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ORIGINAL ARTICLE

Serum level estimation of some biomarkers in diabetic and non-diabetic COVID-19 infected patients

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Abstract

Diabetes, hypertension, and cardiovascular disease all raise the risk of hospitalization and mortality in individuals infected with coronavirus disease 2019 (COVID-19). Higher levels of flogosis mediators such as TNF, C-reactive protein (CRP), IL-1, IL-6, leptin, and resistin, as well as increased levels of TNF, C-reactive protein (CRP), IL-1, IL-6, leptin, and resistin, define diabetes. The goal of this study is to evaluate the levels of D-dimer, total serum bilirubin (TSB), glutamic-oxaloacetic transaminase (GOT), glutamic pyruvic transaminase (GPT), and CRP in diabetic patients with COVID-19 infection to COVID-19 patients without diabetes. Blood samples were collected from individuals with diabetes who had COVID-19 and non-diabetic COVID patients as control. Moreover, D-dimer and CRP were evaluated by using Min Vidus and Latx, respectively, whereas AccEnT 200 system was used to measure the serum level of TSB, GPT, and GOT in the hematology lab. Also demonstrated that the average serum concentration of D-dimer, GOT and CRP was high in diabetic COVID-19-infected patients (980.66 ng/mL, 67.71 U/L, and 27.06 mg/L, respectively) compared with non-diabetic COVID-19-infected patients (791.17 ng/mL, 54.023 U/L and 20.11 mg/L, respectively) ($p < 0.05$), while the situation was inverse for the average concentration of TSB and GTP when their average concentrations were low in diabetic COVID-19-infected patients (12.89 Mmol/L and 59.79 U/L, respectively) ($p > 0.05$). Moreover, the cut-off values for serum D-dimer, TSB, GPT, GOT, and CRP of COVID-19-infected diabetic patients were ≥ 6500 ng/mL, ≥ 350 Mmol/L, ≥ 133 U/L mg/L, ≥ 150 U/L, and ≥ 15.22 mg/L, respectively, represented a perfect test for predicting COVID-19-infected diabetic patients with 100% sensitivity and specificity. In conclusion, serum D-dimer, TSB, GPT, GOT and CRP increased in diabetic COVID-19-infected patients compared to non-diabetic COVID-19 patients and the D-dimer concentration also increases. TSB and CRP were more pronounced among diabetic patients with corona, while liver enzyme concentrations were decreased.

Keywords Diabetic · COVID-19 · D-dimer · TSB · GPT · GOT · CRP

Introduction

The present global pandemic of COVID-19 is the primary reason behind the increase in the number mortalities (World Health Organization 2020a; Lu et al. 2020). The severe acute respiratory syndrome (SARS-CoV-2) called (COVID-19), which first appeared in Wuhan, China in December 2019, caused significant fatalities (World Health Organization 2020a; Lu et al. 2020). Cough, shortness of breath, and fever are the most prevalent medical signs (Huang et al. 2020), as are gastrointestinal symptoms such as nausea, vomiting, abdominal pain, increased total serum bilirubin levels, and elevated liver enzymes like GOT and GPT (Huang et al. 2020; Cheung et al. 2020). The significance of numerous symptoms, comorbidities, inflammation, and hypercoagulability indicators in disease progression and mortality in COVID-19 patients is becoming clearer (Saleh et al. 2020; Moghadasi et al. 2021; Jalil et al. 2020, 2021a, b; Dilfy et al. 2020; Marofi et al. 2021a; Widjaja et al. 2021; Turki Jalil et al. 2021; Sarjito et al. 2021; Jalil 2020). Diabetes, one of the main causes of morbidity, has been found to have a high

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prevalence and is linked to adverse disease progression in COVID-19 (Li et al. 2020a; Guo et al. 2020).

