Original Article

Evaluation of Hematological Parameters and Inflammatory Markers for Disease Severity in Vaccinated and Non-Vaccinated Covid-19 Patients in Erbil-City

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ABSTRACT

SARS-CoV-2 virus caused acute respiratory illness called COVID-19 with rising case mortality rates. One of the preventive measures to arrest the spread of a contagious disease is the use of vaccines. Consequently, we aimed to measure of inflammatory markers, including Angiotensin II, CRP, D-dimer, Ferritin, and Procalcitonin, as well as hematological parameters as biomarker for disease severity in vaccinated and non-vaccinated COVID 19 patients. A total of 133 blood specimens were collected from healthy individuals and patients infected with COVID 19 from November 2021 to May 2022 of both sexes, categorized into two main groups: 50 healthy individuals with 83 patients were classified in to "vaccinated (33) and non-vaccinated (50) group" based on their immunization status with an age range (20-65). According to our results, the majority of patients in the non-vaccinated group had a severe disease, while most of the patients in the vaccine group had a mild to moderate illness. Hematological parameters including WBC and granulocyte count, increased significantly (p value < 0.001), while Lymphocyte and hemoglobin decreased significantly in non-vaccinated patients when compared to vaccinated cases. Regarding inflammatory parameters, CRP, D-dimer, Ferritin, and, procalcitonin significantly elevated in non-vaccinated individuals compare to vaccinated patients and healthy control group ($P<0.001$). The optimal cut-off values for angiotensin II, PCT, D-dimer, Ferritin, and CRP were determined by ROC Curve Analysis in COVID-19 patients. In conclusion, vaccine plays a major role in regulating inflammatory markers patients with COVID-19. These findings reaffirm the vaccine's effectiveness in reducing disease severity compared to non-vaccinated patients.

Keywords: Vaccine, COVID-19, SARS-CoV-2, Hematological parameter, Inflammatory biomarkers.

1- Introduction

COVID-19 is a respiratory disease caused by SARS-CoV-2, a recently discovered coronavirus. The latest COVID-19 outbreak began in late 2019 in Wuhan, China. On March 11, 2020, the World Health Organization (WHO) will declare the outbreak a pandemic. The global COVID-19 caseload is quickly increasing on a daily basis, especially outside of mainland China, where the virus's epicenter is shifting from China to other parts of the world [1]. The main routes of transmission are respiratory droplets; if a healthy individual comes into direct contact with an infected or any of his things, including garments or door handles, SARS-CoV-2 can always be spread. Aerosol transmission (airborne transmission) of SARSCoV-2 has been reported in studies, but there has been no clear study on neonatal infections (mother to child). Transmission can be prevented by keeping a 2-meter gap between two persons, wearing masks while out, and isolating affected people [2, 3]. The human angiotensin-converting enzyme 2 (ACE2), a vital part of the renin-angiotensin system (RAS), binds to the viral spike protein to allow SARS-CoV-2 entry into pulmonary and

cardiac cells. [4]. SARS-CoV-2 has a 2–14 day incubation period before symptoms appear; nevertheless, asymptomatic infection has been recorded in certain cases. Fever and respiratory problems including coughing and shortness of breathing are common in SARS-COV-2 infected people. "(Acute respiratory distress syndrome ARDS)", organ failure, and septic shock can all result from severe and critical illnesses, and they can all be death [5]. According to WHO Coronavirus (COVID-19) Dashboard, nearly 767.9 million (2,465,545 in Iraq) confirmed cases have been reported globally since the 8th of July 2023, and about 6.9 million people had died counting 25,375 in Iraq, as well as total of 13.4 vaccine doses (9,557,364 in Iraq) have been administered.

One of the most effective medical therapies ever implemented in human history, vaccinations have significantly lowered the incidence of infectious diseases in many countries [6]. Vaccine clinical development and approval typically take 5 to 10 years, and only 10% of vaccine concepts are approved for the market. Nevertheless, the COVID-19 pandemic marked a significant turning point in medical history since, less than a year after the discovery of the first SARS-CoV-2 patient [7]. Since the beginning of the pandemic, there have been 336 vaccine candidates developed, and 32 vaccines are currently approved for usage across the globe. A large-scale vaccination campaign to stop the spread of SARS-CoV-2 and reduce its severity in afflicted patients was authorized for emergency use on December 11, 2020, by the US Food and Drug Administration (FDA).BNT162b2 (Pfizer Inc/BioNTech SE) and mRNA-1273 (Moderna Therapeutics Inc.) are two of the approved vaccines that are based on messenger RNA (mRNA) [8]

