Original Research

Inflammatory Factors And Their Association With Disease Severity In Patients With COVID-19

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Abstract:

Background: Inflammatory factors play a very important role in causing inflammation. These inflammatory factors and proteins are the regulators of inflammatory responses. Considering the high transmission power and the pandemic caused by COVID-19, it is necessary and important to determine the effective factors in the prognosis of this disease.

Method: This study was carried out by descriptive method and based on secondary data analysis in the files of hospitalized patients with covid-19 in the first six months of 2021 by census method. The data collection tool is a checklist (data collection form). Three categories of variables including epidemiological variables, clinical variables, and laboratory variables were extracted from the patient's files and analyzed.

Results: The data of 302 patients with COVID-19 hospitalized in the ICU department of Peymaniyeh Hospital were collected. The majority of patients were over 50 years old. There was no significant relationship between the severity of the disease and all of the demographic, clinical, and laboratory variables ($P>0.05$), except for the number of hospitalization days that in patients with severe disease, severity was significantly higher than in patients with moderate disease severity ($P=0.001$); CRP, ERS, and LDH in patients with severe disease severity were significantly higher than patients with moderate disease severity ($P<0.05$); But there was no significant relationship between other laboratory characteristics and disease severity ($P<0.05$).

Conclusion: It can be concluded that patients over 50 years of age who are admitted to the ICU require more careful care and elderly patients may have a higher chance of contracting COVID-19.

Keywords: Inflammatory factors, Disease severity, Covid-19.

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Introduction

In late December 2019, cases of pneumonia of unknown cause were reported in Wuhan, China, which had a very high rate of spread. At first, the cause of the disease was unknown, but due to the rapid spread of the disease, a possible infectious agent was considered for it, which had high transmissibility. With the measures taken by the team of the American Center for Control and Prevention (CDC) and the World Health Organization (WHO), a viral agent belonging to the group of coronaviruses, but with completely different genetic characteristics from other coronaviruses, was isolated from the samples of infected patients. This new virus, within a few weeks, covered almost most countries, and in a short period of time, in January 2020, a new type of coronavirus called SARS-COV-2 was introduced as the cause of its creation (1.2). SARS-COV-2 is considered the most dangerous virus of the coronavirus family. The symptoms caused by SARS-COV-2 infection can vary from person to person, but according to various studies conducted in this field, the most common symptoms of the disease include fever, cough, fatigue and body pain, shortness of breath, and digestive symptoms. Such as; diarrhea, constipation, nausea and vomiting (1-3). According to a study report, 48% of deaths due to this disease included people who had an underlying disease. This association was reported in 30% of blood pressure, 19% of diabetes and 8% of cases of coronary heart disease (3). On the other hand, SARS-COV-2 can cause acute respiratory syndrome in addition to the mentioned symptoms in cases of infected patients, especially in patients with immunodeficiency and underlying diseases (diabetes, blood pressure, heart diseases). Due to the emerging nature and few studies on this disease, the mechanism of acute respiratory syndrome in this disease is not fully known, but lung tissue involvement due to infection with this virus, increased inflammation and inflammatory factors, and finally fibrosis in it can be the main cause of acute respiratory distress syndrome in these patients (4-5). Inflammation is a response caused by damage to living tissues. The inflammatory response is a defense mechanism that allows evolved organisms to protect themselves against possible infections and injuries. The purpose of inflammation is to limit (localize) and eliminate the damaging agent or to eliminate the damaged tissue components so that the body can begin to heal (5). The inflammatory response includes changes in blood flow, increased permeability of blood vessels, and migration of fluids, proteins, and white blood cells (leukocytes) from circulation to the site of tissue damage (6). Inflammatory factors play a very important role in causing inflammation, which includes cytokines, interleukins, tumor necrosis factors, chemokines, interferon, lymphocytes, and inflammatory proteins (7). These inflammatory factors and proteins are the regulators of inflammatory responses. For example, cytokines are regulators of the chemotaxis process, interferon is responsible for the resistance of cells against viral diseases, and tumor necrosis factors also act as lipopolysaccharide-induced necrosis mediators of cancer cells (6-7). Most of the acute-phase proteins are produced in the liver and are poured into the blood (8). Some acute phase proteins increase during inflammation and some decrease, which indicates a change in the functional index of the liver (7, 9). Various studies have been conducted to find out the pathology of the Covid-19 disease and the relationship between this disease and the level of inflammatory factors in the blood. Laboratory findings in a study conducted by Hong and his colleagues in China in 2020 showed that lymphopenia (decrease in the number of blood lymphocytes) and increased levels of ALT, AST, and CRP occur in SARS-COV-2 patients. Also, in this study, a greater increase in plasma levels of IL7, IL1, IL10 and