Diabetic patients are more sensitive to COVID-19-related critical care hospitalizations, mechanical ventilation, and fatalities than those without diabetes (Yuan et al. 2020; Zhang et al. 2020). Several studies have linked inflammatory and coagulability indicators such as serum ferritin, CRP, interleukin-6, fibrinogen, and D-dimers to the severity and development of COVID-19 (Spiezia et al. 2020; Li et al. 2020b; Connors and Levy 2020). D-dimer is a protein fragment that uses itself soon after the degradation of a blood clot. Indeed, D-dimer is one of the most genuine biomarkers for both mortality rate and the severity of any disease. In brief, D-dimer is known as a product of cross-linked fibrin, which helps in the blood clotting process (Fruchter et al. 2015).

D-dimer test and CRP are beneficial for monitoring the patient's progression to COVID-19-related cytokine storm and help in timely medical intervention to reduce fatality. However, the precise role of these markers is still not detected clearly in diabetic COVID-19 patients (Yao et al. 2020). In contrast, recent reports indicate that hepatic injury is not commonly found among patients with COVID-19 (Mao et al. 2020; Schaefer et al. 2020). It is reported that abnormal liver tests are linked to an increased risk of death; therefore, they should be closely monitored throughout hospitalization (Hundt et al. 2020; Lei et al. 2020). However, the predictive usefulness of abnormal liver tests and their link to worse outcomes in COVID-19 patients is still debated (Poggialia et al. 2020). The current study compares diabetic COVID-19-infected patients to non-diabetic COVID-19-infected patients to determine the role of D-dimer, CRP, and certain liver enzymes (GOT, GPT).

Patients and methods

Study design and simples collection

In a prospective controlled study, blood samples were collected from 120 hospitalized COVID-19 patients at Al-Furat General Hospital in Baghdad/Iraq during the period from 1/8/2020 to 11/12/2020 and from 60 individuals with COVID-19 who were non-diabetic as a control group. Blood samples were drawn and information was collected after obtaining consent from all participants. The questionnaire included the name, age, and gender of the patient and healthy individuals in the additional, present study agreed with ethical guidelines of Al-Furat General Hospital.

Laboratory tests

Corona virus was diagnosed in the Virology and Immunology Laboratory at Al-Furat General Hospital by taking a nasopharyngeal swab and investigation was performed by RT-PCR technique. Medical examinations and X-rays were also conducted to follow the development of the health condition and estimate the severity of the infection. Moreover, D-dimer and CRP were evaluated using Min Vidus and Latx, respectively, whereas AccEnT 200 system was used to measure the serum level of TSB, GPT, and GOT in the hematology lab.

Statistical analysis

The information was converted into a digital database structure. The database was checked for flaws and inconsistencies using range and logical data cleaning methods. A statistician's opinion was requested. SPSS version 20 computer software was used in conjunction with Microsoft Excel 2010 and social science statistics for statistical analysis. The prevalence of characteristics such as gender, age, and presence of diabetes mellitus is estimated in percentages. To determine the degree to which two categorical variables, such as viral load and cervical cancer stage, are linked, the Chi-square (χ^2) was used. Some data were discovered to be quantitative continuous outcome variables with a normally distributed distribution. The mean, SD (standard deviation), and SE (standard error) are used to characterize such variables (standard error). An unpaired Student's t test was performed to examine the differences between patients with cases and healthy controls when the data were normally distributed. If the p value of an estimate was less than the level of significance of 0.05, it was considered statistically significant.

Results

During the current study, blood samples were collected from 120 COVID-19 patients, their ages ranged between 20 and 87 years, with an average age of 53.2 years, and most of them were males (ople $N=80$, 67%). Thirty-three percentage of the participants were females ($N=40$) opleas in Table 1 and Fig. 1. Blood samples were collected from healthy people as a control group, their ages ranged from 19 to 87 years, with an average age of 51.68 years, as seen in Table 1, which did not show significant differences in the age between patients and healthy individuals. The results in Fig. 2 showed that the rate of infection with the Corona virus increases in older individuals, as most patients in the intensive care unit were within the age group 75–87 years (34%), followed by 65–75 years (22%) and 55–65 years (21%). On