Early diagnosis of several inflammatory diseases, including malignancies, metabolic disorders, and infections, is greatly aided by hematological characteristics. [9] Hematological parameters such as ferritin, D-dimer, Hb, neutrophil to lymphocyte ratio, platelet to lymphocyte ratio, (WBC count excluding lymphocyte)/lymphocyte, LDH, and lymphocyte count were strongly correlated with patients' prognoses for COVID-19 disease. [10]. Procalcitonin (PCT) is the prohormone for calcitonin; the biologic actions are noticeably varied. It is produced by the C cells of the thyroid gland and K cells of the lung [11]. Procalcitonin had evolved into a potential marker for detection of bacterial infections because larger amount of PCT are found in severe bacterial infections relative to viral infections and nonspecific inflammatory diseases [12]. Recently, many research studies discovered an adverse relationship between high PCT and CoV-2 severity [13]In infectious conditions, PCT is released from nearly all tissues including lung, liver, kidney, pancreas, spleen, colon, and adipose tissues. Currently, PCT is recognized as one of the suitable markers for diagnosis of sepsis or severe sepsis [14] Notably, Ang II is one of the most powerful vasopressors known when connected to its type 1 Ang receptor, making it the main effector molecule of activated RAS. [15]. Angiotensin-converting enzyme 1 (ACE-1) catalyzes the conversion of angiotensin I (Ang-I) into angiotensin II. Blood pressure, heart rate, blood volume, and electrolyte balance are all significantly regulated by Ang-II. Additionally, elevated Ang-II can result in mitochondrial oxidative damage, an excess of reactive oxygen species, and elevated interleukin-6 (IL-6), which can promote inflammation. The components of the RAAS have just recently been tested in the blood of COVID-19 patients, and the results are often debatable [16]

The main role of the protein ferritin, which stores iron, is to regulate cellular oxygen use. Because of its direct immuno-suppressive and pro-inflammatory activities, ferritin is a significant player in immune dysregulation, especially in cases of extreme hyperferritinemia [17]. In COVID-19, ferritin is a recognized indicator of inflammation. However, a variety of variables and comorbidities may obscure the serum ferritin level. [18]. Comprehensive analysis of the current COVID-19 studies was performed to identify any potential associations between ferritin and patients' severe conditions, death, and other crucial clinical characteristics [19]. In COVID-19 patients, levels of C-reactive protein (CRP), an acute phase reactant and active regulator of the innate immune system, are elevated and have been linked to disease severity. CRP can rise up to 100-fold in response to many types of tissue damage, infection, and inflammation. It is mostly produced in the liver upon interleukin-6 stimulation [20]. CRP has been shown to play an extremely important role in COVID-19 pneumonia in terms of forecasting sickness severity, progression, and sequential CRP titers that will help evaluating treatment response during hospitalization and analyzing post-COVID lung fibrosis [21]

D-dimer is a soluble byproduct of fibrin degradation that happens during the breakdown of the clot by the processes of the fibrinolytic system. D-dimer acts as a key biomarker of active coagulation and fibrinolysis, according to numerous researches [22]. A Numerous follow-up studies carried out globally have verified that D-dimer is raised in people with severe COVID-19, and that it is highest in people who are the most seriously ill and do not survive [23]. The presence of extremely high levels of D-dimer in blood plasma is a sign of hyperfibrinolysis in COVID-19 [24]. D-dimer rising after receiving the COVID-19 vaccine indicates a higher chance of thrombocytopenia and thrombosis brought on by the vaccine [25]. It has been demonstrated that individuals with COVID-19 who had a severe course and died had considerably higher D-dimer values [26]. This study aimed to assess the value of hematological parameters and some inflammatory biomarkers, including serum Angiotensin II, PCT, D-dimer, ferritin, and CRP in the early diagnosis and disease severity in Vaccinated and Non-Vaccinated Covid-19 Patients.

2- Material and Methods

2.1. Participants

A total of 133 individuals were enrolled in the study from November 2021 to May 2022. COVID-19 diagnosis was confirmed by a reverse transcription-quantitative (RT-q) PCR of nasal or pharyngeal swab specimens in adults (age 20-65 years) at three hospitals ((West Erbil emergency, Lalav emergency, and Middle Erbil hospital) in Erbil city. The patients were classified into Two groups, 50 patients (25 female and 25 male) were they Non-vaccinated who complaining of mild to severe symptoms, while another 33 the patients (20 female and 13 male) had received full dose of vaccination (two doses) of BNT162b2 ("Pfizer-BioNTech") before the infection and hospitalization. In addition, 50 healthy control (27 female and 23 male).

2.1. Blood Samples

After receiving written informed consent from all participants, a sample of venous blood (about 6 ml) was taken from each participant immediately poured into three different laboratory tubes. Two ml of the blood was in the EDTA test tube used for the measurement of a vital haematological parameter by using an automated haematology analyser (Medonic Mserries, Sweden) to determine WBC, Granulocytes, Lymphocytes, Platelets, and Haemoglobin. Two ml of the whole blood was collected in a serum-separating gel tube for 30 minutes to coagulate. The samples were centrifuged at 4000 RPM for 5 minutes to collect serum for inflammatory tests. CRP and Ferritin levels were determined by Cobase E411 – Roche (Germany), Procalcitonin (PCT) analysis using I CHROMA II instrument (Biotech, Med) and Angiotensin II level evaluated via enzyme-linked immunosorbent assay (ELISA) (Biotech, Germany). The rest of the two ml of blood was collected into sodium citrate Tube, the blood sample centrifuged at 4000 RPM for 15 minutes to collect plasma to evaluate D-dimer level by using Cobas 411- Roche (Germany).