TNF alpha was observed in patients hospitalized in ICU compared to patients not hospitalized in ICU, which can indicate the level of these inflammatory factors on the prognosis and severity of infection caused by SARS-COV- 2 in different patients. (4). In two separate studies, an increase in CRP, ESR, ferritin, and a high level of D. Dimer and severe lymphopenia have been reported in patients with a critical condition who were admitted to the intensive care unit (10-11). In total, the results of epidemiological studies show that contracting SARS-COV-2 disease is associated with hospitalization in ICU and mortality (12), considering the high transmission power and the pandemic caused by this virus, determining the effective factors in the Prognosis and treatment of this disease is necessary and important. Therefore, this study was conducted with the aim of determining the inflammatory factors in patients with covid-19 and its association with the severity of the disease in patients with covid-19 hospitalized in Peymaniyeh Jahrom Hospital in the first six months of 2021.

Methods

In this study, we conducted a secondary data analysis of hospitalized patients with COVID-19 in the first six months of 2021 using a census method. The study included patients who were clinically proven to be infected with COVID-19 by PCR and admitted to the referral hospital for COVID-19. Patients' files that were incomplete for some reason and could not be obtained were excluded. We used a checklist as a data collection tool that included three categories of variables: epidemiological variables (age, gender, underlying diseases), clinical variables (systolic and diastolic blood pressure, heart rate, respiratory rate, temperature, number of days of hospitalization), and laboratory variables (white blood cell (WBC) count, neutrophil count, lymphocyte count, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), creatine phosphokinase (CPK), lactate dehydrogenase (LDH), albumin (Alb), neutrophil/CRP ratio, CRP/ESR ratio, CPK/LDH ratio, Albumin/CRP ratio, neutrophil/lymphocyte ratio). We extracted these variables from the patients' files and analyzed them, specifically the clinical and laboratory variables related to admission and hospitalization. If patients were clinically forced to be admitted to the ICU after being hospitalized in the normal wards, we extracted these laboratory indexes related to the admission and the time of admission to the ICU, and the time of discharge or death are compared. Next, we classified patients into moderate and severe groups and compared these indices in the two groups. Patients were classified in the severe category if they were hospitalized in the ICU or had a poor outcome of death, and the patients who did not have this characteristic were placed in the moderate group. We analyzed the data using SPSS software version 21, using descriptive statistics and inferential statistical tests at a significance level of $P<0.05$.

Results

The information on 302 patients with COVID-19 hospitalized in the ICU department of Peymaniyeh Hospital was collected. 54.4% of hospitalized patients with covid 19 were men. The majority of patients with Covid-19 hospitalized in the ICU were over 50 years old (Table 1). 15.6% of the patients with covid 19 hospitalized in the ICU department of Peymaniyeh Hospital had died and 84.4% had recovered. The majority of patients had a history of previous infection with Covid-19 (81.5%). 61.3% of patients had a history of heart disease, with high blood pressure, diabetes and heart diseases respectively being the most frequent. (Table 1).

The frequency of patient records according to disease severity (moderate, severe) in patients with covid-19 showed that there was no significant relationship between disease

severity and patients' records (P<0.05). (Table 2).

The frequency of clinical features according to disease severity (moderate, severe) in patients with covid-19 showed that the number of hospitalization days in patients with severe disease severity was significantly higher than in patients with moderate disease severity (p=0.001); But there was no significant relationship between other clinical characteristics and disease severity (p<0.05). (Table 3).

