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Evaluation of biochemical characteristics of 183 COVID-19 patients: A retrospective study

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ABSTRACT

Introduction and aim: Coronavirus disease 2019 (COVID-19), with a high mortality rate, has caught the eyes of researchers worldwide and placed a heavy burden on the health care system. Accordingly, this study aimed to evaluate the values of biochemical parameters on the outcomes of COVID-19 patients in Golestan, Iran.

Materials and methods: This retrospective study was conducted on 183 COVID-19 patients (i.e., 94 males and 89 females) between March and September 2020. The biochemical parameters and demographic data of the patients (including age, sex, urea, creatinine [Cr], lactate dehydrogenase [LDH], and creatine kinase [CK]) were obtained from electrical medical records. According to the outcome of COVID-19, the patients were categorized into two groups (i.e., death [$n = 63$] and survival [$n = 120$] groups), and the biochemical parameters and outcomes of COVID-19 were analyzed.

Results: Of the 183 patients, 120 (65.5%) had a non-severe type and recovered from COVID-19, and 63 (34.4%) developed into a critically severe type and died. The mean age of all patients was 56.5 years old. The highest mortality was observed in patients with LDH $\geq$280. The data obtained by the one-sample *t*-test showed that there were significantly higher mean values of urea, Cr, CK, and LDH in COVID-19 patients when compared to their reference intervals ($P<0.0001$ for all).

Conclusions: Some biochemical parameters are effective in the evaluation of dynamic variations in COVID-19 patients. It can be concluded from the results that biochemical parameters and reinforce LDH may be useful for the evaluation of the COVID-19 outcome.

1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was caused by coronavirus disease 2019 (COVID-19), declared a global pandemic by the World Health Organization (WHO) on January 30, 2020 (Lai et al., 2020; Zhou et al., 2020). COVID-19 belongs to a large family Coronaviridae, enveloped, positive-strand RNA virus (Holmes, 1999; Wang and Xu, 2020). It has a typical structure, including the spike protein, membrane, nucleocapsid, and internal proteins (Shang et al., 2020). The most common routes of infection in humans include direct transmission through respiratory droplets and saliva, especially during coughing and sneezing (To et al., 2020). Besides, indirect transmission through contaminated surfaces (e.g., metal, glass, and plastic) could be considered as a secondary infection source (Petrosino et al., 2021; Choi et al., 2021).

The COVID-19 incubation period is usually between 2 and 14 days after the virus enters the body (Kaur and Kaur, 2021). Incidence in men is more than in women (Cho et al., 2021). Most patients after the incubation period showed some clinical manifestations, including respiratory illness, fever, dry cough, fatigue, muscle pain, and shortness of breath (Guan et al., 2020a). No special protocols are needed for treatment, and patients could be recovered by staying at home (Guan et al., 2020a). Underlying diseases, such as hypertension, diabetes, obesity, and cancers, as well as cardiovascular, kidney, liver, and chronic respiratory diseases, are usually observed in severe COVID-19 patients compared with non-severe patients (Gao et al., 2021; Zaki et al., 2020).

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The severity of COVID-19 is defined in three stages as follows: early infection, pulmonary phase, and hyperinflammation phase. In these three stages, biochemical parameters change in different ways (Yang et al., 2020). The first stage occurs at the time of infiltration of the virus; at this stage, lymphocytopenia and thrombocytopenia occur, and the biochemical levels of prothrombin time (PT), C-reactive protein (CRP), lactate dehydrogenase (LDH), and D-dimer increase. The pulmonary phase is determined by biochemical specifications (such as lymphopenia) and increased levels of CRP, alanine aminotransferase (ALT), and aspartate aminotransferase (AST). The hyperinflammatory phase of COVID-19 is the most severe stage; at this stage, multiple inflammatory biomarkers (such as cytokines) remarkably increased, besides biochemical parameters such as CRP, procalcitonin (PCT), LDH, D-dimer, ferritin, cardiac troponin (cTn), B-type natriuretic peptide (BNP)/N-terminal pro-B–type natriuretic peptide (NT-proBNP), and creatinine (Cr) (Ciaccio and Agnello, 2020). Many biochemical parameters have been associated with poor outcomes and represented risk patterns for severe prognosis of COVID-19 in order to demonstrate clinical care; among them, lymphopenia, thrombocytopenia, leukocytosis, CRP, PCT, LDH, AST, ALT, D-dimer, and cTn are the most severe predictors of COVID-19 (Guan et al., 2020b).