Table 1 Comparison of patients and healthy control group according to age mean and gender

Age/year	Patients	Control	*p* value
Range	20–87	19–87	
Mean ± SD	53.2 ± 8.22	51.68 ± 7.77	0.562 [NS]
SE	2.05	3.11	
	N (%)	*N* (%)	*p* value
Female	40 (33)	24 (40)	0.077 [NS]
Male	80 (67)	36 (60)	0.069 [NS]
Total number	120	60	

NS no significant ($p > 0.05$), *SD* standard deviation, *SE* standard error, *N* number

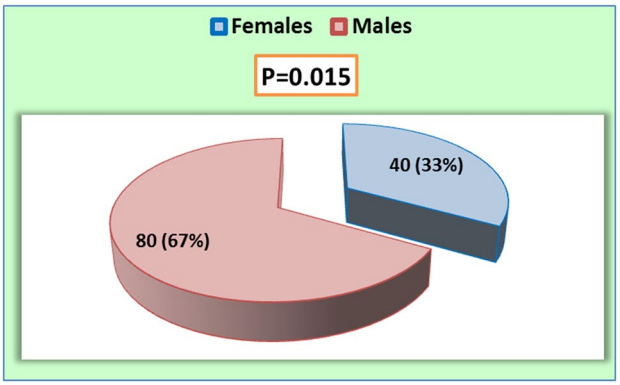

Fig. 1 Distribution COVID-19-infected patients according to gender

the other hand, the studied data showed that 39% of patients suffer from diabetes as in Fig. 3.

To know the impact of the Corona virus on the activity and functionality of organs especially on the liver and blood cells, the current study, was focus on evaluating the level of some vital indicators that could be among the basic medical examinations to determine the health status of patients infected with the Corona virus. In Table 2, the mean of serum D-dimer appeared at a high rate among COVID-19-infected persons (851.68 ng/mL) compared with the healthy subjects (208.69 ng/mL), with clear significant differences ($p = 0.002$). An obvious rise appeared in liver enzymes (65.518 U/L and 58.36 U/L for GPT and GOT, respectively) compared with the healthy subjects (27.128 U/L and 27.179 U/L for GPT and GOT, respectively), accompanied by statistical differences ($p = 0.009$ and 0.0171 for GOP and GOT, respectively) also showed a clear increase in the rate of CRP concentration in the patients (24.63 mg/L) is compared with healthy subjects (9.11 mg/L) ($p = 0.0171$). While there was a slight statistically unclear increase in the

