UL)	102.34	167.69	0.001
Hb (mg/dL)	169.51	102.49	0.000

The COVID-19 group with mean score of 199.68 has a higher level of Ferritin than the non- COVID-19 group with mean score of 73.19 (2.7times). This study also reported that the mean levels of WBC, Ferritin, IL-6, Neutrophil, Hb and lymphocyte respectively with 2.1, 2, 1.9, 1.6 and 1.2 times were significantly higher in COVID-19 patients compared to non-COVID-19 patients. While the mean platelet score in COVID-19 compared to non-COVID-19 group decreased by 1.6 times (Table 2).

Data analysis revealed that there was a strong positive correlation between the serum levels of IL-6 with Ferritin (r=0.554, p=0.000) and significant correlation was identified between IL-6 with WBC(r=0.500, p=0.000), Neutrophil (r=0.441, p=0.000), Lymphocyte (r=0.213, p=0.001), and Hb (r=0.387, p=0.000), while it was an inverse correlation between both IL-6 and Platelet (r=-0.365, p=0.000), (Table 3).

Based on our assessment of whether the laboratory values are interrelated, a significant 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 (Table 3).

In our study, data analysis revealed that there was significant correlation between Haematological indices, except for Lymphocyte with Neutrophil (r=-0.014, p=0. 824) (Table 3).

COVID-19 is a cryptic disease that it could enable sickness ranging from a cold to cytokine storm and acute respiratory syndrome [6]. To date, there is no specific treatment for COVID-19 and few data on the predictive variables of COVID-19 were obtained [16,17]. Therefore, diagnose of disease by measuring inflammatory mediators and hematolocal indices might help clinicians in identifying patients with poor prognosis at earlier stage [18]. Present study demonstrated comprehensive data on the clinical, laboratory and image features of patients with non-COVID-19 and COVID-19 in Kohgiluyeh and Boyer Ahmad (K&B) province.

In our data set of COVID-19, we revealed significant differences in positive chest CT scans and positive RT-PCR results, when comparing subjects with COVID-19 and hyper inflammation with those who did not show expression of hyper inflammation. The results from this review in similarly to other studies from Duan, et al. [19], Poortahmasebi et al. [20], and Udugama et al. [21], indicate that the chest CT scan and RT-PCR should be used for symptomatic and hospitalized covid-19 patients. In the study by Tao et al, in the epidemic area, chest CT scan in comparison with RT-PCR, maybe a more reliable, practical, and rapid method to diagnose COVID-19 [22]. 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 [20,22]. However, a rate of 10-40% RT-PCR false-negative results made this technique insufficient for proper detection [20,23]. We suggest a major obstacle for this low efficacy might be related to sampling errors, markedly inappropriate timing of sampling, which is reflected by variations in viral load in upper versus lower respiratory tract.

In a recent study on patients with COVID-19 in K&B province, our data reported a higher rate of IL-6 in patients with infection than in the general population. Probably, these findings indicate 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 subsequence's including: ICU

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

Variables		Ferritin	IL-6	WBC	Lymphocyte	Neutrophil	Platelet	Hb
Ferritin	R	1	554**	.456**	131*	.449**	-.410**	.278**
	P		.000	.000	.031	.000	.000	.000
IL-6	R		1	.500**	.213**	.441**	-.365**	.387**
	P			.000	.001	.000	.000	.000
WBC	R			1	.148*	.522**	-.355**	.374**
	P				.015	.000	.000	.000
Lymphocyte	R				.1	-.014	-.319**	.248**
	P					.824	.000	.000
Neutrophil	R					1	-.319**	.244**
	P						.000	.000
Platelet	R						1	-.257**
	P							.000
Hb	R							1
	P							

** Correlation is significant at the 0.01 level (2-tailed).

* Correlation is significant at the 0.05 level (2-tailed).