2.3. Statistical analysis

The data was analyzed using (Graph Pad Prism 9.0). Non-parametric Variables with were appropriately reported as mean ± SE. The data of hematological parameters and inflammatory biomarkers presented in this study, the One-Way ANOVA (Kruskal - Walis Test) and spearman correlation test were used to evaluate between-group comparisons for categorical variables, the predictive significance of the study determined severity via receiver operating characteristic (ROC) curve analyses and the results were expressed as area under the curve (AUC), cut-off value, specificity, and sensitivity. A P value of 0.05 was used to determine statistical significance. The symbol of (*) indicate extremely significant differences between patient and healthy control groups; the sign of (ns) represents non-significant differences between groups.

3. Result

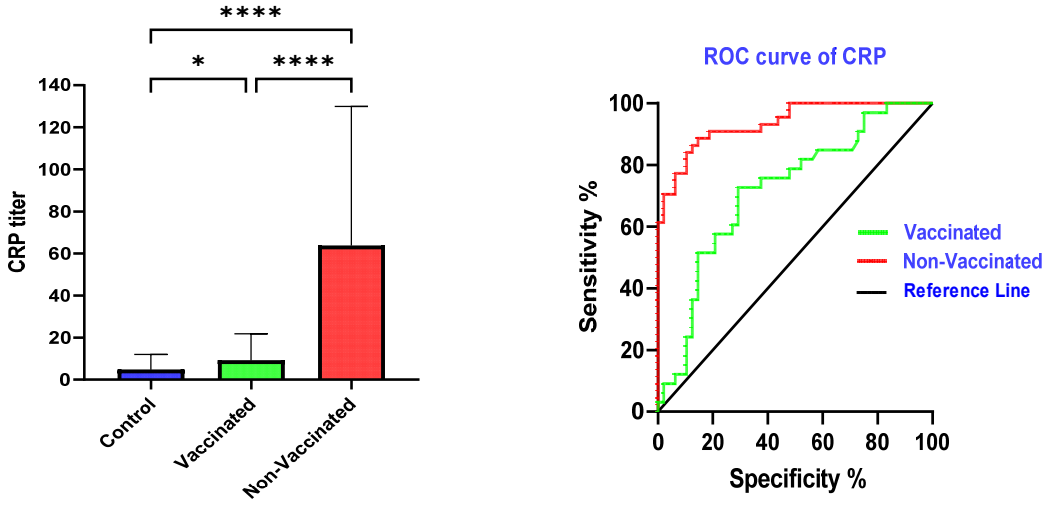
Regarding to our results, Covid-19 patients leads to leukocytosis. The mean ± SD of WBC counts increased significantly (p value < 0.0001) in the Non-vaccinated Covid-19 group patients versus healthy group. On the other hand, a mean of WBC vaccinated patients significantly decreased to (7.57 ± 0.48) as compared to Non-vaccinated group (13.51± 1.03) with p.value of < 0.0001. While lymphocyte counts decreased significantly in Non-vaccinated groups (1.54 ± 1.77) when compared to vaccinated and control groups with the mean value of (2.04 ± 1.04 and 2.39 ± 0.78), respectively, but statistically non-significant differences were observed between healthy and vaccinated groups of Covid-19 patients. The mean granulocyte count was significantly higher in non-vaccinated patients (13.08 ± 13.26) than vaccinated group (4.37 ± 2.65) and normal individuals (5.41 ± 2.22) with p.value < 0.0001. There was a significant differences recorded in monocyte
Count in vaccinated and non-vaccinated patients with mean value of (1.000 ± 1.16 and 1.046 ± 2.20) respectively compares to control group (0.63 ± 0.19) with p value 0.0076. As shown in table 1, Hemoglobin concentration decrease significantly in non-vaccinated group as a value of (12.76 ± 1.78) and increased significantly in vaccinated patients as a value of (14.54 ± 1.85) compare to healthy group (13.89 ± 1.618) with p value of <0.0001. About platelet count, there was no significant association between control (236.6 ± 63.18) and patient groups (vaccinated and non-vaccinated) giving mean of (215.3 ± 68.32 and 252.6 ±114.9) respectively.

