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Original Research

Enoxaparin Effect on Interleukin-10 Levels in Iraqi Patients with COVID-19: A Case–Control Study

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Abstract

Background: Coronavirus disease 19 (COVID-19), an infectious disease resulting from a virus known as severe acute respiratory syndrome coronavirus 2 (SARS-COV-2), was discovered in China in 2019 and causes several mild to moderate respiratory conditions. This study aimed to reveal the changes in serum interleukin-10 (IL-10) and other parameters in Iraqi COVID-19 patients compared with healthy controls by studying the effects of enoxaparin and evaluating the potential of IL-10 as a disease activity marker. **Methods**: This was a case–control study that included 180 samples: 90 patients hospitalized with COVID-19 from November 2022 to 20 April 2023 (40 patients had never used enoxaparin, whereas 50 patients had taken enoxaparin) and 90 healthy, age- and sex-matched control. There were 44 female patients and 46 male patients. The mean age of the patients and controls was 53.8 years *vs.* 50.8 years, respectively. The sandwich enzyme-linked immunosorbent assay (ELISA) method was used to measure IL-10 levels, while other parameters were assessed using the colorimetric method. **Results**: The results of the study indicated highly significant changes between the patients and healthy controls in IL-10, D-dimer, and C-reactive protein (CRP) levels, as well as liver and renal functions. These findings elucidated a significant change between enoxaparin patients and non-enoxaparin patients in IL-10, D-dimer, and CRP levels. However, the liver and renal functions were not significantly altered. The Spearman's rank correlation test investigated the relationship between serum IL-10 and CRP. **Conclusions**: The results displayed a strong positive relationship between IL-10 and CRP. There were no significant differences between the other analyzed parameters; consequently, the patients had higher concentrations of IL-10, D-dimer, and some other parameters than the healthy controls. Additionally, IL-10 may be used as a marker of disease activity. Enoxaparin will likely help control IL-10 and D-dimer concentrations in patients since IL-10 levels decreased in patients treated with enoxaparin.

Keywords: COVID-19; interleukin-10; enoxaparin; D-dimer; C-reactive protein

1. Introduction

Coronavirus disease 19 (COVID-19) is an infectious viral disease known as severe acute respiratory syndrome coronavirus 2 (SARS-COV-2), which was discovered in Wuhan, Hubei Province, China, in December 2019 [1]. The biphasic effects of the COVID-19 disease began with an innate immune response that subsequently developed into a response of adaptive immunity. However, individuals could experience a severe immune response and develop serious symptoms. The pathophysiology of SARS-CoV-2 is distinct from those of its predecessors, Middle East Respiratory Syndrome (MERS) and SARS-CoV-1; poor outcomes were associated with viremia and large viral loads in the lung at the time of death [2–4]. A system of categorization for SARS-CoV-2 variation classification was developed by the Centers for Disease Control and Prevention (CDC) with the SARS-CoV-2 Interagency Group (SIG). These determine the degree of threat to public health, represented by four types of classification: Variants are variants of high consequence (VOHC), variants of concern (VOC), variants of interest (VOI), and variants being monitored (VBM) [5]. The COVID-19 virus is a bat-borne zoonotic that causes severe pneumonia, prolonged fever, loss of taste or smell, dry cough, dyspnea, myalgia, chills, headaches, and malaise among humans [6]. However, the incidence of comorbidities such as cancer, diabetes, hypertension, and cardiovascular disease correlates to the severity of COVID-19 infection [7].

Measuring circulating D-dimer concentrations in clinical practice is a sensitive biomarker for identifying thrombotic disorders such as pulmonary embolism. As a result, measuring D-dimer levels in patients with COVID-19 helps to rapidly identify those with severe conditions, pulmonary consequences, and a significant risk of prothrombotic conditions combined with venous thromboembolism [8]. This helps with risk classification and the early implementation of treatment strategies, such as using enoxaparin, an anticoagulant that could lower morbidity and death associated with COVID-19 [9].

