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Original Article

Biochemical Markers in Covid-19 Patients in Tripoli, Libya; A Retrospective Study

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ABSTRACT

Covid 19 can cause fatal pneumonia and serious complications. In the course of the disease the levels of different biochemical parameters increased and these parameters provide important information about the prognosis of the disease. The aim of this study was to investigate these biomarkers and to evaluate the relationship between biochemical parameters and length of stay in Covid 19 patients. A retrospective study was conducted from October 2020 to December 2021. A total of 156 Covid 19 patients hospitalized in Meitiga Military hospital were included. The demographic characteristics, length of stay, and biochemical parameters of the patients were scanned from the hospital's database and patient files and recorded. Patients were grouped according to the length of stay; 1st group: after 3 to 5 days, 2nd group: from 8 to 12 days, and 3rd group: after 13 days and more. Most of admitted cases were males, the majority of the participants were in age above 65 years old. CRP, FER, LDH, and D-dimer were gradually increased to the maximum mean; 131.4±67, 1052.3±710.1, 586±128.9, and 1196.2±409.1, respectively after 8 to 12 days and return to normal range after 13 days. To conclude, there is a positive correlation between the levels of these biomarkers and the prolongation of hospitalization in COVID-19 patients and these parameters can be associated with the severity disease.

Keywords: Covid, Biochemica, parameters, Retrospective, Tripoli, Libya

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INTRODUCTION

By the end of a year 2019, this year has become a horrifying and unforgettable memory because of an outbreak of atypical pneumonia cases of viral infection were detected in Wuhan, capital of the province of Hubei, China. This outbreak is leading to respiratory disease. It had linked directly to the wet animal market, which abolished the world's normal lifestyle and health condition [1]. The etiological agent of this disease was later identified to be a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [2]. This disease was later spread to enormous continents of this globe, it has affected over than 200 countries and regions around the world [3]. On March 2020, the cumulative number of confirmed cases had reached 218,785 globally, including 8,949 deaths. Of the total confirmed patients, about 19.9% were severe cases,

which have a mortality rate of about 20% [4]. For all of these reasons world health organization (WHO) compelled to recognize this outbreak as a pandemic on March 11th, 2020 and SARS-CoV-2 were named as coronavirus disease 2019 (COVID-19) [5]. In last 20 years, this is the 3rd serious worldwide outbreak which has infected numerous nations, paralyzing the people's lives were compelled them to restrict themselves at home [3,6]. Nowadays, the cumulative cases are reached to more than 750 million including nearly 7 million deaths [7]. The clinical spectrum of COVID-19 can vary from asymptomatic infection, fever, dry cough, diarrhea, nausea, lethargy, asthenia, myalgia, barely symptomatic disease, mild upper respiratory symptoms, to severe viral pneumonia with respiratory failure, or critical condition to even death [8]. This ailment is transmitted from person to person through direct contact or via droplets in sneezing or coughing from the diseased person [9]. Major risk factors that increase the severity of the COVID-19 disease and its mortality rate are; age, gender, and comorbidities. In several studies, it has been shown that the average age of critically ill COVID-19 patients was old age, above 63 years old, and the majority of the cases were males [10]. Different molecular techniques were developed, nucleic acid detection through samples taken through nasopharyngeal swabs serves as a gold standard [11]. Many biochemical markers have been used in routine practice as changes in these markers have been reported in various studies and could serve as prognostic markers in COVID-19 disease severity [12]. COVID-19 infection manifested raised; D-dimers, ferritin (FER), C-reactive protein (CRP), lactate dehydrogenase (LDH), pro-calcitonin (PCT), alanine transaminase (ALT), aspartate aminotransferase (AST), prothrombin time (PT), and activated partial thromboplastin clotting time (APTT), all of these parameters are widely used for risk stratification [13,14]. The anti-inflammatory parameters including FER, CRP, LDH, and D-dimer are the most important ones among these tests [15]. Hence, knowledge about the prognosis of infection and its relevance to comorbidities could provide valuable information on risk stratification and decision making in severely affected COVID-19 patients. A few local studies had been done to evaluate laboratory biomarkers of COVID-19 patients. Thus, this study was carried out retrospectively to assess the levels of biochemical marker of COVID-19 patients in Tripoli, Libya.

METHODS

Study Population

This study included 156 COVID-19 patients were hospitalized in the isolation wards and Intensive care units (ICUs) of Meitiga Military hospital (MMH), Tripoli, Libya. All patients were diagnosed as COVID-19 positive via pharyngeal swab done by RT-PCR. The period of this study was from October 2020 to December 2021. The data were scanned retrospectively from patient files obtained from the hospital database having all the COVID-19 positive patient information collectively. Patients with active tuberculosis or hepatitis B and C, suspected or proven bacterial infection focus, and pregnant women were excluded from the study.

Study Design and Data Collection

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The patients were divided into Three groups, according to length of stay in the hospital: group I; after 3 to 5 days, group II; from 8 to 12 days, group III; after 13 days and above. The demographic characteristics and laboratory findings of the patients were statistically analyzed according to these groups. The data were obtained from hospitals' database and patient files. Demographic characteristics such as age, gender, date of admission, and hospital stay of the patients were recorded. Additionally, laboratory biochemical parameters including CRP, FER, LDH, and D-dimer was all verified in very fine details.

