Scientific Foundation SPIROSKI, Skopje, Republic of Macedonia
Open Access Macedonian Journal of Medical Sciences. 2022 Aug 17; 10(B):2082-2086.
https://doi.org/10.3889/oamjms.2022.10154
eISSN: 1857-9655
Category: *B - Clinical Sciences*
Section: *Infective Diseases*

Correlation of Biomarkers in Severe COVID-19 Patients Cross-sectional Study

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Edited by: Slavica Hristomanova-Mitkovska
Citation: Esmaeel NA, Abd Alsalam AS. Correlation of Biomarkers in Severe COVID-19 Patients Cross-sectional Study. Open-Access Maced J Med Sci. 2022 Aug 17; 10(B):2082-2086. https://doi.org/10.3889/oamjms.2022.10154
Keywords: Covid-19; Renal function tests; Liver function tests; Lactate dehydrogenase; Glutamic-oxaloacetic transaminase; Glutamic-pyruvic transaminase; Alkaline phosphatase; Urea; Creatinine
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Received: 17-May-2022
Revised: 08-Jun-2022
Accepted: 07-Aug-2022

Funding: This research did not receive any financial support
Competing Interest: The authors have declared that no competing interest exists

Abstract

BACKGROUND: In patients with coronavirus disease-19 (COVID-19), serious biomarkers (liver function tests and renal functions tests) (urea, creatinine, GOT, GPT, and LDH) are determined immediate to assess in prognosis of the severity of disease.

AIM: The aim of the study was to determine correlation between biomarkers (liver function tests and renal functions tests) (urea, creatinine, GOT, GPT, and LDH) among COVID-19 patients.

METHODS: A cross-sectional study, a total of 90 COVID-19 patients who attending in the Al-Hussein Medical City in Karbala, Iraq, participated in the present study within a month's time in late December 2021 to early January of 2022. All COVID-19 patients with positive SARS-COV-2 real-time RT-PCR results were reviewed. The patients were classifying according SPO_2 into three groups (mild, moderate, and severe groups). The demographic data (sex, age, and SPO_2) were collected while the biomarkers (liver function tests and renal functions tests) for all patients were done by bio-base instrument (ACCENT-200 ALAT KIT).

RESULTS: The white blood cell "WBC" and neutrophil in moderate and severe groups had substantially greater counts ($p = 0.005$) when compared with mild group while lymphocytes were considerably decreased in the severe and moderate groups ($p = 0.005$). In the moderate group, there was positive significant correlation among neutrophils and serum LDH ($r = 0.451^*$, $p = 0.014$). There was no significant correlation between neutrophils and liver function tests. Furthermore, in the moderate patient group, a strong positively correlating notably among lymphocytes and serum LDH. Moreover, the concentration of serum GOT, GPT, and LDH ($p = 0.05$, $p = 0.08$, and $p = 0.5$) was higher levels in severe group when compared to moderate and mild groups, on the other hand, the renal function tests (urea and creatinine) were high serum levels in severe group than mild and moderate groups.

CONCLUSION: The serum concentration of urea, creatinine, GOPT, GPT, and LDH was high in severe COVID-19 patients group, although there was no statistically significant in ALP, GPT, and urea among COVID-19 patient's groups (mild, moderate, and severe group). The present study found no significant correlation between biomarkers (liver function tests and renal function test).

Introduction

Near the end of 2019, a cluster of pneumonia patients with an unknown cause developed in Wuhan, Hubei Province, China. Since then, outbreaks and unusual human infections have resulted in over 80,000 laboratory-confirmed cases in mainland China (updated on March 23, 2020). 2019-nCoV, a novel coronavirus, has been shown to be the cause of this hitherto inexplicable respiratory illness. Finally, on February 11, 2020, the World Health Organization "WHO" released the standard format for this new coronavirus "COVID-19." The ICTV dubbed "SARS-CoV-2" the following day [1].

