Brazilian Journal of Biology®

ISSN 1519-6984 (Print)
ISSN 1678-4375 (Online)

Original Article

D-dimer and HbA1c levels findings in COVID-19 Iraqi patients

Descobertas dos níveis de D-dímero e HbA1c em pacientes iraquianos com COVID-19

K. S. Al-Jubury[a], O. Abdulmunem K.[a*], D. K. J. Alshareef[a], M. Al-Jubury[b] and M. I. Jameel[c]

[a]Iraqi Ministry of Health, Baghdad Medical City, Training and Human Development Center, Baghdad, Iraq
[b]University College Dublin, College of Science, Dublin, Ireland
[c]Koya University, Faculty of Science and Health, Department of Medical Microbiology, Koya, Kurdistan Region, Iraq

Abstract

On March 11, 2020, the World Health Organization (WHO) declared a new coronavirus infection caused by the SARS-CoV-2 virus as a pandemic, making it the 11th pandemic of the 20th and 21st centuries. This study investigated the clinical and laboratory results (D-dimer, conventional coagulation, and HbA1c biomarker concentrations) of 150 patients (75 male and 75 female) with confirmed COVID-19 pneumonia and 50 controls (25 male and 25 female). For disease diagnosis, all COVID-19 patients were given a Real-Time Reverse Transcription Polymerase Chain Reaction Assay (RT-PCR). The findings revealed that D-dimer and HbA1c levels in COVID-19 patients were significantly higher (P 0.001) at the time of admission; In COVID-19 patients, there was also a strong correlation between D-dimer levels and HbA1c levels (P 0.001). In conclusion, COVID-19 patients are more likely to have a poor prognosis if their D-dimer and HbA1c levels remain uncontrolled over a lengthy period. To lower the likelihood of a bad prognosis in COVID-19, patients with higher levels of D-dimer and HbA1c should be continuously monitored.

Keywords: COVID-19, D-dimer, HbA1c, RT-PCR.

Resumo

Em 11 de março de 2020, a Organização Mundial da Saúde (OMS) declarou uma nova infecção por coronavírus causada pelo vírus SARS-CoV-2 como uma pandemia, tornando-a a 11ª pandemia dos séculos XX e XXI. Este estudo investigou os resultados clínicos e laboratoriais (D-dímero, coagulação convencional e concentrações de biomarcadores HbA1c) de 150 pacientes (75 homens e 75 mulheres) com pneumonia por COVID-19 confirmada e 50 controles (25 homens e 25 mulheres). Para o diagnóstico da doença, todos os pacientes com COVID-19 receberam um Ensaio de Reação em Cadeia da Polimerase com Transcrição Reversa em Tempo Real (RT-PCR). Os achados revelaram que os níveis de D-dímero e HbA1c em pacientes com COVID-19 foram significativamente maiores (P 0,001) no momento da admissão. Em pacientes com COVID-19, também houve uma forte correlação entre os níveis de D-dímero e os níveis de HbA1c (P 0,001). Em conclusão, os pacientes com COVID-19 têm maior probabilidade de ter um prognóstico ruim se seus níveis de D-dímero e HbA1c permanecerem descontrolados por um longo período. Para diminuir a probabilidade de um mau prognóstico na COVID-19, os pacientes com níveis mais altos de D-dímero e HbA1c devem ser monitorados continuamente.

Palavras-chave: COVID-19, D-dímero, HbA1c, RT-PCR.

1. Introduction

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is the name given to a new human coronavirus that was found in Wuhan, China, in December 2019 by the International Committee on Taxonomy of Viruses (ICTV) (Yu et al., 2020). The WHO recently designated the SARS-CoV-2 sickness as coronavirus disease 2019 (COVID-19). To more accurately classify patients who could need hospital or intensive care unit admission, a risk stratification based on clinical, laboratory, and radiological considerations look essential. Several laboratory biomarkers are first utilized to predict or diagnose COVID-19 infections but their accuracy in determining the prognosis and severity of infections, as well as the concentrations at which they produce frightening results must be assessed (Hashem et al., 2021). The majority of COVID-19 cases start with symptoms like fever, exhaustion, and upper respiratory issues like coughing, loss of taste and smell, and shortness of breath before they progress to more serious issues like acute respiratory distress syndrome (ARDS), pneumonia, and multiorgan failure (Yahya et al., 2021).