In most diagnosed COVID-19 cases, patients with severe and critical conditions often show increased concentrations of inflammatory cytokines, including interleukins (ILs) [10]. However, some cytokines act as anti-inflammatory factors, such as interleukin-10 (IL-10), and

can reduce the inflammation process during the infection [11]. As a thromboembolic-inhibiting drug, enoxaparin is recommended for COVID-19 patients, and its low-molecular-weight heparin drug appeared to be effective in various venous and arterial thromboembolic disorders [12, 13]. Polypharmacology and medication repurposing provide new opportunities for rationally designing and identifying therapeutics for the COVID-19 pandemic through identifying medications that may interact with target proteins [14,15]. Therefore, compared with healthy controls, this study aimed to evaluate changes in serum IL-10 levels alongside some other parameters in Iraqi COVID-19 patients. Additionally, to study the effects of enoxaparin medication on Iraqi COVID-19 patients and evaluate IL-10 as a potential disease activity marker.

2. Materials and Methods

2.1 Subjects

This was a case–control study that included 180 samples: 90 with COVID-19 (46 males and 44 females) were treated at Dharri Al-Fayyad General Hospital (40 patients had never used enoxaparin anticoagulant, whereas 50 patients had taken enoxaparin anticoagulant previously). A further 90 age- and sex-matched patients were included as controls. Blood samples were collected, divided into sodium citrate tubes and gel tubes, centrifuged for 15 min, and frozen at (–20 °C). The research was approved by the University of Technology (UOT) Biological Research Ethical Committee, with the registration number AS-AC 44728, and performed in accordance with the requirements of the World Medical Association Declaration of Helsinki Ethical Principles (2013). Informed consent was obtained from patients willing to participate in the trial. The descriptive statistics of patients are illustrated in Table 1.

Table 1. Descriptive statistics of patients.

Characteristics	Patients n = 90
Age	n (%)
20–40 years	18 (20)
40–60 years	40 (45)
>60 years	32 (35)
Gender	n (%)
Female	44 (49%)
Male	46 (51%)
Treatment	n (%)
Patients receiving enoxaparin	40 (44%)
Patients not receiving enoxaparin	50 (56%)
Continuous positive airway pressure (CPAP)	n (%)
Yes	33 (37)
No	57 (63)

The selection of COVID-19 patients was conducted according to the National Health and Health Committee [16] at Dharri Al-Fayyad General Hospital from 11 November 2022 to 20 April 2023. Patients were divided according to whether they had previously administered the enoxaparin anticoagulant. All patients were over 18 years old. Every patient who took part in the study provided informed permission.

The exclusion criteria included all individuals who had a history of acute pulmonary embolism, chronic inflammatory diseases, such as rheumatological diseases, and liver and kidney failure, as well as pregnant or lactating women. Additionally, patients with diseases such as cardiovascular disease, diabetes, and hypertension that influence biomarker readings were excluded.

2.2 Methods

In this study, the Roche Cobas e411 (Roche Diagnostics GmbH, Mannheim, Germany) instrument was used to conduct several laboratory tests, including blood urea nitrogen, creatinine, aspartate, and alanine transaminase, D-dimer, and C-reactive protein (CRP) levels.

Human serum IL-10 concentrations were measured using the sandwich ELISA method (Cat. No.: E-UNEL-H0084; Elabscience, Houston, TX, USA), which increases the specificity and sensitivity of the antigen by using a purified antibody to capture it in the serum.

2.3 Statistical Analysis

The Statistical Package for Social Sciences (SPSS) (version 26.0, Armonk, NY, USA: IBM Corp.) was utilized for data analysis. Descriptive statistics of patients are presented as numbers (percentages). Results are presented as mean $\pm$ standard error mean (SEM). Independent sample *t*-tests were utilized to compare the data. The Spearman's rank correlation test was considered. The level of significance was set at $p < 0.05$.