The genus Coronavirus, family Coronaviridae, order Nidovirales. All include coronaviruses (CoVs) [2]. As suggested, the coronavirus have single-stranded positive sense (+ssRNA) in their genome. They are known as "corona" viruses because of their distinctive appearance under electron microscopy due to the presence of "club-shaped" surface protein projections (crown) [3]. The CoVs are pleomorphic, with a tiny genome spanning 27–32 kilobytes and a length ranging from 80 to 160 nm [4].

Direct or indirect contact with mucosal membranes may transmit infectious respiratory droplets or fomites (eyes, nose, mouth, etc.). Time and proximity to the infected/infected person increase the risk of transmission [4]. Acute heart damage and severe pneumonia were the primary causes of COVID-19 infection in the respiratory system, which was accompanied with ground-glass opacity. A significant increase in cytokines and chemokines was found in individuals with "COVID-19 infection," including "IL1-, IL7-/IL8, and TNF-/VEGFA" in addition to basic FGF2 and GCSF/GMCSF. These patients also had elevated levels of IFN-, IP10, and MCP1 and MIP1/MIP1. Pro-inflammatory cytokines such as interleukin1, interleukin2, interleukin7, interleukin10, GCSF, IP10,

MCP1, MIP1, and TNF have been detected in some of the critically sick patients admitted to the ICU [5].

"Severe acute respiratory syndrome-2," like "Severe acute respiratory syndrome," uses the human "angiotensin-converting enzyme 2" (ACE2) to gain access to cells. The type I membrane protein ACE2 is the culprit when it comes to heart and cardiovascular disease. One transmembrane helix and a 40-residue intracellular region make up the collectrin-like CLD domain (CLD) at the end of the full-length ACE2. Ace2 also interacts directly with CoV S proteins, cleaving angiotensin (Ang) I, and releasing angiotensin-(1–9) [6]. In the pre-fusion condition of CoVs, the S protein of the virus is found in contact with the host cell's membrane. The pre-fusion trimer is destabilized when the S1 subunit comes into contact with host cell receptor, causing the S1 subunit to be shed and S2 subunit to transform into its post-fusion shape [7]. Host cell receptor interactions may be initiated by the S1 RBD's hinge-like conformational modifications that conceal or expose receptor binding components. To test whether the SARS-S CoV-2 virus might infect humans, researchers analyzed the protein's receptor-binding domain (RBD), which is in direct contact with ACE2 SARS-CoV-2. "S" protein may have a "10–20 folded" greater affinity for "human (ACE2) than SARS-CoV, according to biophysical and structural studies. The ACE2-B0AT1 complex may be able to bind two S proteins at the same time, according to structural studies [8].

A large percentage of individuals with acute renal impairment were found among those who had been diagnosed with "SARS-CoV-2" infection. Some patients had renal failure who needed dialysis as a result. The quick clinical deterioration that some patients experience is one of the most common problems we're seeing in these individuals. Therefore, it seems that early identification the risk factors for severe illness and mortality in these individuals is a top priority. In the previous research, acute kidney injury seen in "5–15% of SARS and MERS-CoV" infections, with the fatality rate of "60–90%" [9].

ALT and AST values were found to be increased in these investigations, with a range of 14–53% [10]. It's also possible that SARS-CoV-2 caused the liver damage seen in a patient who died of "COVID-19" since pathology on liver biopsy samples from that patient revealed "minor microvascular steatosis and modest lobular and portal activity in their livers" [11]. Lactate dehydrogenase (LDH) is a glycolytic cytoplasmic enzyme present in virtually every tissue. In general, its elevation suggests tissue injury. Possible subclinical tissue damage was indicated by our observation of increased LDH in the early stage of extreme COVID-19 cases [12]. Elevated LDH has been associated with a higher risk of ARDS, need for intensive care, and mortality [13]. However, ALT, AST, total bilirubin, and other liver function indices were significantly increased in patients with severe COVID-19 compared to patients with mild COVID-19, and the liver function indices gradually returned to normal during recovery [12].