The Medical City Teaching Hospital (MCTH), Baghdad, reported the first protocol adopted by the Iraqi MOH in April 2020 (Allawi et al., 2020). Iraq is comprised of two major groups of people: those who are illiterate and ignorant about the epidemic and thought it was a great

*e-mail: osamamunem@gmail.com
Received: August 11, 2022 – Accepted: November 18, 2022

political game because of the country's continuing protests, as well as a knowledgeable group that holds the view that the virus exists, is lethal, and should be handled carefully (Al-Kuraishy, 2021).

Contrarily, growing evidence indicated that people with an illness that was fast getting worse might be experiencing a significant autoimmune reaction. As a result, it was advised to utilize immunomodulating medications such as dexamethasone, tocilizumab, and anakinra in patients with severe COVID-19 infections (Darweesh et al., 2021). Several studies are currently being conducted to better understand the clinical characteristics and pathophysiology of COVID-19, the patient's demographics (such as age and gender), and the effects of different treatment regimens on mortality and morbidity (Tsatsakis et al., 2020; Khan et al., 2020; Gudadappanavar and Benni, 2020; Jin et al., 2020; Peckham et al., 2020; Al-Zidan, 2020). According to reports, roughly half of the patients had higher-than-normal D-dimer levels, which are associated with a poor prognosis (Yu et al., 2020). Therefore, in accordance with our experience, thrombus development and treatment response may be evaluated using biomarkers that can identify thrombus formation at an earlier stage. However, inconsistent information has been published with respect to hospital pre-admission or at-admission assessments of glycaemic control in relation to COVID-19-related mortality in diabetic patients (Prattichizzo et al., 2022).

The significance of HbA1c for the care of COVID-19 patients is still unknown, even though this backdrop suggests it is wise to examine glycosylated hemoglobin (HbA1c) upon hospital admission for COVID-19. HbA1c reflects the average level of glycemia during the preceding 2 to 3 months. Scholars have identified a substantial relationship between COVID-19 patients' hospital-entry HbA1c level and disease progression or mortality, whereas others have not (Valle et al., 2022). The present study aims to highlight D-dimer and HbA1c levels in COVID-19 Iraqi patients at Baghdad Medical City and compare them to the recovery phase.

2. Methods

2.1. Study design and participants

This research was carried out at Baghdad Medical City which is a range of teaching and hospital facilities in the period between the January and May 2022. Patients admitted to Baghdad's Medical City Teaching Hospital (MCTH) with confirmed COVID-19 by RT-PCR (ARCHITECT *c*4000) test were chosen for this study to detection of the viral RNA by Mag-Bind® FFPE DNA/RNA 96 Kit, Germany. On admission and throughout the hospital stay, samples for laboratory tests were collected. An automatic hematology analyzer was used to collect peripheral venous blood for a routine blood test. COVID-19 was diagnosed based on at least two positive RT-PCR test results obtained from MCTH and Central Laboratories (Yu et al., 2020). Our investigation included 150 cases (75 men and 75 women) and 50 negatives as control. Three different researchers gathered the demographic data, and clinical features of each patient including their medical history, comorbidities, exposure history, signs and symptoms, and laboratory results from the e-medical record systems of these two centres.

2.2. Study groups

Based on this outcome, groups were divided into:

- Group 1: 75 male COVID-19 patients.
- Group2: 75 female COVID-19 patients.
- Group3: 25 male negatives (control).
- Group3: 25 female negatives (control).

2.3. Ethical approval

The ethical committee of the Public Administration, Baghdad Medical City, Baghdad, Iraq, approved the study protocol (IRB no. 23977). Following an IRB waiver of consent, patients' records were reviewed retrospectively. Information that could lead to the identification of patients was covered up by assigning a code to each patient to maintain data privacy and confidentiality as provided by the guidelines of the Helsinki Declaration.