3. Results

3.1 Main Results

The characteristics of COVID-19 patients and healthy controls are presented in Table 2, and the results depict a significant change between patients and healthy controls in their IL-10, D-dimer, CRP, alanine aminotransferase (ALT), aspartate aminotransferase (AST), urea, and creatinine levels.

Table 3 lists the characteristics of COVID-19 patients receiving and those not receiving enoxaparin therapy. The results revealed significant changes in IL-10, D-dimer, and CRP levels between enoxaparin and non-enoxaparin patients, whereas there were no significant differences in ALT, AST, urea, and creatinine levels.

3.2 Gender Differences

There were no significant changes between females and males in all IL-10, D-dimer, CRP, ALT, AST, and

Table 2. The characteristics of patients and healthy controls.

Parameters	Healthy controls	Patients	95% CI	*p*-value
	Mean ± SEM	Mean ± SEM		
	n = 90	n = 90		
Age (years)	50.86 ± 1.53	53.82 ± 1.84	–1.78–7.69	0.22
BMI (kg/m^2)	24.03 ± 0.19	24.54 ± 0.46	–0.49–1.52	0.316
IL-10 (pg/mL)	91.24 ± 7.97	708 ± 22.06	570.89–663.87	0.001**
D-dimer (µg/mL)	0.98 ± 0.55	10.79 ± 2.83	4.087–15.542	0.001**
CRP (mg/dL)	7.08 ± 0.99	29.91 ± 3.11	16.35–29.3	0.001**
ALT (U/L)	18.26 ± 0.71	57.15 ± 5.19	28.48–49.31	0.001**
AST (U/L)	17.15 ± 0.70	59.57 ± 4.93	33.95–51.48	0.001**
Urea (mmol/L)	25.27 ± 0.63	72.79 ± 4.28	38.70–55.77	0.001**
Creatinine (mmol/L)	0.47 ± 0.02	3.25 ± 0.27	2.24–3.32	0.001**

** $<$ 0.01: Highly significant.

BMI, body mass index; IL-10, interleukin-10; CRP, C-reactive protein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; SEM, standard error mean.

Table 3. The characteristics of COVID-19 patients receiving enoxaparin therapy and those not.

Parameters	Patients receiving enoxaparin	Patients not receiving enoxaparin	95% CI	*p*-value
	Mean ± SEM	Mean ± SEM		
	n = 40	n = 50		
Age (years)	53.31 ± 2.83	54.24 ± 2.45	–8.34–6.48	0.804
BMI (kg/m^2)	24.12 ± 0.4	24.89 ± 0.79	–2.65–1.1	0.414
IL-10 (pg/mL)	527 ± 22.4	853 ± 17.53	270.21–381.72	0.001**
D-dimer (µg/mL)	3.86 ± 0.88	16.60 ±5.02	2.39–22.89	0.02*
CRP (mg/dL)	21.47 ± 2.53	36.76 ± 5.12	4.11–26.91	0.01*
ALT (U/I)	56.62 ± 4.95	57.79 ± 9.82	–21.50–20.68	0.912
AST (U/I)	65.86 ± 7.07	52.71 ± 4.32	–29.63–5.29	0.134
Urea (mmol/L)	70.67 ± 4.32	75.73 ± 7.92	–1.45–32.11	0.560
Creatinine (mmol/L)	3.67 ± 0.38	2.83 ± 0.36	–1.74–0.42	0.123

* $<$ 0.05: Significant.

** $<$ 0.01: Highly significant.

urine levels of patients with COVID-19, whereas creatinine showed a highly significant difference, as shown in Table 4.

3.3 ROC Analysis Results

The receiver operating characteristic (ROC) curve is used to diagnose severe COVID-19 cases. Research results show that IL-10 activity can discriminate between patients and controls, as illustrated in Fig. 1, with an AUC equal to 0.996.