Methods

A cross-sectional method, the present study was carried out on December 2021 and January 2022 with a total 90 COVID-19 patients. The patients were classifying according SPO_2 into three groups mild (≥ 95%), moderate (91–94%), and severe (≤90%). Inclusion criteria were positive COVID-19 patients according to the real-time PCR. The demographic data (sex, age, and SPO2) were collected while the biomarkers (liver function tests and renal functions tests) (urea, creatinine, GOT, GPT, and LDH) for all patients were done by bio-base instrument (ACCENT-200 ALAT KIT). To collect blood samples from 90 patients, 5 mm of venous blood was drawn, which then underwent centrifugation at 1500 rpm.

Statistical analysis

Statistical analyses were performed using SPSS Statistical Package for the Social Sciences (version 25.0 for Windows, SPSS, Chicago, IL, USA). Quantitative data are represented as men ± SD. ANOVA test was used to differences among groups. $p < 0.05$ was considered statistically significant.

Results

Table 1 shows the demographic information for the reference site. SpO_2 % was used to determine the severity of the condition in this investigation. "SARS-COV-2" patients were divided into mild (≥95%), moderate (91–94%), and severe (≤90%) groups based on their SpO_2 percentage. Males made up 60% of the group, while females made up 40%. The general mean

Table 1: Baseline characters of the studied group

Parameters	Statistic	
Total number	90	
Gender (%)		
Male	54 (60)	
Female	36 (40)	
Age (mean ± SD)	56.57 ± 14.83	
SpO2 (mean ± SD)	91.3 ± 5.4	
Variable	Mean ± SD within groups	p
Severity		
Severe group	63.93 ± 13.12	0.245
Moderate group	60.60 ± 13.76	
Mild group	45.17 ± 10.29	
Oxygen saturation		
Severe group	85.4 ± 5.3	0.005
Moderate group	92.53 ± 1.1	
Mild group	95.96 ± 0.9	

SD: Standard deviation. Values expressed as mean ± SD significant differences at the (p≤0.05) level.

was 56.57 ± 14.83, with a range of ages from 25 to 89 years in the population. Mean age among severe group was 63.93 ± 13.12 while in moderate and mild illness groups was 60.60 ± 13.76 and 45.17 ± 10.29 (p = 0.245), as shown in Table 1.

Table 2 shows the comparison mean between biomarker (liver function and renal function tests) in COVID-19 patient. Among the liver function tests, the GPT and GOT show high serum levels (53.28 ± 50.25 and 43.65 ± 23.05) in severe group when compared with mild group (34.05 ± 17.50 and 31.48 ± 12.40). The hematological parameters in moderate and severe patients exhibited significantly higher WBC and neutrophil counts (p = 0.005) than mild COVID-19 patients group. On the other hand, the concentration of serum LDH was higher in moderate group (478.85 ± 214.18) when compared with mild and severe groups (p = 0.005).

Table 2: Comparison mean of parameter of the studied groups

Variable	Mean ± SD			p
	Mild ill (n = 30)	Moderate ill (n = 30)	Severe ill (n = 30)	
WBCs	7.167 ± 2.4587	13.67 ± 7.48	13.78 ± 5.76	0.005
Neutrophil	53.20 ± 13.52	75.15 ± 24.39	79.73 ± 16.24	0.005
Lymphocytes	23.52 ± 9.36	10.65 ± 10.44	10.91 ± 16.09	0.005
ALT (GPT)	34.05 ± 17.50	53.16 ± 36.78	53.28 ± 50.25	0.08
AST (GOT)	31.48 ± 12.40	39.97 ± 19.84	43.65 ± 23.05	0.05
ALP	74.04 ± 25.47	83.34 ± 39.64	86.30 ± 58.71	0.5
LDH	190.45 ± 64.40	478.85 ± 214.18	440.21 ± 255.71	0.005
Urea	25.07 ± 7.755	28.13 ± 9.313	29.93 ± 10.282	0.1
Creatinine	0.387 ± 0.177	0.5433 ± 0.20288	0.633 ± 0.215	0.001

SD: Standard deviation , WBC: White blood count, ALT: Alanine aminotransferase, GPT: Glutamic-pyruvic transaminase, AST: Aspartate aminotransferase, GOT: Glutamic-oxaloacetic transaminase, ALP: Alkaline phosphatase, LDH: Lactate dehydrogenase.