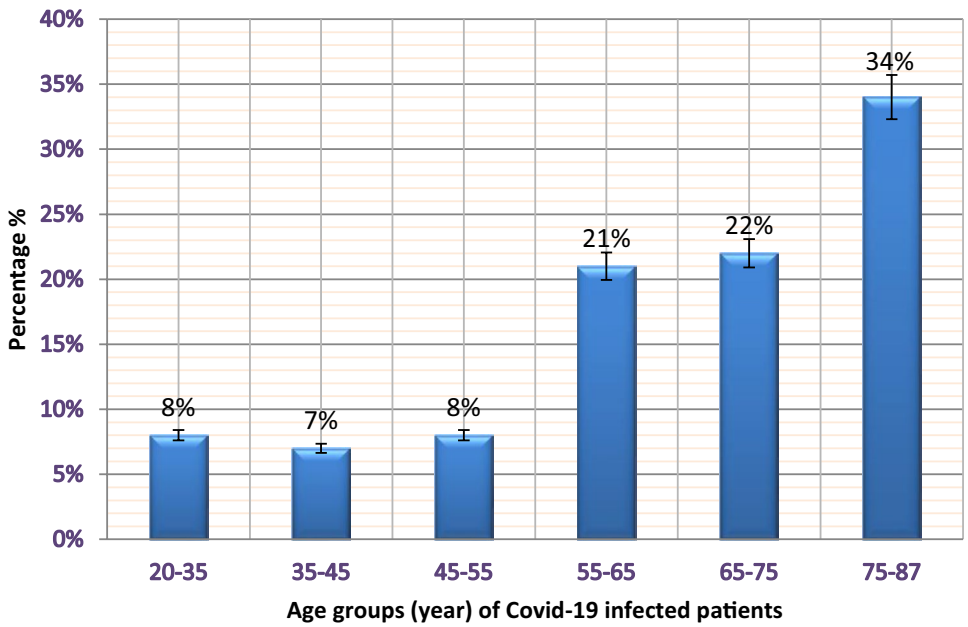

Fig. 2 Prevalence of COVID-19 infection according to age range or groups

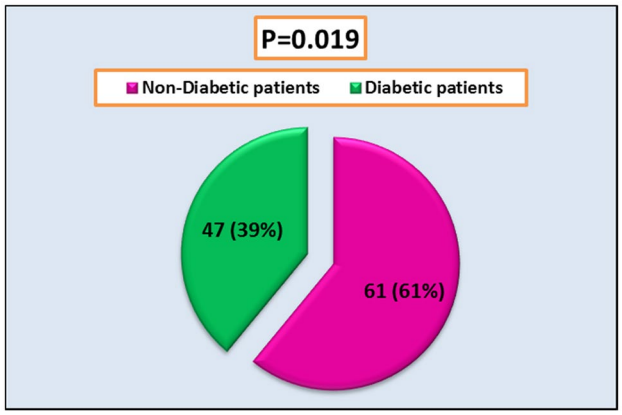

Fig. 3 Frequency diabetic mellitus among COVID-19-infected patients

Table 2 Comparison between mean serum level of serum D-dimer, TSB, GPT, GOT and CRP of cases and controls

Biomarkers	Patients	Control	*p* value
D-dimer (ng/mL)	851.68	208.69	0.002*
TSB (Mmol/L)	13.331	10.01	0.181 [NS]
GPT (U/L)	65.518	27.128	0.009*
GOT (U/L	58.36	27.179	0.0171*
CRP (mg/L)	24.63	9.11	0.0119*

NS no significant ($p > 0.05$)

*Significant association ($p < 0.05$)

concentration of TSB (13.331 Mmol/L) in the COVID-19 patients compared to healthy people (10.01 Mmol/L).

Table 3 demonstrates that the average serum concentration of D-dimer, GOT and CRP was high in diabetic COVID-19 patients (980.66 ng/mL, 67.71 U/L, and 27.06 mg/L, respectively) compared with non-diabetic COVID-19 patients (791.17 ng/mL, 54.023 U/L, and 20.11 mg/L, respectively) ($p < 0.05$), while the situation was inverse for the average concentration of TSB and GPT when their average concentrations were lowered in diabetic COVID-19 patients (11.89 Mmol/L and 59.79 U/L, respectively) ($p > 0.05$).

As shown in Table 4, the optimum cut-off values for serum D-dimer, TSB, GPT, GOT, and CRP of COVID-19-infected diabetic patients were ≥ 6500 ng/mL, ≥ 350 Mmol/L, ≥ 133 U/L mg/L, ≥ 150 U/L, and ≥ 15.22 mg/L, respectively. As they are represented a perfect test for predicting COVID-19-infected diabetic patients with 100% sensitivity and specificity, i.e. can establish a possible diagnosis of COVID-19 infection of diabetic patients with 100% confidence. At the same time, testing the optimum cut-off values for serum D-dimer, TSB, GPT, GOT and CRP of COVID-19-infected non-diabetic patients were ≥ 6100 ng/mL, ≥ 400 Mmol/L, ≥ 140 U/L mg/L, ≥ 130 U/L, and ≥ 11.36 mg/L, respectively, and they were shown to be associated with a perfect test for predicting COVID-19 patients among non-diabetic patients. Hence, positive serum D-dimer, TSB, GPT, GOT and CRP at these cut-off values are 100% sensitive and specific as shown in Table 5.