In general, the mortality rate of this virus is 3.4%, which is higher in the elderly and patients with underlying diseases compared with other patients (Ghany et al., 2020). In this regard, this retrospective study analyzed biochemical parameters of COVID-19 patients both in survival and death groups, which may help to identify critical factors and provide appropriate clinical intervention early. Accordingly, to achieve this purpose and obtain related information, we measured some biochemical parameters using kidney function tests (urea and Cr), biochemical index of muscle and heart damage (creatine kinase [CK]), and biochemical index of liver disease (lactate dehydrogenase [LDH]) related to COVID-19 patients.

On the other hand, few studies have been performed to evaluate and compare biochemical parameters in COVID-19 patients with their reference intervals and their mortality. Also, the association of biochemical parameters with mortality rate has not yet been explained in Iran. Therefore, measuring the serum levels of these indices was one of the main objectives of this study to provide better management of COVID-19 patients.

2. Material and methods

2.1. Population study

The data of 183 samples (94 males and 89 females; median age: 56.7 years old) were obtained from a general hospital, in Golestan, Iran, between March 20, 2020 to September 30, 2020. The biochemical parameters and demographic data of 183 patients were obtained from electrical medical records. Since this study was a retrospective study, there was no potential risk to patients and no link between the patients and researchers. Laboratory confirmation of COVID-19 was based on the detection of SARS-CoV-2 RNA using reverse transcriptase-polymerase chain reaction (RT-PCR) analysis of a nasopharyngeal swab specimen in accordance with the Centers for Disease Control and Prevention Guidelines.

2.2. Observation indices

Patients' age, sex, mortality, recovery, and blood biochemical indexes were retrospectively analyzed. Cases were divided into two groups, i.e., death and survival groups. The blood biochemical analysis included urea, Cr, LDH, and CK. The relationships between major blood biochemical indices and death and survival, as well as between age and sex, were analyzed to understand the effects of the above-mentioned parameters on the COVID-19 outcome. Also, we evaluated the major blood biochemical indices in COVID-19 patients and compared them

with their reference intervals.

2.3. Statistical analysis

GraphPad Prism 9 (GraphPad, Inc., La Jolla, CA, USA) was used for statistical description and analysis of test data. Continuous variables were expressed as median or simple ranges if appropriate. Categorical variables were summarized as counts and percentages. The Kolmogorov–Smirnov test was used to verify the normality of the distribution of continuous variables. The one-sample t-test was performed to compare biochemical parameter levels (mean ± SD) with their reference intervals. The significant differences are shown as $*P < 0.05$, $**P < 0.01$, $***P < 0.001$, and $****P < 0.0001$.

3. Results

Table 1 summarizes the demographic and biochemical characteristics of the 183 patients included in this study. Of the 183 patients, 120 (65.5%) had a non-severe type and recovered from COVID-19, and 63 (34.4%) developed into a critically severe type and died. The mean age of all patients was 56.5 years old. In detail, the mean ages of the subjects in death and survival groups were 66.3 and 51.5 years old, respectively. Fifty-five patients (30%) were ≥40–<60 years old, of which 13 patients (23.63%) died, and 42 patients (76.36%) recovered. Thirty-five patients (19.1%) were <40 years old, of which five patients (14.28%) died, and 30 patients (85.71%) recovered.

However, 93 patients (50.8%) were ≥60 years old, of which 45 patients (48.38%) died, and 48 patients (51.61%) recovered. These data clearly showed that the mortality rate increased with age, especially in patients older than 65 years old. The prevalence rate was truly higher in males (94 patients; 51.3%) than in females (89 patients; 48.6%) in this

Table 1
Demographic and biochemical characteristics.

	All patients ($n = 183$)	COVID-19 outcome	
		Death ($n = 63$)	Survival ($n = 120$)
Age			
Median, year	56.57	66.30	51.57
Distribution			
0–<40 y	35 (19.1%)	5 (14.28%)	30 (85.71%)
≥40–<60 y	55 (30%)	13 (23.63%)	42 (76.36%)
≥60 y	93 (50.8%)	45 (48.38%)	48 (51.61%)
Sex			
Male	94 (51.3%)	34 (36.17%)	60 (63.82%)
Female	89 (48.6%)	29 (32.58%)	60 (67.41%)
Biochemical parameters (normal value)			
Urea			
15–45 (mg/dL)			
<15	12 (6.5%)	0	12 (100%)
≥15–<45	97 (53%)	31 (31.95%)	66 (68.04%)
≥45	74 (40.4%)	32 (43.24%)	42 (56.75%)
Cr			
0.5–1.2 (mg/dL)			
<0.5	4 (2.1%)	0	4 (100%)
≥0.5–<1.2	86 (47%)	34 (39.53%)	52 (60.46%)
≥1.2	93 (50.8%)	29 (31.18%)	64 (68.81%)
LDH			
140–280 (U/L)			
<140	2 (1.1%)	0	2 (100%)
≥140–<280	1 (0.5%)	1 (100%)	0
≥280	180 (98.4%)	62 (34.44%)	118 (56.55%)
CK			
20–200 (U/L)			
<20	0	0	0
≥20–<200	108 (59%)	31 (28.70%)	77 (71.29%)
≥200	75 (41%)	32 (42.66%)	43 (57.33%)