Table 3 shows correlations between neutrophil counts and liver function tests. In moderate COVID-19 patient group, there was positive significant correlation between neutrophils and serum LDH (r = 0.451*, p = 0.014). There was no significant correlation between neutrophils with liver function tests.

Table 3: Pearson's correlation coefficient of neutrophils among liver functions in studied groups

Parameters	PC and p value	Neutrophils		
		Mild group (n = 30)	Moderate group (n = 30)	Severe group (n = 30)
ALT (GPT)	*R*	−0.040	0.196	0.149
	p	0.835	0.327	0.441
AST (GOT)	*R*	−0.011	0.055	0.309
	p	0.953	0.787	0.102
ALP	*R*	0.112	0.244	−0.007
	p	0.555	0.219	0.969
LDH	*R*	0.023	0.451*	0.242
	p	0.916	0.014	0.197

*Correlation is significant at the 0.05 level. PC: Pearson's correlation, ALT: Alanine aminotransferase, GPT: Glutamic-pyruvic transaminase, AST: Aspartate aminotransferase, GOT: Glutamic-oxaloacetic transaminase, ALP: Alkaline phosphatase, LDH: Lactate dehydrogenase.

Table 4 shows that correlation analyses were done between lymphocytes with liver function tests in COVID-19 patients. There was no significant correlation between lymphocytes with liver function tests. On the other hand, there was positive significant correlation notably among lymphocytes with lactate dehydrogenase in moderate covid-19 patient groups.

Table 5 shows that correlation analyses were done among the renal function test with liver function tests in COVID-19 patients. There was no significant correlation between urea with liver function tests among the patient groups. Moreover, there was no significant correlation between creatinine with liver function tests among the patient groups.

Table 4: Pearson's correlation coefficient of lymphocytes among liver functions in studied groups

Parameters	PC and p value	Lymphocytes		
		Mild group (n = 30)	Moderate group (n = 30)	Severe group (n = 30)
ALT (GPT)	R	−0.040	−0.208	−0.041
	p	0.835	0.299	0.835
AST (GOT)	R	−0.011	−0.141	−0.149
	p	0.953	0.482	0.442
ALP	R	0.112	0.062	−0.066
	p	0.555	0.759	0.735
LDH	R	0.023	−0.528**	−0.126
	p	0.916	0.003	0.506

**Correlation is significant at the 0.01 level (two tailed). PC: Pearson's correlation, ALT: Alanine aminotransferase, GPT: Glutamic-pyruvic transaminase, AST: Aspartate aminotransferase, GOT: Glutamic-oxaloacetic transaminase, ALP: Alkaline phosphatase, LDH: Lactate dehydrogenase.

Discussion

The general mean age was 56.57 ± 14.83, as shown in Table 1. Yang *et al*. research indicated the severity of COVID-19 over the age of 50 [14]. Gender was also shown to have a role in the degree of disease in Table 1. Team 2020, COVID-19 was shown to be more frequent in males than in women [15]. Jin *et al*., 2020, according to the clinical severity categorization, men are more likely than women to acquire more severe instances [16].

Chen *et al*., 2020 and Anurag *et al*., 2020, reported a statistically significant difference in WBC counts and neutrophil percentage (p = 0.000). WBC and neutrophil counts in severe patients were statistically significant (p = 0.003 and p = 0.002, respectively) in comparison to moderate instances [17], [18]. Dawood *et al*., 2020, reported that COVID-19 severity patients were shown to be correlating with lymphopenia [19]. The fact that COVID-19 patients showed no significant differences in GPT and GOT, these results seem to be consistent with the previous research [20]. The "SARS-CoV-2" virus binding to the cholangiocyte "angiotensin-converting enzyme 2 (ACE2)" and causes a systemic inflammatory response as well as liver damage (ACE2) [21]. LDH had greatly risen in most patients, but "ALT and AST" revealed no-significant changes, according to Chen *et al*., 2020 [22].