Table 1: Comparison of hematological parameters between healthy and COVID-19 cases

Parameters	Control	COVID-19 cases		p.value
		Vaccinated	Non-Vaccinated	
WBC (10^9/l)	8.57 ± 0.358	7.57 ± 0.48	13.51± 1.03	0.0001
Lymph (10^9/l)	2.39 ± 0.78	2.04 ± 1.04	1.54 ± 1.77	0.0001
Mono (10^9/l)	0.63 ± 0.19	1.000 ± 1.16	1.046 ± 2.20	0.0076
Gran (10^9/l)	5.41 ± 2.22	4.37 ± 2.65	13.08 ± 13.26	0.0001
HGB (g/dl)	13.89 ± 1.61	14.54 ± 1.85	12.76 ± 1.78	0.0001
PLT (10^9/l)	236.6 ± 63.1	215.3 ± 68.32	252.6 ±114.9	0.2819

Parameters	Control	COVID-19 cases		p.value
		Vaccinated	Non-Vaccinated	
The mean difference is significant at the 0.05 level				

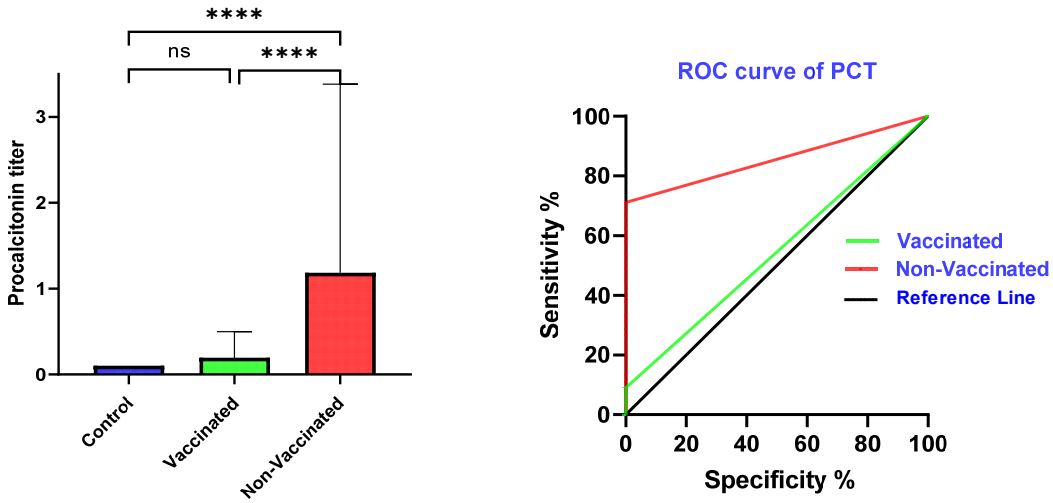
The current study found that the mean ± SD values of CRP were significantly higher in vaccinated and non-vaccinated patients as compared to that found in control group (9.14 ± 12.64 mg/l and 63.71 ± 66.21mg/l) respectively versus 4.69 ± 7.26 mg/l in control), also there was a significant difference between vaccinated and non- vaccinated patients with P value <0.0001 (Figure 1A). The optimal cut-off values of CRP for predicting severity in CoV-2 patients were determined via ROC curve analysis for vaccinated was 2.79 mg/l, sensitivity= 72.73%; specificity= 70.83%; AUC = 0.717 and non-vaccinated was 5.395 mg/l, sensitivity = 90.91%; specificity = 81.25%; AUC = 0.936. That is shown in (Tables 2 and Figure 1B)



(A) **(B)**

Fig.1. A: Comparison of CRP level in Covid-19 group patients and healthy control.
B: ROC curve of CRP level

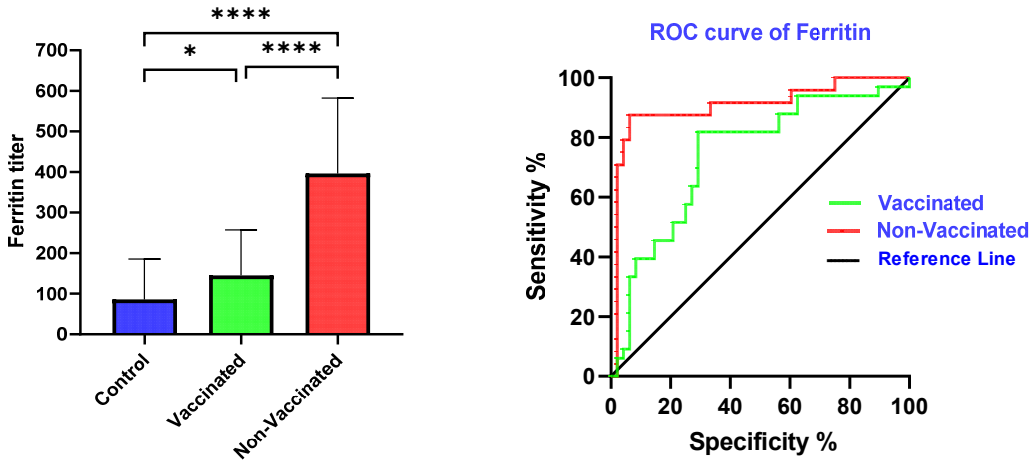
Serum Procalcitonin level is one of the important biomarkers of CoV-2 patients, PCT was a highly significant increase in non-vaccinated patient (1.278 ± 2.19 ng/ml) as compared with control group (0.1 ±0.0 ng/ml), but there was no significant difference between the vaccinated (0.1945 ± 0.3 ng/ml) and control group; in addition, there was a significant difference (P< 0.0001) between the vaccinated and non-vaccinated patients as shown in (Table 2 and figure 2A). By using (ROC) Curve analysis, the cut-off values of PCT for predicting severity in COVID-19 patients were shown to be < 0.110 ng/ml (sensitivity = 71.11%; specificity= 75.00 %; AUC = 0.855) in unvaccinated groups while in vaccinated patients was 0.620 ng/ml, the sensitivity, specificity and AUC were 9.091%, 100% and 0.545, respectively)