Table 3 Comparison of mean serum level of D-dimer, TSB, GPT, GOT and CRP among diabetic and non-diabetic COVID-19-infected patients

Biomarkers	Non-diabetic patients	Diabetic patients	Control	X^2	*p* value
D-dimer (ng/mL)	791.17	980.66	208.69	28.37	0.001*
TSB (Mmol/L)	15.55	11.89	10.01	1.055	0.204 [NS]
GPT (U/L)	68.17	59.79	27.128	5.48	0.0381*
GOT (U/L	54.023	67.71	27.179	7.09	0.0288*
CRP (mg/L)	20.11	27.06	9.11	4.87	0.0332*

NS no significant ($p > 0.05$)

*Significant association ($p < 0.05$)

Table 4 Validity parameters for the optimal cut-off value for selected quantitative indices when used as a test to diagnosis COVID-19-infected diabetic patients differentiating it from healthy control

Positive if ≥ cut-off value	Sensitivity%	Specificity %	Accuracy%	PPV%	DP%
D-dimer ≥ 6500 ng/mL	100.0	100.0	100.0	100.0	50.00
TSB ≥ 350 Mmol/L	100.0	100.0	100.0	100.0	50.00
GPT ≥ 133 U/L	100.0	100.0	100.0	100.0	50.00
GOT ≥ 150 U/L	100.0	100.0	100.0	100.0	50.00
CRP ≥ 15.22 mg/L	100.0	100.0	100.0	100.0	50.00

PPV positive predictive value, *DP* disease prevalence

Table 5 Validity parameters for the optimal cut-off value for selected quantitative indices when used as a test to diagnosis COVID-19-infected non-diabetic patients differentiating it from healthy control

Positive if ≥ cut-off value	Sensitivity%	Specificity %	Accuracy%	PPV%	DP%
D-dimer ≥ 6100 ng/mL	100.0	100.0	100.0	100.0	60.00
TSB ≥ 400 Mmol/L	100.0	100.0	100.0	100.0	60.00
GPT ≥ 140 U/L	100.0	100.0	100.0	100.0	60.00
GOT ≥ 130 U/L	100.0	100.0	100.0	100.0	60.00
CRP ≥ 11.36 mg/L	100.0	100.0	100.0	100.0	60.00

PPV positive predictive value, *DP* disease prevalence

Discussion

The current study's findings revealed that the incidence of coronavirus infection is rising among the elderly, particularly among males, and this observation was echoed by Vrillon et al. (2020), who reported that COVID-19 infection was more common in older males and that the factors associated with death were male sex, history of cardioneurovascular disease, dyspnea, and low blood sugar. Richardson et al. treated 5700 people in New York with COVID-19. Who discovered 60.6% mortality in 155 patients aged 80–89 years and 63.2% mortality in 44 subjects aged more than 90 years (Vakili-Samiani et al. 2021; Richardson et al. 2020). Early reports from China indicated a rise in the severity of disease and mortality among individuals aged 60 and up (World Health Organization 2020b), and a similar trend was observed in Europe, with mortality rates as high as 10% in adults aged 70 and up compared to 1% in young adults (Onder et al. 2020). Older patients had a higher demand for intensive care unit (ICU) admission and mechanical breathing than younger individuals (Hanan et al. 2021; Liu et al. 2020). These findings match the clinical outcomes of other respiratory viral diseases such as influenza and severe acute respiratory syndrome (SARS). When compared to younger individuals, seasonal flu is known to affect the elderly and those with numerous comorbidities more severely and is related to higher mortality (Walker et al. 2020; Mertz et al. 2013). In current data, the mean of serum D-dimer, TSB, GPT, GOT and CRP of D-dimer test increased in COVID-19 patients compared to healthy individuals and the elevation of D-dimer. TSB and CRP were more pronounced among diabetic patients with COVID-19 disease, while their liver enzyme concentrations decreased.