2.4. Statistical analysis

The RStudio version 1.2.5033 was used to perform all the meta-analyses in this study, with p-values <0.01 being considered significant for all of the meta-analyses. The Wilcoxon signed-rank test was used to perform the non-parametric statistical hypothesis tests for the test of significance between different groups. Continuous measurements were presented as mean ± SD for the normally distributed datasets, or as median Inter quartile range (IQR) if they were not normally distributed. Furthermore, categorical variables were expressed as counts (%). Spearman's correlations analysis was used to evaluate the relationship between the biomarkers.

3. Result

All patients on admission were confirmed by RT-PCR as this facility was a designated referral center for the novel coronavirus disease. A total of 362 patients were screened at MCTH between Jan. 20 and Jun 30, 2022, and out of this number, 150 cases (75 men and 75 women) were classified as shown in Table 1. The patients were between the ages of 19 and 61 (Figure 1). Regarding the presenting symptoms, fever and lower respiratory tract (LRT) symptoms, particularly a dry cough, predominated. As shown in Table 1, the percentages of dyspnea, cough, and fever ranged from 33% to 62%, and 67%, respectively. Most of the COVID-19 patients experienced a fever, cough, myalgia, chest pain, shortness of breath, diarrhea, inappetence, and exhaustion when they were first admitted. In addition, there were several variations in the laboratory results.

The mean age of the recruited patients was 36.7±9.1 years with a range of 19 to 61 years; the median age is 36 IQR (Q1=29.0, Q3=42.0) as shown in Table 1. In both groups (Male and Female), the mortality rate was 0/150 (0%) in mild-moderate patients.

Table 1. Clinical and demographic characteristics of COVID-19 patients included in the study at the time of admission.

	Patients Number (*n* = 150)
Age (years)	
< 45	**115 (76.6%)** **
≥45	**35 (23.3%)** **
Mean ± SD	**36.7±9.1***
Symptoms, n (%)	
Dyspnea	**50 (33%)** **
Cough	**93 (62%)** **
Fever	**100 (67%)** **

*Mean ± SD; standard deviation; n ˛ 150. **Percentage %.

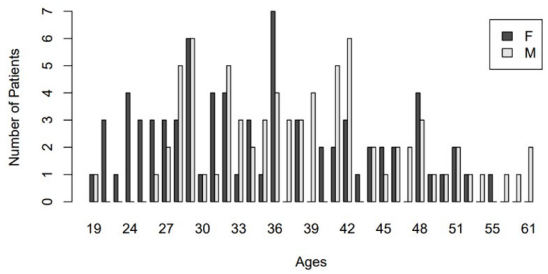

Figure 1. Patients are sub-classified according to age and gender (*n*= 150).

Spearman's correlations analysis was conducted between the levels of D-dimer and HbA1c biomarkers in the patients to establish a correlation between D-dimer and HbA1c levels (see Table 2).

A positive correlation was established between the levels of D-dimer and HbA1c levels in COVID-19 patients in this study (P 0.001). In both groups, there were positive relationships between D-dimer and HbA1c levels (Acute phase and Recovery phase). A simultaneous examination of the relationships between these markers and the outcomes of therapies in COVID-19 patients showed that the D-dimer and the same biomarkers earlier mentioned continued to have robust relationships, as shown in Table 3. The findings of the D-dimer test for the acute phase showed high statistically significant differences (p<0.001) with recovery phase groups (Table 3). For HbA1c, the acute phase was statistically significant in comparison with the recovery phase (p<0.001).

Figure 2A-2D shows the distributions of D-dimer and HbA1c levels of COVID-19 patients with various clinical staging who were hospitalized but survived. Clinical staging revealed that the levels of D-dimer and HbA1c increased significantly with increasing severity of COVID-19 at admission. The median D-dimer at the acute phase = 2.920 mg/L IQR (Q1= 2.223, Q3= 3.670) while in recovery phase = 1.470 mg/L IQR (Q1= 1.090, Q3= 2.007). The median HbA1c for the acute phase = 5.950 mg/L IQR (Q1= 5.400, Q3= 6.575) while in recovery phase = 6.900 mg/L IQR (Q1= 6.000, Q3= 8.000).