(A) **(B)**

Fig. 2.A: Comparison of PCT level in Covid-19 group patients and healthy control.
B: ROC curve of PCT level

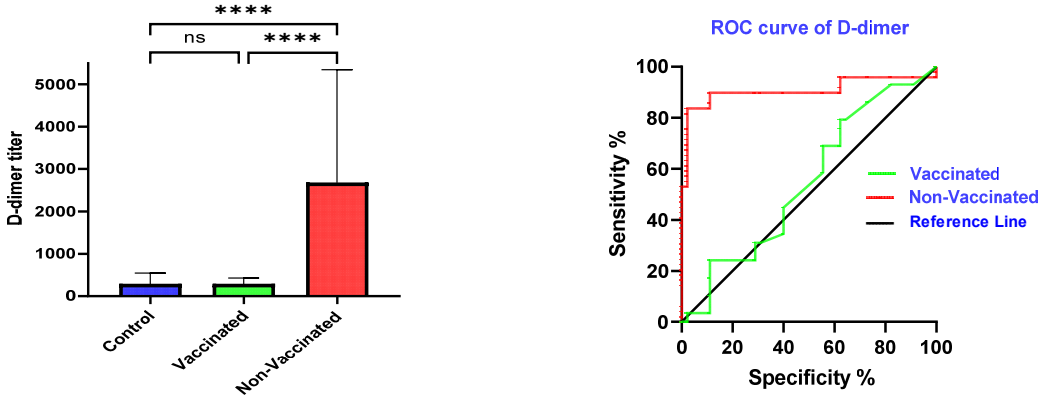
The results of recent study found that the mean ± SD values of ferritin were significantly higher in vaccinated (145.4 ± 111.9 ng/ml) and non-vaccinated (396.4 ± 185.6 ng/ml) patient groups when compared to that found in control group (85.89 ± 99.63 ng/ml). On the other hands, there was a significant difference (P Value <0.0001) between vaccinated and non-vaccinated groups (Figure 3A). The optimal cut-off values of ferritin for predicting severity in Covid-19- patients were determined via ROC curve analysis were vaccinated 102.5 ng/ml, sensitivity, specificity and AUC were = 81.82%, 70.83% and 0.741, respectively, as well as in non-vaccinated was <163.5 ng/ml, sensitivity = 87.50%; specificity = 93.75%; AUC = 0.906 as illustrated in (Table 3 and Figure 3B)



(A) **(B)**

Fig.3. A: Comparison of Ferritin level in Covid-19 group patients and healthy control.
B: ROC curve of Ferritin level

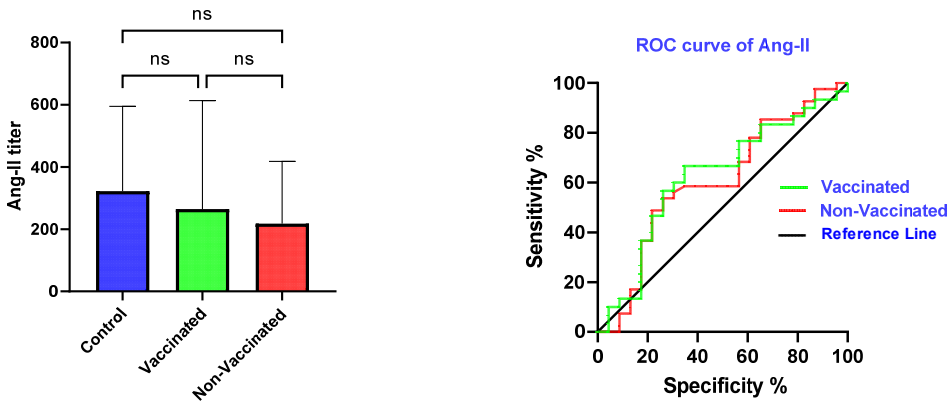
D-dimer is the most significant marker of CoV-2 patients, the results of our study as documented in (Figure 4A and Table 2), showed that concentration of d-dimer increased significantly from (282.6 ±261.9 ng/ml) in the control group to (2748 ± 2670ng/ml) in non-vaccinated group with P value < 0.0001. Furthermore, the mean ± SD values of D-dimer significantly decreased to (283.8 ± 146.0 ng/ml) in individuals who taken vaccine as compare to non-vaccinated patient groups. Statistically, there was no significant deference between vaccinated and non-vaccinated patient groups. ROC curve analysis used for predicting severity in Covid 19 patients, in vaccinated group the cut-off values of D-dimer was 195.0 ng/ml, the sensitivity, specificity and AUC were 79.31%, 37.78% and 0.5479, respectively. Along with, cut-off values in non-vaccinated patients were 345.5, as well as, the sensitivity, specificity and AUC were 89.80%, 88.89%; and 0.907, respectively with P value of <0.0001 as indicated in (Table 3 and Figure 4B).