3.4 Correlation Test Results

Potential relationships between IL-10 and other factors were assessed in COVID-19 patients and illustrated in Table 5. The Spearman's rank correlation test was used to investigate the relationship between serum IL-10 and CRP. The findings indicate that IL-10 and CRP have a significant positive relationship (r = 0.31, p = 0.003), as displayed in Fig. 2, whereas the other parameters were shown to be non-significant.

4. Discussion

In severe instances, elevated D-dimer typically occurs with pulmonary thrombosis conditions [17], which supports the D-dimer results between COVID-19 patients and controls. Moreover, the significant mean difference in D-dimer levels between enoxaparin therapy patients and non-enoxaparin therapy patients might relate to enoxaparin. Indeed, there is evidence that anticoagulant therapies are advantageous in situations with severe COVID-19, and D-dimer levels greater than 1 g/mL were linked to a decreased death rate after administering anticoagulants [18]. However, enoxaparin seems to play a more protective role against thrombosis [19]. Although there are better drugs available [20], enoxaparin as a therapeutic drug is effective in reducing D-dimer levels in a variety of situations, such as pregnancy [21] and gynecologic cancer [22]. Additionally, the degree of inflammation and the severity of the disease are strongly associated with elevated CRP levels, as shown in the present work findings, especially in non-enoxaparin patients who showed a significantly high CRP level. It is

Table 4. Gender differences between COVID-19 patients.

Parameters	Female	Male	95 % CI	*p*-value
	Mean ± SEM	Mean ± SEM		
	n = 44	n = 46		
Age (years)	50.29 ± 2.53	57.19 ± 2.61	–14.14–0.34	0.061
BMI (kg/m^2)	24.68 ± 0.9	24.41 ± 0.32	–1.61–2.14	0.777
IL-10 (pg/mL)	709 ± 30.87	708 ± 31.82	– 8.95–8.69	0.379
D-dimer (µg/mL)	14..95 ± 5.36	6.81 ± 1.99	–19.62–3.34	0.152
CRP (mg/dL)	24.86 ± 4.59	34.74 ± 4.13	–2.39–22.14	0.113
ALT (U/L)	59.55 ± 7.39	54.15 ± 7.22	–26.26–15.49	0.543
AST (U/L)	57.91 ± 6.35	61.08 ± 6.12	–14.38–20.73	0.849
Urea (mmol/L)	77.44 ± 7.33	67.79 ± 4.43	–7.45–26.74	0.259
Creatinine (mmol/L)	1.90 ± 0.28	4.54 ± 0.36	1.72–3.57	0.001**

** < 0.01: Highly significant.

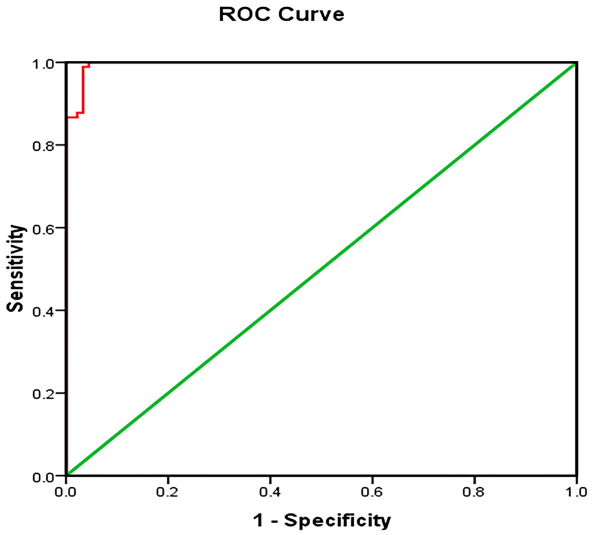

Fig. 1. Receiver operating characteristic (ROC) curve for interleukin-10 (IL-10).

Table 5. Correlation between IL-10 and other parameters in COVID-19 patients.