Data Analysis

Data were summarized by median and numbers (percentage). The statistical analysis was carried out using SPSS software version 26. A comparison between several groups was undertaken, with the t-test to analyze the results. The statistical significance threshold was determined to be ($P<0.05$).

RESULTS AND DISCUSSION

Demographic Characteristics

This study included 156 patients admitted to the MMH isolation wards and ICUs from October 2020 to December 2021. All cases were positive by the PCR assay test. Most of them were males (n=97; %=62.2). This is in accordance with the observation made by various studies [16,17]. Although, this result differs from other findings of the studies from Romania and China which both revealed that a slight increase in females' patients in both adult and elder groups of COVID-19 patients [18,19]. The ages of the subjects were categorized into different age groups, Group A; age below 40 years old, Group B; age between 40 and 65 years old, Group C; age above 65 years old. The majority of the participants were in Group C (n=84; %=54), followed by Group B with 40% (n=63) of participants, whereas, Group A was the least age group between all participated with 6% (n=9) of participants as shown in figure 1. The youngest patient was male of 17 years old and the oldest patient was female of 94 years old, however, both of them are discharged. These results are found to be consistent with previous studies in Spain [16], Egypt [17], China [19], and Turkey [20].

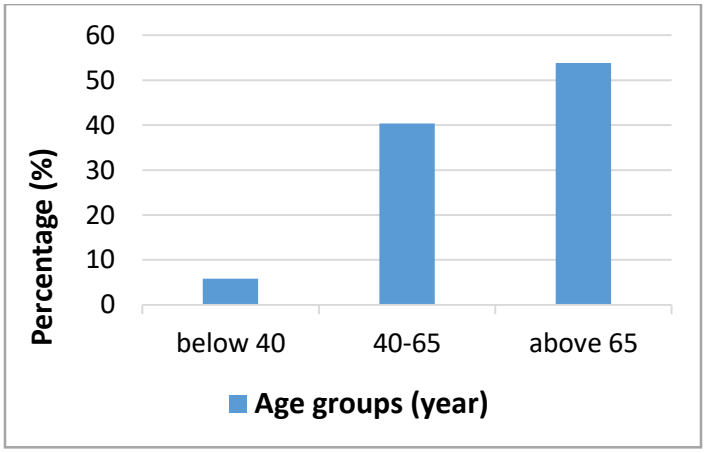

Figure 1. Age distribution of study participants in percentage.

Biochemical Parameters Determination

Among the total included patients, 142 (91%) presented data for CRP, 136 (87.2%) for LDH, 98 (62.8%) for FER and 88 (56.4%) were tested for D-dimer (Table 1). Measurements indicated a CRP concentration of 70±36.7 mg/L, a FER concentration of 688.6±388.6

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ng/mL, a LDH concentration of 519.2±115.8 U/L, and a D-dimer concentration of 784.6±267.5 ng/mL (Table 1). The American Society of Hematology found that in the COVID-19 hypercoagulable state with elevated D-dimer was notable, similar findings were observed in our results [21]. CRP, FER, LDH, and D-dimer were all elevated. The clinical prognosis of COVID-19 disease is divided into three different phases, early infection, pulmonary, and anti-inflammatory phases, and each phase has a typical biochemical marker. The early infection phase begins with infiltration of the virus in to the lung parenchyma, with symptoms characterized by fever and cough similar to typical upper respiratory tract infection. The most important laboratory finding during this phase is lymphopenia. In the pulmonary phase, lung infection develops in the form of viral pneumonia and increased levels of CRP are prominent as well as lymphopenia and elevation of transaminases [15]. The inflammatory phase is characterized by ARDS caused by systemic inflammation or cytokine storm. During this phase, patients are usually treated in the ICU. During this period, cardiac and kidney damages caused by the complications of COVID-19 are quite common. In addition, increased levels of CRP, D-dimer, LDH, and FER, are observed at the forefront, during this phase [15]. The increased levels of these parameters are directly associated with the severity of the disease, the mortality rate and the length of stay in the hospital [19].

Table 1. Biochemical parameters of the studied sample.

Levels	No.	%	Mean	SD
CRP	142	91%	70	36.7
FER	98	62.8%	688.6	388.6
LDH	136	87.2%	519.2	115.8
D-dimer	88	56.4%	784.6	267.5

CRP; C-reactive protein (mg/L), FER; ferritin (ng/mL), LDH; lactate dehydrogenase (U/L), D-dimer (ng/mL)

According to Table 2, the Mean±SD of all parameters every five days from signs and symptoms of COVID-19 infection appearance, the results were increased after 8 to 12 days with highly significant differences ($P<0.05$) rather than after 3 to 5 days and after 13 days. A similar study conducted in Iraq demonstrated that the levels of these biomarkers has gradually increased after (3-5) days from starting the signs and symptoms of COVID-19 infection and reached the maximum levels after (8-10) days. In spite of that, it decreased after (13-15) days before reaching to normal range [22].