(A) **(B)**

Fig.4. A: Comparison of D-dimer level in Covid-19 group patients and healthy control.
B: ROC curve of D-dimer level

Regarding the results of the current study, the Mean ± SD values of serum angiotensin II slightly declined from 321.9 +40.31 in control group to 264.4 +63.64 and 218.1 + 31.23 in vaccinated and non-vaccinated patients groups, respectively, but there was not reach at significant level (Table 2 and Figure 5A). The optimal cut-off values of angiotensin II for predicting severity in Covid 19 patients were determined via ROC curve analysis were vaccinated 215.9 pg/ml, sensitivity = 66.67 %; specificity = 65.22%; AUC= 0.623 and non-vaccinated 129.1 pg/ml, sensitivity = 53.66 %; specificity = 73.91%; AUC = 0.605 as showed in (Table 3 and Figure 5B).



(A) **(B)**

Fig.5.A: Comparison of Ang-II level in Covid-19 group patients and healthy control.
B: ROC curve of Ang-II level

Table 2: Comparison of inflammatory markers between healthy and COVID-19 cases

Parameters	Control	COVID-19 cases		p. value
		Vaccinated	Non-Vaccinated	
CRP(mg/l)	4.69 ± 7.26	9.14 ± 12.64	63.71 ± 66.21	0.0001
D-dimer (ng/ml)	282.6 ±261.9	283.8 ±146.0	2748 ± 2670	0.0001
Ferritin (ng/ml)	85.89 ±99.63	145.4 ±111.9	396.4 ± 185.6	0.0001
PCT (ng/ml)	0.1 ±0.0	0.1945 ± 0.3	1.278 ± 2.19	0.0001
Ang-ll (pg/ml)	321.9 ± 273.4	264.4 ± 348.4	218.1 ±199.9	0.1208

The mean difference is significant at the 0.05 level

Table 3. ROC curve analysis of inflammatory markers in Covid-19 group patients.

Inflammatory biomarker		AUC	Cut off value	Sensitivity (%)	Specificity (%)	P. value
CRP (mg/l)	Vaccinated	0.7172	2.790	72.73	70.83	0.0009
	Non-Vaccinated	0.9361	5.395	90.91	81.25	0.0001
Ferritin	Vaccinated	0.7418	102.5	81.82	70.83	0.0002
(ng/ml)	Non-Vaccinated	0.906	163.5	87.50	93.75	0.0001
Ang-ll	Vaccinated	0.623	215.9	66.67	65.22	0.0708
(pg/ml)	Non-Vaccinated	0.605	129.1	53.66	73.91	0.0923
D-dimer	Vaccinated	0.5479	195.0	79.31	37.78	0.488
(ng/ml)	Non-Vaccinated	0.9075	345.5	89.80	88.89	0.0001
PCT (ng/ml)	Vaccinated	0.5455	0.6200	9.091	100	0.488
	Non-Vaccinated	0.8556	0.1100	71.11	100	0.0001

To correlate D-dimer values with hematological parameters and other inflammatory biomarkers, the Spearman correlation coefficient was calculated, and the results are shown in Table 4. D-dimer displayed a highly significant positive correlation with CRP, WBC, and granulocytes at the level of p value < 0.01 and it showed significant positive correlation with PCT in the non-

vaccinated group at the level of p value 0.05. However, there was not significant association observed between D-dimer and other biomarkers in vaccinated group.

Table 4: Correlation of D-dimer with hematological and inflammatory markers in Covid-19 group patients.