Bawiskar *et al*., 2020, reported that the higher total leukocyte counts in COVID-19 patients with impaired liver function parameters [23]. In the study by "Yu *et al*.," patients. with high ALT had more severe liver damage, suggesting that hypoxemia may play a role. Hepatocytes may be damaged by cytokines, reactive oxygen species, and nitric oxide generated by Kupffer cells, which remove germs and endotoxins from the portal venous system. In addition, the cytokines released by neutrophils have the potential to further harm hepatocytes. White blood cell and neutrophil counts were observed to be significantly greater in individuals

Table 5: Pearson's correlation coefficient of renal function tests among liver functions in studied groups

Parameters	PC and p	Urea			Creatinine		
		Mild group (n = 30)	Moderate group (n = 30)	Severe group (n = 30)	Mild group (n = 30)	Moderate group (n = 30)	Severe group (n = 30)
ALT (GPT)	R	0.022	0.147	−0.052	0.084	0.365	−0.088
	p	0.908	0.456	0.787	0.658	0.067	0.650
AST (GOT)	R	0.009	0.101	0.064	0.116	0.281	0.012
	p	0.961	0.608	0.743	0.542	0.165	0.950
ALP	R	0.166	0.148	−0.210	0.284	−0.049	−0.146
	p	0.381	0.451	0.273	0.128	0.811	0.448
LDH	R	0.110	−0.081	−0.150	0.206	−0.129	−0.301
	p	0.616	0.670	0.428	0.346	0.512	0.106

PC: Pearson's correlation, ALT: Alanine aminotransferase, GPT: Glutamic-pyruvic transaminase, AST: Aspartate aminotransferase, GOT: Glutamic-oxaloacetic transaminase, ALP: Alkaline phosphatase, LDH: Lactate dehydrogenase.

with increased ALT, and both indices had substantial positive relationships with aminotransferases [24]. Another study by Moorthy *et al*., there was negative correlation between liver function tests with the WBC [25]. Diaz *et al*. research found that although the influence of lymphocytes on AST, ALP, and even ALT was lost toward the end of the study, the relationship between lymphocytes and AST, ALP, and even ALT remains robust [26].

"Hepatic enzyme levels" have been shown to be excellent prognostic indicators. The amount of serum aminotransferases in people with chronic kidney disease (CKD) is lower than in the general population, according to various studies. The levels of aminotransferase in the blood of persons with end-stage renal disease are substantially lower than in the general population [27]. In a study conducted by Kumar *et al*., this was proven to be true in all COVID-19-positive people, independent of renal function level. When we compared Groups 2 and 1, we saw a statistically significant rise (p = 0.05). There were also significantly higher serum ALT levels in Groups 1 and 2 than in Group 3, which was statistically significant [28]. As a consequence, the difference between Groups 1 and 2 was statistically significant (p 0.05). This suggests that. serum "AST and ALT levels are greater in COVID-19 CKD patients than in non-CKD patients," which is unexpected. In contrast, serum ALP levels in Group 1 (mild) were significantly lower than in Groups 2 and 3 (moderate and severe), indicating a greater association between ALP values with kidney disease than in the non-CKD group [29].

There are a few limitations in the present study that should be mentioned. The liver function markers were not calculated over a set length of time. However, medicines utilized before to admission, such as antivirals, were difficult to come by, which might have contributed to the abnormalities in liver function seen on admission.

Conclusion

The study showed that the concentration of GOT, GPT, and LDH was high in severe COVID-19 (p = 0.05, p = 0.05, and p = 0.01) when compared with mild group. The concentration levels of urea and creatinine were still within normal range in severe covid-19 patient groups. The study shows no significant correlation between biomarkers (liver function tests and renal function tests) in "COVID-19 patients." This study clearly shows that COVID-19 is accompanied by notable changes in hematological and biochemical profiles, which may help in early identification of COVID-related complications and may facilitate supportive medical care for positive patient outcomes.

Acknowledgments

We sincerely offer gratitude to all the health-care providers fighting against in COVID-19 pandemic. We would like to thank all the patients whose data were involved in the study. We also acknowledge the hospital staff for their efforts in collecting the information.

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