D-dimer test appropriately shows the presence of blood clots in the patient's body, even in lungs, who are having severe forms of COVID-19. In such conditions, the patient may face shortness of breath and difficulty in breathing. A D-dimer test is the ultimate solution in such cases. Therefore, the present research is in agreement with the study of Mishra et al., patients with diabetes exhibited higher D-dimer levels that were statistically significant (Ngafwan et al. 2021; Mishraa et al. 2020), with peak D-dimer levels of 1509 2420 ng/mL (mean SD) versus 515 624 ng/mL (mean SD) in adults without diabetes. When clinical characteristics and risk factors are unclear, clinicians face a substantial challenge in improving outcomes in patients with COVID-19 and underlying diabetes mellitus (Jalil et al. 2021c; Zhang et al. 2021). However, a recent small retrospective single-center observational research in China looked at the clinical features and outcomes of 48 individuals with severe COVID-19 and diabetes and showed no significant difference in the frequency of problems between diabetic and non-diabetic patients. As a result, larger sample numbers and well-designed clinical studies are still required to identify the specific risk factors and representative characteristics (Yan et al. 2020).

Diabetes mellitus plagued roughly one-third of patients who died with COVID-19 in recent studies from China and the United States (Zhou et al. 2020; Lim et al. 2021); patients with diabetes had a twofold increase in fatal outcomes than those without (Marofi et al. 2021b; Remuzzi and Remuzzi 2020). Patients with diabetes were more likely to require invasive mechanical ventilation, be hospitalized in the ICU, and experience severe renal damage when compared with non-diabetic patients (Lim et al. 2021). COVID-19's high severity in diabetes might be due to increased susceptibility to infections, dysregulation of the innate immune response, or abnormalities in cell-mediated immunity (Bornstein et al. 2020). Type 2 diabetes is defined by increased levels of flogosis mediators such as TNF, CRP, IL-1, IL-6, leptin, and resistin, as well as an abnormal synthesis of liver enzymes such as GOT and GPT. Furthermore, (Randeria et al. 2019) type 2 diabetes is associated with increased oxidative stress, platelet aggregation, and endothelial dysfunction. All these alterations might be the underlying causes of diabetes-related chronic diseases such as coagulation, liver disease, hypertension, and cardiovascular disease. Severe hyperglycemia during infection can lead to a substantial increase in inflammatory mediators such as cytokines, CRP, and TSB, which can lead to multiple organ failure and severe cardiovascular events (Bornstein et al. 2020).

The current findings are in agreement with the finding of Paliogiannis et al. that severe COVID-19 patients have significantly higher bilirubin concentrations (SMD: 0.48 mol/L; 95% CI 0.11–0.85 mol/L, $p = 0.012$) (Abosaooda et al. 2021;

Paliogiannis and Zinellu 2020). Unfortunately, there is a paucity of information on the role of TSB, liver enzymes, and their effect in diabetic patients infected with the Corona virus, therefore, more study is required to confirm the current findings.

Conclusion and recommendation

These findings suggest that diabetic COVID-19 patients are more prone to coagulation problems, liver problems, and inflammatory storms. As a result, COVID-19 infection combined with diabetes probably increases the risk of hypercoagulability and organ failure, both of which have a poor prognosis. However, more research on the clinical significance of these results is required. Optimum cut-off values for serum D-dimer, TSB, GPT, GOT and CRP of Covid-19 infected diabetic patients are $\geq$ 6500 ng/mL, $\geq$ 350 Mmol/L, $\geq$ 133 U/L mg/L, $\geq$ 150 U/L, and $\geq$ 15.22 mg/L, respectively, since they are represented a perfect test for predicting COVID-19-infected diabetic patients with 100% sensitivity and specificity.

Declarations

Conflict of interest All authors declare, have no conflict of interest. This study was self-funded.

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