Parameters	Patients categories			
	Vaccinated		Non-Vaccinated	
	Spearman correlation	P. value	Spearman correlation	P. value
CRP (mg/l)	-0.2328	0.2243	0.5576 ***	0.0001
Ferritin (ng/ml)	-0.1393	0.4710	0.2720	0.0707
PCT (ng/ml)	-0.07343	0.7050	0.3310 *	0.0323
Ang-ll ((pg/ml)	0.1837	0.3689	-0.1030	0.5382
WBC (10^9/l)	0.2217	0.2763	0.4373 **	0.0034
Lym (10^9/l)	0.09333	0.6502	-0.2154	0.1654
Mono (10^9/l)	0.1877	0.3586	-0.08145	0.6081
Gran (10^9/l)	-0.05762	0.7798	0.4217 **	0.0049
HGB (g/dl)	-0.2758	0.1727	-0.1556	0.3131
PLT (10^9/l)	-0.2466	0.2246	0.03466	0.8233

**: Correlation is significant at the 0.01 level (2-tailed).

* : Correlation is significant at the 0.05 level (2-tailed).

4. Discussion

COVID-19 considered as one of the most severe pandemics which affect people. Millions of patients died as a result of the disease-causing virus SARS-CoV-2 spreading through many regions of the world. The virus has caused severe respiratory sickness in infected people, but it has also affected a number of other organs due to its capacity to bind to respiratory tissues, trigger cytokine storms, and travel throughout the body. [27]

Despite the fact that vaccination has been shown to protect patients, some recent studies have revealed the presence of infection even in completely immunized individuals, raising questions regarding the effectiveness and duration of protection offered by the vaccinations. [28, 29]. In order to determine whether receiving the COVID-19 vaccine had positive health consequences in comparison to those who have not, it was crucial to conduct research. As a result, we evaluated various clinical outcomes in COVID-19 patients who had received two doses of the vaccine in this trial and contrasted the results with those of patients who had not received any vaccine. In comparison to patients who had not got the vaccine, we discovered that vaccination helped patients who had received at least one dose of it recover more quickly.

As shown in (Table 1), the findings of our investigation showed that non-vaccinated COVID-19 patients had greater total leukocyte counts, granulocytes, and monocytes with fewer lymphocytes than vaccinated patients. These findings are consistent with those of other studies. [30-32] who revealed that indications of prognosis in CoV-2 patients included lymphopenia, higher leukocyte counts, and less lymphocyte counts in severe patients. Other studies that confirm our findings were the retrospective study included 26 vaccinated and 26 non-vaccinated COVID-19 patients. They found a significant differences in total leucocyte count, and differential counts of neutrophils, lymphocytes, eosinophil, monocytes, and basophils between vaccinated and non-vaccinated patients[33]. In addition, [34] which found that total lymphocyte count was lower in those who had received vaccine, while TLC was higher in COVID-19 patients who had vaccinated. On the other hand, according to this study, hemoglobin concentration decrease significantly in non-vaccinated group and recorded a high score in vaccinated patients as compared to healthy individuals. This is consistent with the retrospective study of [35] who recorded that COVID-19 patients admitted to hospitals frequently had anemia and impaired iron homeostasis. A greater ferritin/transferrin ratio predicted the requirement for ICU hospitalization and mechanical ventilation, and initial anemia was linked to an increased fatality rate. Furthermore, [36] studies on 206 patients who were hospitalized in an Internal Medicine unit with COVID-19, they evaluated into the prevalence, cause, and clinical importance of anemia. Also, [37] revealed that in patients admitted in hospital for COVID-19, anemia is significantly linked with progression of the illness and mortality.

C-reactive protein (CRP), an powerful regulator of the innate immune system, has been linked to severity of SARS COV-2 [38]. As illustrated in Figure 1, the results showed a high level of serum CRP in non-vaccinated patients with COVID-19 compared to vaccinated group. In COVID 19 pneumonia, CRP has been shown to have an essential role in determining disease severity, disease progression, and CRP titers that will aid in evaluating therapy response while the patient is hospitalized [21]. The reported data by [33] that conducted research in India that was similar to our findings in that non-vaccinated patients' CRP levels were much higher than those of the vaccine group. Another current study that support our findings which done on 54 patients of COVID-19 [34], they observed that the CRP value was significantly reduced in the group that received immunization than in the group that did not receive vaccine ($P = 0.05$). Additionally, [39] studied on 142 Covid-19 patients, who observed that the concentration of

serum CRP in unvaccinated group higher 12 times than in vaccinated patients. According to reports, CRP levels in severe Covid-19 patients may increase prior to any CT findings are seen. As a result, CRP can be utilized to identify severe individuals at early stages of illness [40]