The frequency of laboratory characteristics according to disease severity (moderate, severe) in patients with covid-19 showed that CRP, ERS, and LDH in patients with severe disease severity were significantly higher than in patients with moderate disease severity (p<0.05).But there was no significant relationship between other laboratory characteristics and disease severity (p<0.05). (Table 4)

Discussion

54.4% of hospitalized patients with covid 19 were men. In various studies about Covid-19 patients, different results have been reported about the gender composition of patients admitted to the intensive care unit. Similar to our study, some studies have shown that men are more likely than women to be admitted to the ICU due to severe complications of Covid-19 (13-16). In our study, the majority of patients with Covid-19 hospitalized in the ICU were over 50 years old. According to the research conducted in this field, it seems that most of the patients in the ICU of COVID-19 are elderly. In fact, according to global reports, elderly patients mainly suffer more from COVID-19 and its side effects. In addition, the side effects of COVID-19 may be more severe for the elderly, including chronic obstructive pulmonary disease and heart disease. However, it should be noted that this is highly dependent on the specific circumstances of each disease, including the patient's previous health and associated risk factors (17-19). In our study, the mortality rate of patients hospitalized in ICU was 15.6% and 84.4% had recovered. The death rate in patients admitted to the COVID-19 ICU may be different in other studies. This rate is significantly influenced by factors such as the type of disease, patient's age, basic health status, treatment strategy and medical interventions, and time of disease diagnosis. In addition, the number of patients and the way of selecting the samples and the criteria used may also be different in different studies (20-21). For example, a study may show that the death rate of patients admitted to the COVID-19 ICU is higher or lower than 15.6%. To examine this issue more closely, it is necessary to look at more comprehensive studies and statistics on patients hospitalized in the COVID-19 ICU around the world. According to meta-analysis studies, this rate was between 35 and 45% at the beginning of the pandemic (20). In another meta-analysis study, this rate was estimated at 37% (21). But in other studies, this rate was reported between 20 and 38% in 16 reviewed studies (22), which is somewhat similar to our results. It seems that with the passage of time, the death rate of patients hospitalized in the COVID-19 ICU has decreased. Our study was conducted in Jahrom City. However, in similar studies conducted in Jahorm City, which investigated COVID-19 patients hospitalized in the ICU of this city in different waves of COVID-19, the mortality rate was not reported (23). But in another study in 2023, the mortality rate in ICU patients was 7.6% (24). Our study showed that initial vital signs are not related to the severity of corona disease in the ICU. But most of the research show that basic vital signs such as blood pressure, heart rate and breathing of Covid-19 patients in the ICU are related to the severity of the disease (25). The results of a study showed that Covid-19 patients who needed the ICU usually had higher heart rates, higher breathing rates and lower oxygen levels (26). Also, another study showed that, mostly

in elderly patients with COVID-19, initial vital signs can be related to the severity of the disease (27). But another study in the same department in Jahrom city, was conducted to examine the patients with COVID-19 after 12 weeks of discharge from the ICU of the hospital. In this study, 383 patients were examined and the results showed that SPO2 increase after 6 weeks after discharge can be used as an early tool to predict respiratory complications after 12 weeks, while CRP examination after Discharge of patients after 12 weeks is not recommended due to ineffectiveness in predicting respiratory complications. Risk factors related to respiratory complications include the history of admission to the intensive care unit and the drop in SPO2 after 6 weeks of patient discharge (28). So it seems that the time of measuring inflammatory factors and vital signs is decisive. Meanwhile, our study showed that CRP, ERS, and initial LDH were significantly higher in patients with severe disease severity than in patients with moderate disease severity. Numerous studies have been conducted on the disease of Covid-19 and their results are in many cases consistent with our findings. For example, several studies have shown that CRP and ESR levels increase in patients with higher disease severity, and these two indicate the presence of inflammation in the body (29-31). Also, some studies have shown that the level of LDH also increases in patients with higher severity of the disease and indicates a defect in the body's cellular function (31). In addition, some other studies have shown that patients suffering from severe disease typically have higher levels of other inflammatory markers such as IL-6 and TNF-α (30). In general, inflammatory markers such as CRP and ESR have always been of interest in inflammatory diseases, and this issue has been confirmed in COVID-19 patients as well (31).