Abbreviations: Cr, creatinine; LDH, lactate dehydrogenase; CK, creatine kinase.

population. Also, the mortality rate was higher in males (34 deaths; 36.17%) than in females (29 deaths; 32.58%). Subsequently, the survival rate was lower in males (60 cases; 63.82%) than in females (60 cases; 67.41%).

In patients with urea ≥15–<45 and ≥45 mg/dL, the proportions of mortality and survival were 31 (31.95%) to 66 (68.04%) and 32 (43.24%) to 42 (56.75%), respectively. Also, our results showed that all patients with urea <15 mg/dL recovered.

In patients with a Cr level ≥0.5–<1.2 and ≥1.2 mg/dL, the proportions of mortality and survival were 34 (39.53%) to 52 (60.46%) and 29 (31.18%) to 64 (68.81%), respectively. Further, patients with Cr <0.5 recovered.

In patients with LDH level <140, ≥140–<280, and ≥280 U/L, the proportions of mortality and survival were 0 to 2 (100%), 1 to 0 (100%), and 62 (34.44%) to 118 (56.55%), respectively. Based on our results, the highest mortality was observed in patients with LDH ≥280. Also, in patients with a CK level ≥20–<200 and ≥200 U/L, the proportions of mortality and survival were 31 (28.70%) to 77 (71.29%) and 32 (42.66%) to 43 (57.33%), respectively.

As represented in Table 2, the data obtained using the one-sample *t*-test showed that the mean biochemical parameters in patients were significantly different (upper) compared to reference intervals (urea, 95% CI [20.5986–39.4014]; $P < 0.0001$), (Cr, 95% CI [0.5934–1.0465]; $P < 0.0001$), (LDH, 95% CI [414.7302–517.6304]; $P < 0.0001$), and (CK, 95% CI [239.0909–535.7069]; $P < 0.0001$).

4. Discussion

The clinical features and outcomes of COVID-19 patients are very complicated (Bennett et al., 2021). Both symptomatic and asymptomatic COVID-19 patients are the main sources of spreading infection; in other words, infection mainly spreads via respiratory droplets and close contact through aerosol transmission in a closed environment for extended periods (Cortellessa et al., 2021). There are no clear guidelines and research on COVID-19 patients (Stamm et al., 2021). Therefore, it is necessary to focus on laboratory findings, especially biochemical parameters in these patients (Das et al., 2021). Biochemical parameters are usually evaluated as early parameters to monitor the metabolic status and health of organs. The measurement of these parameters in COVID-19 patients is very important to obtain valuable information related to the outcomes of the disease (Statsenko et al., 2021).

In this study, we described the biochemical parameters and outcomes of COVID-19 patients in Golestan, Iran, during six months of the city's outbreak. Overall, a total of 183 patients with COVID-19 were included in this study. The profile of laboratory values was tracked in all patients. Our findings showed that urea, CK, and LDH had certain advantages in predicting the outcomes of the disease. Indeed, with increasing levels of urea, CK, and especially LDH, the mortality rate increased. In this regard, LDH ≥280 U/L had a very poor outcome and prognosis so that, when the general conditions of the patients worsened, the values of biochemical parameters, especially LDH, significantly increased. Indeed, the proportion of patients with LDH levels greater

than 280 U/L was particularly high (over 98%).

Therefore, early detection of LDH values has a great prognostic value. In this regard, Dang Wang et al. suggested that some biochemical parameters, such as LDH, could be considered as a prognostic marker in COVID-19 patients, which is consistent with our results (Wang et al., 2020). Our data indicated that of the total death (n = 63), 32 had abnormal CK, and 62 had abnormal LDH, which is consistent with Deng et al.'s systematic and meta-analysis review; they showed that the levels of CK were abnormal in 13% of patients, and 52% of patients had a high level of LDH (Deng et al., 2020).