As showed in (Figure 3A and Table 2), the statistical data of ferritin revealed that a significant differences between groups. Serum ferritin level recorded higher score in non-vaccinated patients than individuals who has taken vaccine. The presence of ferritin made it simpler predict the decline of COVID-19 patients [41]. Iron deficiency caused by iron metabolism may facilitate COVID-19 infection. Ferritin is regarded as a helpful COVID infection indicator [42]. Increased ferritin is related to a progression of the disease. These results are consistent with what has been published in other investigations. [43-46]. Our study about ferritin is consistent with those of a number of other studies. According to the findings of [33], non-vaccinated CoV-2 patients with severe illnesses had ferritin levels that were almost 34.1 times greater than those in the group who had received vaccine. Similarity, the analyzed data of [47] demonstrated that the mean concentration of blood ferritin was more than two times higher ($p < 0.0001$) in unvaccinated patients than in those who had received vaccine. The CoV-2 case's ferritin rate was influenced by a number of variables, such as older age, sex, heredity, and iron consumption. [48]. Another findings that agree with our results [49] It has been carried out on fifty patients from the province of Diyala who are not vaccinated and 300 who are. They found that the ferritin concentration had the greatest mean value in patients who had not received vaccine and the lowest mean value in those who had.

D-dimer is a marker for active fibrinolysis that is still occurring and subsequently, coagulation. It evaluates the intensity of the host reaction. A study by [50] demonstrated that the patient's chance of developing sepsis and septic shock increased with higher D-dimer levels. Remarkably disease progression prediction was obtained for D-dimer. These results are in line with the findings of our investigation, which showed significant variation between the concentrations of D-dimer in the non-vaccinated group and patients who had received vaccine. Furthermore, [51] investigated that individuals who took the COVID-19 vaccine in two doses had significantly lower amounts of D-dimer than patients who didn't get the vaccine. Because of this, the D-dimer is a helpful indicator of coagulation and fibrinolysis activation under particular clinical circumstances. [52]. The significant coagulation indicator of COVID-19, elevated levels of D-dimer are brought on by both hyperfibrinolysis and hypercoagulation [24]. Also, [23] declared that D-dimer plays an essential role in determining disease intensity in COVID-19 pneumonia.

As a consequence of our research, we determined that non-vaccinated patients had mean serum PCT levels that were about 6.5 times higher than vaccinated cases. [53] who found that higher serum PCT levels were associated with a roughly 5-fold increased risk of significant disease development in CoV-2 patients. Additionally, a meta-analysis revealed that COVID-19 patients' elevated procalcitonin levels may be caused by bacterial infections or by the increased release of certain cytokines, most notably interleukin-6 [54].In contrast, [55] in their study showed that procalcitonin had no significant correlation with the status of vaccination with a p-value of more than 0.05. In another study conducted in Turkey, patients aged ≥ 65 years who admitted in hospital for COVID-19 were retrospectively analyzed in 2 class: non-vaccinated and vaccinated [56] they discovered that the mean level of blood procalcitonin was lower in patients who had received vaccine than in unvaccinated patients (0.834.73 vs. 1.076.66). Furthermore,[39] investigated that serum PCT in non-vaccinated patients about 1.89 times higher than in vaccinated group. In individuals with a COVID-19 infection, elevated PCT levels are linked to high incidents of severe COVID-19 infections. Physicians may benefit from routinely measuring PCT in patients with COVID-19 infections to help them make clinical decisions about whether to admit patients to the ICU [57].

Other laboratory values about angiotensin II did not show a statistically significant difference between the vaccinated and unvaccinated groups with healthy cases in our study. Angiotensin II is vasoconstrictive, pro-inflammatory, and encourages organ damage [58]. Ang II levels were significantly greater in critically ill COVID-19 patients compared to controls and patients with mild COVID-19 symptoms [59]. In addition, Angiotensin II causes fibrinolysis to be impaired and thrombin production to rise. In individuals with severe COVID-19, elevated levels were substantially correlated with viral load and lung damage [15]. Also, [16] They found that patients with COVID-19 presenting with critical condition had greater plasma levels of Ang-II at hospital admission than those arriving with severe disease. This research was done in Brazil. According to this information, Ang-II may be a biomarker that might be used to identify hospitalized patients who have a worse COVID-19 prognosis. The small patient population, gender, age, and other comorbidities may be to blame for the disagreement over our findings. The disparities between the genders in Ang-II levels may indicate reduced ACE2 loss in female patients. [60]

6. Conclusion

In conclusion, vaccination has a significant impact on COVID-19 patients' ability to control inflammatory indicators. It appears that vaccinations stop disease progression; thus, the severe illnesses were lower in the vaccinated group. Increased the level of CRP, D-dimer, ferritin, and PCT were correlated with non-vaccinated COVID-19 disease. Furthermore, based on hematological indicators, we reach the conclusion that the vaccine successfully lowers the severity rate of COVID19 patients. Total lymphocyte counts and granulocytes were higher in vaccinated COVID-19 patients. Meanwhile, the lymphocytes and hemoglobin values were lower in vaccinated COVID-19 patients than non-vaccinated ones. As a result, the severity rate

was lower in the vaccinated group than in the non-vaccinated cases. Our research confirms the need for ongoing mass immunization campaigns against COVID-19 in order to build up a population's overall immunity and COVID-19 protection.

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