Limitations

There are several limitations to this study that should be considered. First, the study was conducted through a census method and based on secondary data analysis, which may have limited the accuracy of the data collected. Second, the study was conducted in only one hospital, which may limit the generalizability of the findings. Third, the study did not include long-term follow-up of patients after hospitalization, which may limit the ability to fully understand the prognosis and outcomes of patients with COVID-19. Additionally, the study did not evaluate the impact of potential confounding factors such as treatment and comorbidities, which may affect the relationship between the variables analyzed and the severity of the disease.

Conclusion

According to the results of this study, it can be concluded that patients over 50 years of age who are admitted to the ICU require more careful care and elderly patients may have a higher chance of contracting corona. Also, the results showed that the primary vital signs are not related to the severity of the corona disease in the ICU, but the level of some clinical indicators such as CRP, ERS, and LDH was higher in patients with more severe disease.

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Table & Figure:

Table 1: Frequency of patients with COVID-19 hospitalized in the ICU department of Peymaniye hospital according to demographic variables

Demographic variables		n	%
Sex	Male	161	54.4%
	Female	135	45.6%
Age, years	<20	5	1.7%
	20-30	13	4.3%
	31-40	52	17.2%
	41-50	39	12.9%
	51-60	60	19.9%
	61-70	65	21.5%
	71-80	33	10.9%
	>80	35	11.6%
Hemodialysis	Yes	4	1.3
History of previous illness	No	117	38.70
	Blood Pressure	85	28.15
	Diabetes	39	12.91
	Heart disease	25	8.28
	Hyperlipidemia	10	3.31
	Asthma	5	1.66
	Chronic liver diseases	5	1.66
	Other	16	5.34
History of previous Covid-19		246	81.5
Mechanical ventilator		9	4.1%

Table 2: Frequency of patient records according to disease severity (moderate, severe) in hospitalized patients with Covid-19

		Disease severity				P-value
		Moderate		Severe		
		Frequency	%	Frequency	%	
Chemotherapy	Yes	0	0.0%	1	1.2%	0.27
	No	221	100.0%	80	98.8%	
Dialysis	Yes	2	0.9%	2	2.5%	0.29
	No	219	99.1%	79	97.5%	
History of previous COVID-19	Yes	42	19.0%	14	17.3%	0.87
	No	179	81.0%	67	82.7%	

Table 3: Frequency of clinical features according to disease severity (moderate, severe) in patients with COVID-19

	Disease severity				P-value
	Moderate		Severe		
	Mean	SD	Mean	SD	
SPB	120.56	18.80	119.16	22.79	0.589
DBP	75.67	12.05	74.43	13.06	0.44
HR	89.47	17.14	91.73	20.64	0.34
Number of breaths	23.22	13.71	23.31	10.67	0.96

Table 4: Frequency of laboratory characteristics according to disease severity (moderate, severe) in patients with covid-19 hospitalized

	Disease severity				P-value
	Moderate		Severe		Moderate
	Mean	SD	Mean	SD	
WBC. count	8.41	6.24	9.07	9.31	0.49
neutrophil	74.02	14.78	78.37	14.04	0.055
Lymphocyte.	21.23	12.51	19.30	14.84	0.34
CRP	45.75	39.95	59.56	52.43	0.017
ERS	39.52	27.82	52.14	38.03	0.003
CPK	153.41	232.73	194.68	351.84	0.25
LDH	558.41	340.90	658.89	356.19	0.030
ALb	3.43	0.52	3.34	0.58	0.21
ALT	53.69	134.96	40.28	28.40	0.40
AST	39.31	93.86	39.75	29.53	0.97
neu/lymph ratio	6.12	6.71	7.75	7.52	0.13
ALb/CRP	0.36	0.71	0.25	0.44	0.206
CPK/LDH	0.50	1.81	0.73	3.23	0.44
CRP/ERS	1.84	2.99	2.60	7.23	0.215
Neut/CRP	7.72	14.39	6.00	13.76	0.44