Table 2. Compare D-dimer with another biomarker of COVID-19 patient Spearman's correlation test (n = 150).

D-dimer (mg/L)	Acute phase	Recovery phase
HbA1c	p<0.001*	p<0.001*

*The correlations between D-dimer Hemoglobin (HbA1c) at acute and recovery phase in COVID-19 patients P<0.001.

Table 3. Wilcoxon signed rank test for D-dimer and HbA1c levels in both acute and recovery phases.

	D-dimer (mg/L)	HbA1c
Acute phase	p<0.001*	p<0.001*
Recovery phase	p<0.001*	p<0.001*

*The Wilcoxon signed rank test between acute phase and recovery phase for D-dimer and HbA1c levels in COVID-19 patients P<0.001, number size 150.

As stated earlier, there was a correlation between D-dimer levels and HbA1c indicators. Then, the exact relationship between D-dimer and HbA1c levels in COVID-19 patients was evaluated and the result showed that both HbA1c levels and D-dimer levels dropped significantly following therapy (Figure 3).

4. Discussion

Since it was first described in December 2019 in Wuhan, China, the COVID-19 pandemic infection has become a global health concern. This study was carried out on COVID-19-infected patients at Baghdad Medical City in Baghdad, Iraq, as a representative sample of COVID-19-infected patients in Iraq. In this study, we followed up on 150 COVID-19-infected patients ranging in age from 19 to 61 years. Their hemoglobin and D-dimer levels, as well as their primary symptoms, were investigated.

One of the fragments formed when plasmin cleaves fibrin to dissolve clots is called a D-dimer. The assays are frequently employed as a step in a diagnostic process to rule out the presence of thrombosis. However, the levels of plasma D-dimer are also increased by any pathologic or non-pathologic procedure that boosts fibrin synthesis or breakdown. Additionally, COVID-19 patients may experience increased blood viscosity due to heavy sweating, high fever, and hypercoagulable conditions as a result of the activation of the coagulation system (Tang et al., 2020). Examples of such conditions include arterial thrombosis, deep vein thrombosis/pulmonary embolism, disseminated intravascular coagulation, cancer, chronic liver disorders, pregnancy, inflammation, post-trauma and post-surgery state, and vasculitis (Linkins and Lapner, 2017; Yao et al., 2020).

Tang et al. (2020) reported that among 183 COVID-19 patients, cases with severe symptoms had D-dimer levels that were almost 3.5 times greater than those of their non-severe peers. This was also supported by Yao et al. (2020) who noted that patients with severe illnesses had considerably higher D-dimer levels than other patients based on a retrospective