Table 2 The Mean±SD of all parameters every 5 days from COVID-19 infection.

Parameters	After (3-5) days	After (8-12) days	After 13 days
CRP	63.7±29.9	131.4±67	33±13.2
FER	521.8±253.9	1052.3±710.1	491.6±201.7
LDH	479.9±110.4	586±128.9	491.6±108.2
D-dimer	770.1±254	1196.2±409.1	387.5±139.3

CRP parameter

The levels of CRP were increased after 3 to 5 days from signs and symptoms of COVID-19 infection appearance (Mean±SD=63.7±29.9) and progressively increased after 8 to 12 days (Mean±SD=131.4±67). On

the other side, it decreased rather than the beginning after 13 days (Mean±SD=33±13.2) as shown in Table 2. CRP levels may diagnose severe pneumonia caused by COVID-19. The level of CRP was dramatically elevated in highly infected SARS-CoV-2 patients [23]. In a study examining the biochemical parameters in COVID-19 cases, it was found that CRP level increased 3 days after hospitalization in patients with severe disease and the CRP levels decreased dramatically after 9 days of hospitalization [21].

FER parameter

The levels of FER were increased after 3 to 5 days from signs and symptoms of COVID-19 infection appearance (Mean±SD=521.8±253.9) that gradually increased after 8 to 12 days (Mean±SD=1052.3±710.1). Furthermore, it decreased rather than the beginning after 13 days (Mean±SD=491.6±201.7), Table 2. This might support the idea that assumes hyperferritinemia is linked to immune activation in SARS-CoV-2 virus infection, and that FER would be used to estimate illness severity and the size of the cytokines storm [24]. Furthermore, the cause of the elevated plasma FER amount, as well as the protein's possible function in inflammation shortly after the onset of COVID-19 illness, remains unknown [25]. Active FER formation can occur during the progression of inflammatory disorders. The release of serum FER might be attributed to macrophages, which generate cytokines and make up the bulk of immune cells within the lung tissues. FER production can also be triggered by inflammatory stimuli such as cytokines like IL-6 [26]. In a meta-analysis, it was found that many biochemical parameters increased in patients with severe COVID-19, however, high level of FER was found to be one of the most important parameters in COVID-19 patients [27]. Similarly, in our study, we found that FER level was significantly higher in COVID-19 patients; prolongation of the length of stay in the hospital was associated with the severity of the disease.

LDH parameter

According to Table 2, the levels of LDH were increased after 3 to 5 days from signs and symptoms of COVID-19 infection appearance (Mean±SD=479.9±110.4) and gradually raised after 8 to 12 days (Mean±SD=586±128.9). On the other hand, it slightly increased rather than at the beginning after 13 days (Mean±SD=491.6±108.2). In the damaged cells, LDH is secreted from inside. The level and activity of LDH throughout the blood increase [28]. Many shreds of evidence assume that serum LDH levels can be used as a non-specific indication of cell death in different illnesses [29]. Excessive LDH implies tissue hypoperfusion, which might reflect the disease severity and alter the prognosis [29]. Early results from COVID-19 individuals revealed substantial variations in LDH values between patients and those who did not have the severe condition [30]. Similar study was found that LDH levels were still significantly higher within 6-9 days, and LDH was suggested to be a more important indicator of treatment response [24].

D-dimer parameter

The levels of D-dimer were increased after 3 to 5 days from COVID-19 infection (Mean±SD=770.1±254) and gradually elevated after 8 to 12 days (Mean±SD=1196.2±409.1). On the other hand, it reduced rather than at the beginning after 13 days (Mean±SD=387.5±139.3) as reported in Table 2. In

COVID-19 patients, endothelial dysfunction is mainly limited to the lungs as they are the first and most commonly affected organs in these patients. D-dimer is an indirect marker of thrombus formation that increases in COVID-19 patients suggesting the development of thrombus, particularly in ARDS patients, indicating poor prognosis. However, as an indirect marker, a significant increase in D-dimer suggested a benefit from heparin infusion in a large group of ARDS patients [31]. In addition, high D-dimer levels have been associated with mortality, severe disease, admission to the ICU and an increased risk of pulmonary embolism [32,33]. Even more, an upward trend of D-dimer within the course of COVID-19 has been related with deceased patients [34]. The limitations of the study were as follows; it was a single-center retrospective study, this influences the generalization of data and increase the probability of selection bias; In the present study, missing some data was a major limitation as laboratory examinations were not implemented daily on all patients, especially those who were minimally symptomatic in the general isolation ward. Patients who died at a given time all affected the statistical analysis.

CONCLUSION

Most of cases in our study were males and the majority of them were in the age above 65 years old. Many different biochemical markers had been studied including CRP, FER, LDH, and D-dimer tests, hence, all of them were statistically significant associated with the inflammatory prognosis process in COVID-19 patients. To conclude, there is a positive correlation between the levels of these biomarkers and the prolongation of hospitalization in COVID-19 patients and these parameters can be associated with the severity disease.

Disclaimer

The article has not been previously presented or published, and is not part of a thesis project.

Conflict of Interest

There are no financial, personal, or professional conflicts of interest to declare.

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