R: Pearson correlation

P: P-Value

admission, asthma, and death [24]. In the analysis by Zhang et al. IL-6 level in patients with COVID-19 have dramatically enhanced [25]. Similarly, in research by Ruan et al. reported higher levels of IL-6 in COVID-19 patients compared to non-patients [26]. Overall, elevations in IL-6 levels between patients with COVID-19 were identified in all previous studies [13,27-29]. 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. IL-6 has anti-inflammatory properties and modulates several aspects of the immune system including hematopoiesis, accumulation of neutrophils, expression of the adhesion molecules, expression of chemokines and their receptors [30].

In our study cohort, data analysis revealed that there was a high significant level of ferritin in COVID-19 patients compared to that of non-COVID-19 patients. Similar observations have been reported by scientists from China, Italian and the United States. In Yehuda et al. study, high levels of Ferritin (hyperferritinemia) have been associated with increased illness severity and adverse outcomes, including COVID-19 [31]. In the study with Guan et al, Ferritin was significantly elevated in more cases of COVID-19 Compared with control group [19]. 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 [32]. About ferritin, 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 [28]. Recently, some scientific secrets by Ruscitti et al. reported. They discovered the role of the H-chain of ferritin in activating macrophages (macrophage activating syndrome; MAS) to increase the secretion of inflammatory cytokines and cytokine storms in COVID-19 patients [33]. 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 signalling molecules of the body [13]. These studies complete our understanding of the pathogenesis of the high levels of ferritin including the infection with COVID-19, and may contribute clinicians to apply more aggressive treatment for those patients.

In the study, COVID-19 cases had elevated levels of haematological indices (except for Platelet), compared with non- COVID-19 cases. The results showed, the COVID-19 can cause some haematological indices changes between cases. Several studies have shown the common presenting haematological 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. [28]. Guan et al. found that lymphocyte had significantly increased in most patients of COVID-19, while platelets had decreased [19]. In Huang et al. research, COVID-19 infection is associated with alterations in the WBC and lymphocyte count [34]. In Dawei et al. study, Compared COVID-19 patients received ICU care with non-ICU patients who had significantly elevated neutrophil and WBC count, as well as lymphocyte were significantly decreased [35]. Interestingly, Hu Yun et al. showed that among Covid-19 Positive Patients, the platelet count during the disease course were decreased [36]. Similarity, Lippi et al. was showed that a low platelet count correlated with higher disease severity [37]. So, the Results of this study reported the changes in haematological 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.

Although, strong correlation between inflammation markers including IL-6, together with serum ferritin, WBC count, and neutrophil in COVID-19 patients compared to non 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 was 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. 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.

CONCLUSION

In conclusion, inflammatory markers especially IL-6 and Ferritin and haematological parameters (WBC, Lymphocyte, Neutrophil, Platelet and Hb) were positively correlated with the severity of COVID-19. Measurement of IL-6, Ferritin and haematological indices might be workable tests to diagnosis, monitoring and prognosis of patients with COVID-19.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The Research project (No. 990000) was approved by the Ethic Committee of Yasuj University of medical sciences; IR.YUMS. REC.1399.003. Informed consent form was obtained from all subjects.

CONSENT FOR PUBLICATION

Informed consent was obtained from all Subjects. This Informed Consent Form had two parts:

Information Sheet (to share information about the study). Certificate of Consent (for signatures if participants choose to participate).

AVAILABILITY OF DATA AND MATERIAL

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

COMPETING INTERESTS

None declared

CONFLICTS OF INTEREST

The authors have no actual or potential conflict of interest to declare in relation to this study.

CONTRIBUTION AUTHOR

Parviz Yazdanpanah and Jalal Pouranfard conceived the study hypothesis. Farzad Vafaei and Sajad Afrouz, designed the study and undertook the literature search, study selection and data abstraction. Saeed javidan sirat and Sajad Afrouz, analyzed the data. All authors interpreted the data, wrote the manuscript, and edited the manuscript critically for important intellectual content.

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