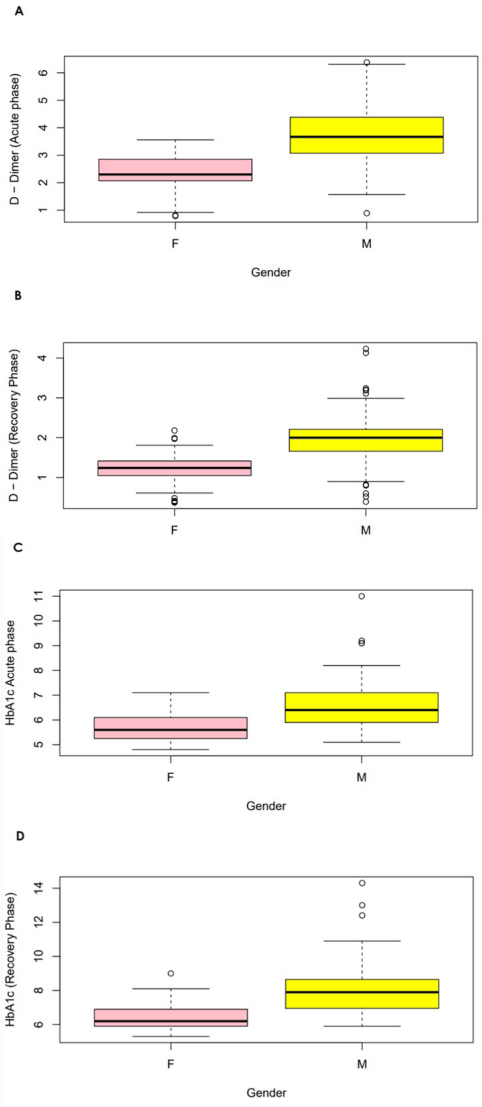

Figure 2. Box plot chart showing the Inter quartile range of D-dimer and HbA1c value relationship with gender, a: D-dimer value in the acute phase; b: D-dimer value in recovery phase; c: HbA1c value in the acute phase; d: HbA1c value in the recovery phase. Number size 150 (75 male and 75 female).

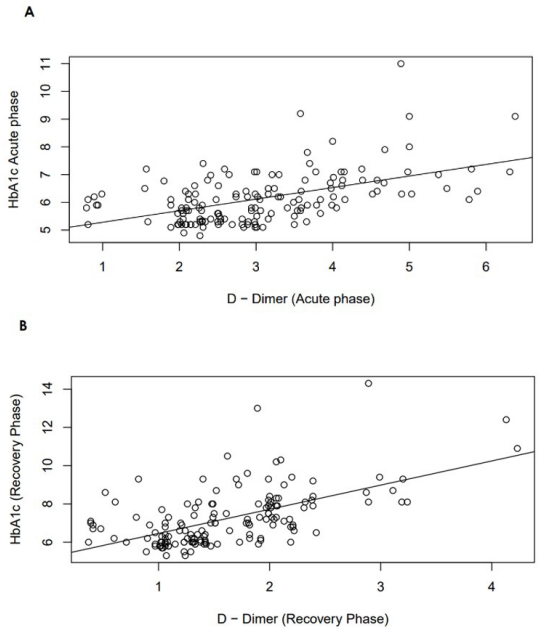

Figure 3. Scatter plot showing a correlation between; a: D-dimer with HbA1c in case of Acute phase; b: D-dimer with HbA1c in case of the Recovery phase.

analysis of 248 COVID-19 patients at a Wuhan hospital. In severe and critical cases of COVID-19 infection, HbA1c has been recognized as an acceptable diagnostic measure for the rapid determination of the background glucose metabolic state. HbA1c level upon admission can aid in identifying patients that are yet to be diagnosed but are at high risk of developing diabetes as it is one of the most prevalent comorbidities in COVID-19 patients associated with poor outcomes (Liu et al., 2021). The considerable variability of the dichotomous variable HbA1c in the meta-analysis was acceptable because the I2< 50% value was acceptable, and the sensitivity analysis demonstrated the robustness and reliability of the outcome. Two prior population-based investigations revealed that those with HbA1c > 7.5 percent had a greater rate of COVID-19-related death (Zhu et al., 2021). Zhu et al. (2021) reported higher levels of inflammation markers, such as C-reactive protein, interleukin-6, tumor necrosis factor-a, procalcitonin, and ferritin, as well as D-dimer and fibrinogen in patients with high levels of HbA1c. The outcome of the present study suggests that increased levels of D-dimer and HbA1c, as well as disseminated coagulopathy, are frequent in severe cases of COVID-19 infection, just as found in other severe infections like Ebola, Zika, systemic human immunodeficiency virus, and Chikungunya virus infections. Therefore, urgent research is aimed at determining the usefulness of adjunctive antithrombotic therapies (such as anticoagulants, thrombomodulin, and antithrombin) in the management of severe COVID-19 infections. This study provides scientific evidence that high levels of HbA1c and D-dimer are predictive of COVID-19 in-hospital mortality. COVID-19 patients with high D-dimer and HbA1c levels are advised to heed their doctor's instructions and rigorously monitor and control the level of their blood sugar. Clinicians can employ D-dimer and HbA1c levels as early COVID-19 risk assessment tools.

5. Conclusion

Elevated baseline D-dimer and HbA1c levels in COVID-19 infections are associated with inflammation but have little predictive value for thrombosis. COVID-19 patients should have their D-dimer levels constantly monitored because abnormal changes in HbA1c and D-dimer levels may indicate the need for anticoagulant therapy.

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