Parameters	r	*p*-value
IL-10 vs. D-dimer	0.118	0.267
IL-10 vs. CRP	0.310	0.003**
IL-10 vs. ALT	–0.076	0.478
LI-10 vs. AST	0.198	0.061
IL-10 vs. urea	–0.118	0.270
IL-10 vs. creatinine	0.141	0.183
D-dimer vs. CRP	–0.117	0.272
D-dimer vs. ALT	0.014	0.898
D-dimer vs. AST	0.01	0.926
D-dimer vs. urea	0.013	0.901
D-dimer vs. creatinine	–0.150	0.157

** < 0.01: Highly significant.

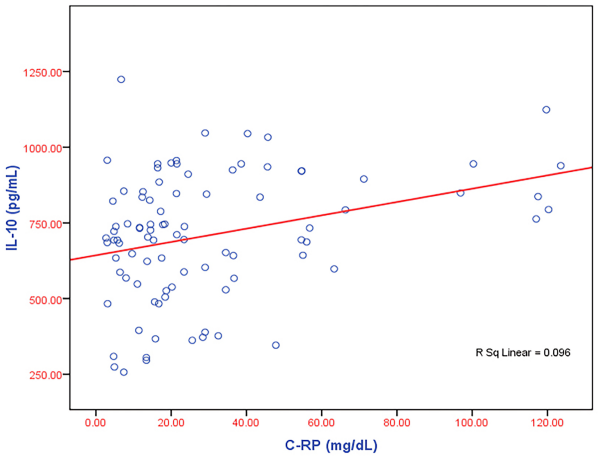

Fig. 2. Spearman's rank correlation analysis shows the relationship between IL-10 and CRP.

well known that the crucial defensive mechanisms against the infection are the inflammatory response and coagulation activation, which interact synchronously rather than acting separately [23]. As a result, CRP is a crucial indicator for diagnosing and evaluating infectious COVID-19 severity since CRP is an inflammatory marker that increases significantly in the early stage of the disease [24,25].

According to the study results, a highly significant elevated IL-10 mean level between COVID-19 patients and healthy controls was found, more precisely in severe cases who were not treated with enoxaparin; however, the inhibitory function of IL-10 probably plays an essential role in suppressing the immune system, controlling the viral progress, and disease activity [26]. There was evidence that the inflammatory characteristics of IL-10 were associated with the severity of COVID-19, which appeared in the number of patients entering the ICU, although there were limited changes in IL-10 levels between moderate and severe patients [27]. Given the extensive medical care provided to COVID-19 patients to reduce lung damage related

to inflammation, it is crucial to analyze IL-10 levels as an initial indication of the severity of the disease and assess the response of patients to a particular treatment [28].

In severe conditions, the release of macrophages and monocytes, crucial sources of IL-10, increased. On the other hand, as a pro-inflammatory cytokine, using IL-10 therapy with high doses in another condition, such as Crohn's disease, enhances some (IFN) secretion, which might be possible in COVID-19 [29]. Generally, there is evidence in previous studies that the inflammatory responses, such as the production of the IL-10 cytokine, are related to COVID-19 pathogenesis [30,31], even on the first day following infection. The elevated serum IL-10 levels alongside other cytokines, such as IL-4, IL-6, and IL-11, have been positively associated with COVID-19 severity, despite SARS patients who did not have that variety in IL-10, even in severe cases [32]. Although there is evidence of an IL-6 cytokine correlation with lung damage in COVID-19, the therapy response behavior of IL-6 has not been proven [33]. Since IL-10 plays a crucial role in regulating the proliferation of endothelial cells in many conditions, a relationship between IL-10 and thrombosis has been demonstrated [23]. However, the mean decreases in IL-10 levels in patients treated with enoxaparin therapy also support the possibility of an enoxaparin influence on IL-10 levels.