However, our results indicated that Cr levels in COVID-19 patients decreased, while Deng et al. reported that Cr levels increased in 8% of COVID-19 patients (Deng et al., 2020). Also, in a retrospective study, serum urea and Cr levels in 100 COVID-19 patients showed that 35 (35%) patients had elevated levels of serum urea nitrogen (SUN) and Cr (Mahmoudi et al., 2020). Regarding Cr levels, our conflicting results may be due to the small sample size of our study, needing to be confirmed by further studies.

Taken together, our study showed that COVID-19 patients have different levels of altered biochemical parameters, which may indicate dysfunction of several organs. Also, biochemical markers, such as LDH, can be used for monitoring COVID-19 patients and reflect the severity and outcome of the disease. Further, our data demonstrated that biochemical values were different from reference values, which were shown in other studies as well (Yağcı et al., 2021; Huang et al., 2021; Letelier et al., 2021). The current study also showed that age affected the disease outcome when other influencing conditions were not considered.

As expected, the highest mortality rate was detected in patients ≥60 years old. Indeed, the proportion of dead patients over 60 years old was more than 48.38%, while the overall mortality rate was varied between countries (Letelier et al., 2021). The lowest mortality rate was observed in China in patients aged ≥80 years old (3.1%), and the highest rates were observed in New York State (20.99%) and the United Kingdom (20.8%) (Letelier et al., 2021). Our data showed that in Iran, the mortality rate in patients aged ≥60 years old was higher compared to other countries, and these patients should be prioritized regarding preventive measures. There were some obvious limitations to our study as follows: The time of data extraction was limited; the number of patients was limited; and the clinical history and the rest of the laboratory tests of patients were incomplete.

5. Conclusions

The effect of biochemical parameters is crucial in the appropriate management of COVID-19, for example, to assess the prediction risk and the outcome of the disease. Changes in these biochemical factors indicate abnormalities in various tissues and organs, indicating the development of COVID-19. Urea, CK, and LDH show the most predictive parameters of severe COVID-19; LDH as an important biomarker is associated with poor outcomes in these patients. Considering the biochemical parameters, it could be concluded that in patients >60 years old, LDH >240 U/L could indicate the critical stage of COVID-19. Biochemical parameters are also effective in the evaluation of dynamic variations in COVID-19 patients. Therefore, we suggest that biochemical parameters and reinforce LDH may be useful for the evaluation of the COVID-19 outcome. However, larger studies are needed to confirm these findings in Iranian patients. Another interesting area of research is the study of immunological and hematological parameters (such as inflammatory cytokines, lymphocytes, and immunoglobulins A, M, and G); by assessing these indicators (serum test) and finding their correlation with demographic characteristics (such as age and gender), we can provide a clearer picture of how COVID-19 is progressing.

Table 2
The one-sample *t*-test results, comparing the mean of biochemical parameters with their reference intervals.

Biochemical parameters	Mean difference	95% CI		P value[a]
		Lower	Upper	
Urea	30	20.5986	39.4014	<0.0001
Cr	0.81995	0.5934	1.0465	<0.0001
LDH	466.18033	414.7302	517.6304	<0.0001
CK	378.39891	239.0909	535.7069	<0.0001

Abbreviations: Cr, creatinine; LDH, lactate dehydrogenase; CK, creatine kinase.
[a] *P* values indicate differences between the mean of biochemical parameters and reference intervals. A *P* value <0.05 was considered statistically significant.

Abbreviations

SARS-CoV-2 Severe Acute Respiratory Syndrome Coronavirus 2
COVID-19 Coronavirus Disease 2019
LDH lactate dehydrogenase
CK creatine kinase
Cr creatinine

CRediT authorship contribution statement

Alireza Tahamtan and Hadi Razavi Nikoo researched literature and conceived the study. Seyed Mostafa Mir wrote the first draft of the manuscript. Mehdi Sheikh Arabid, Abdul Wahab Moradi and Saeed Ardakanian involved in protocol development, and data analysis. Alijan Tabarraei reviewed and edited the manuscript and approved the final version of the manuscript.

Declaration of competing interest

All authors (Seyed Mostafa Mir, Alireza Tahamtan, Hadi Razavi Nikoo, Mehdi Sheikh Arabi, Abdul Wahab Moradi, Alijan Tabarraei) have approved the manuscript and agree with submission. The authors declare that there are no conflicts of interest to the publication of this article, financial and/or otherwise. The final manuscript has been seen and approved by all authors and that they have taken due care to ensure the integrity of the work.

The authors declare that there is no conflict of interest.

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