One of the suspected causes of mortality and morbidity in COVID-19 patients was associated with comorbidities since some cytokines, such as IL-10, are elevated in many conditions. In a previous study on encephalitis related to COVID-19, there was an effect of IL-10 in accelerating viral destruction by increasing $CD8^{+}$ cell activity and reducing inflammation [34]. Geriatric patients have a higher risk of being infected with COVID-19 and have a more severe outcome compared to young people due to having more comorbidities or impairment of immunity [35]. Older COVID-19 patients are more affected by systemic immune hyperactivation that increases IL-10 levels and other cytokines, which increases blood viscosity and the risk of severe thromboembolism. A higher enoxaparin dosage will be required since thromboprophylaxis is a crucial technique in preventing the development of various pulmonary diseases, with or without COVID-19. As a result, there might be a very high risk of older people suffering serious bleeding complications [36,37].

Noting that COVID-19 affects the digestive as well as respiratory systems [38], the liver can also be affected, as shown in the results of the liver function tests (AST and ALT), which were significantly higher than normal in COVID-19 patients, indicating that anomalies in liver metabolism and increased morbidity and death were among the direct effects of the infection. That appeared clearly in the second wave of the pandemic, where patients were admitted with severe liver damage, as shown by a greater frequency of variceal bleeding, acute renal damage, and hepatic encephalopathy [39]. Many causes contribute to liver damage, although the most common is the systemic inflammatory response to COVID-19 [40]. In addition to that, the results of this investigation displayed that there is no relationship between D-dimer, ALT, and AST levels, in contrast to a prior study that demonstrated that the association between D-dimer, ALT, and AST could be used to predict changes in liver function and a negative patient diagnosis [41]. Compared to healthy controls, the results of the renal function tests (urea and creatinine) were determined to be higher in patients with COVID-19, indicating that decreased renal function commonly occurs in patients with COVID-19 and is one of the main reasons for mortality [42], especially in creatinine, which, depends on nutrition and muscle mass, while both the gastrointestinal tract and renal tubular cells can release creatinine [43]. Therefore, this elevation may be caused by patients whose digestive systems are affected. However, the increase in creatinine levels in patients does not agree with some studies that linked the decrease in serum albumin, which is connected to muscle breakdown, with the reduction in serum creatinine [44].

Limited data on the association between inflammatory indicators and disease severity in patients with COVID-19 is available. As with enoxaparin treatment, the study's findings indicated a correlation between reducing levels of the pro-inflammatory cytokine IL-10 and reducing CRP, consistent with previous research results [29]. In addition, according to the ROC results, and since IL-10 is elevated earlier than other proinflammatory cytokines in COVID-19 patients [24], IL-10 might be used as a potential marker of COVID-19 activity.

In this study, there were some limitations owing to some of the patients dying after 3 days in the intensive care unit. In addition to quarantine conditions, some were on CPAP most of the time, meaning we could not obtain crucial patient information, such as radiographic data.

5. Conclusions

Following the analysis of the data gathered during this research, it can be concluded that patients with COVID-19 have higher IL-10 and D-dimer levels, alongside some other parameters, compared to healthy controls. In addition, IL-10 may be used as a marker of COVID-19 activity. Enoxaparin will likely help control IL-10 and D-dimer levels in COVID-19 patients, as the IL-10 levels decreased in patients treated with enoxaparin.

Availability of Data and Materials

The data are unavailable for readers because it contain a personal information of patients. However, data will be provided when editor or reviewers requested.

Author Contributions

AMG designed the experiments, Supervised, directed and managed the study; NHH performed experiments and collected data; MSH prepare manuscript, editing article, and discussed the results and strategy; AMM analyses the results and processing data; All authors final approved of the version to be published. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity. All authors contributed to editorial changes in the manuscript.

Ethics Approval and Consent to Participate

The research was approved by the University of Technology (UOT) Biological Research Ethical Committee, with the registration number AS-AC 44728 and done in accordance with the requirements of the World Medical Association Declaration of Helsinki Ethical Principles (2013). Informed consent was obtained from patients willing to participate in the trial.

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Conflict of Interest

The authors declare no conflict of interest.

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