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Comparative study of vaccinated and non-vaccinated patients of covid19 in inflammatory markers in Diyala governorate.

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ABSTRACT

This study was conducted in Diyala Governorate from September 2021 to October 2022 and included the study of chemical variables known as inflammatory markers such as LDH, D DIMER, CRP and FERRITIN. These chemical variables change and affect both vaccinated and unvaccinated corona patients. This study was conducted first to determine these variables, study them with vaccinated patients, and compare them with non-vaccinated patients. Secondly, to study the types of vaccines that were given against corona disease and know whether one type is better than the other according to these variables, knowing that these variables mentioned represent the severity of the disease, the result was that the present study shows there are significant differences ($p < 0.05$) between LDH, D dimer, and ferritin parameters and study groups. The LDH, D dimer and ferritin parameters scored the highest mean value in Unvaccinated patients (442.46 ± 150.78 , 1016.16 ± 400.77 , and 290.61 ± 122.02) and the lowest mean value in vaccinated patients (232.95 ± 111.82 , 929.46 ± 340.54 , and 58.55 ± 25.80) respectively compared to healthy groups. The LDH scored the highest mean value in unvaccinated females (448.50 ± 166.33), and least mean value in vaccinated males (192.01 ± 88.85), D dimer scored the highest mean value in vaccinated males (1115.36 ± 500.26), and the least mean value in healthy males (357.54 ± 83.25), ferritin scored highest mean value in unvaccinated males (382.95 ± 150.79), and least mean value in vaccinated females (53.19 ± 21.44) compared to other values. The present study showed significant differences ($p < 0.05$) between CRP parameters and vaccine types. The CRP scored the highest mean value in patients with the Pfizer vaccine (214.65 ± 88.51) and the lowest mean value with AstraZeneca (125.36 ± 55.40).

Keywords: COVID-19, inflammatory markers, D-dimer

INTRODUCTION

Towards the end of December, a mysterious illness known as pneumonia of unknown origin broke out in Wuhan, Hubei Province, China ¹. At least 9720 people have been infected in China, 213 have died, and 106 have been diagnosed in 19 other countries as of 31 January 2020. A few days later, three independent laboratories identified the cause of this strange pneumonia as a new coronavirus (nCoV) ². D-dimer is a marker of fibrinolysis and fibrin turnover that may be

measured indirectly. Hemostatic problems and intravascular thrombosis are marked by this molecule, which has unique qualities as both a biological marker and an indication. D-dimer is a soluble fibrin degradation product that results from the systematic breakdown of vascular thrombi via the fibrinolytic process. As a result, the D-dimer serves as a useful marker of coagulation and fibrinolysis activation in specific clinical situations³. D-dimer is elevated in severe instances, mostly due to pulmonary thrombosis⁴. Anticoagulant medication may assist individuals with severe COVID-19 with dynamic variations in D-dimer level and a poor prognosis due to COVID-19⁵.

In cases of severe hyperferritinemia, ferritin plays an important role in immunological dysregulation by exerting immunosuppressive and proinflammatory actions that contribute to the cytokine storm.⁶ means "(Yulianti et al. The cytokine storm syndrome has been linked to fatal results of COVID-19. There has been speculation that the cytokine storm syndrome influences the severity of the condition⁷.

Several clinical disorders, such as hemolysis, cancer, severe infections and sepsis, liver illnesses, and hematologic malignancies, are associated with high blood levels of lactate dehydrogenase (LDH), an enzyme involved in the conversion of lactate to pyruvate in the cells of most bodily tissues. Various studies now imply that blood LDH levels are a non-specific signal of cellular death in many illnesses, and the present knowledge on the dynamic shift in LDH in COVID-19 pneumonia was relatively still⁸. The vaccine's development takes time since it must be effective and safe. A high degree of safety must be maintained while immunizing healthy individuals⁹. All human beta coronaviruses share the SARS-CoV-2 genome sequence, yet they are all genetically and structurally distinct. SARS-CoV and MERS-CoV share 77% and 50% genetic similarities, respectively¹⁰.

Some people succumb to the sickness, while others are extensively infected with SARS-CoV-2 but show no symptoms of the illness¹¹. COVID-19 is a concerning disease because of the high prevalence of infection, the lengthy incubation period, and the mild to moderate symptoms many people have. Due to research suggesting that COVID-19 might be transmitted without symptoms, vaccination is essential¹².

C-reactive protein (CRP) is a blood test that measures inflammation indirectly. Its concentration is unaffected by age, gender, or physical condition¹³.

The complement system and phagocytosis can both be activated by high CRP levels. As a result, harmful microorganisms infiltrating the body are cleared, and pneumonia may be detected early using this test¹⁴. In some situations, activation of the complement system and the subsequent release of inflammatory cytokines might aggravate tissue injury¹⁵.

MATERIALS AND METHODS

Four hundred blood samples (50 non-vaccinated and 300 vaccinated, 50 control) were collected from individuals between the beginning of September 2021 to the end of October 2022 from health centers and hospitals within Diyala province. Blood samples were divided into vaccinated COVID-19 patients (300) and unvaccinated COVID-19 patients (50) aged 15-90 years. The samples were collected from people with COVID-19 after being diagnosed with the infection through examination in the RT-PCR machine located in the Public Health Department- Baquba Teaching Hospital - Diyala Health Department. Patients' questionnaires are filled with gender, age, vaccine type, and chronic diseases. The healthy samples of 50 individuals included (24 males and 26 females) within

age groups 15-90 years. Their asymptomatic status, COVID-19 antibodies and the reverse transcriptase Real-time-PCR (RT-PCR) result were negative.

Measurement of biochemical tests (D dimer, LDH, FERRITIN, CRP) in serum.

Biochemical tests were performed for 350 patients and 50 controls using the Cobas Integra system plus 400 auto-electrolysis devices (Roshe), which analyzes the results of the following laboratory test LDH parameter. This device is characterized by speed and accuracy, as 400 results are extracted in one hour. Another device for (D DIMER/FERRITIN/CRP). It is an alias 6 Logitech device (made in Korea). Fluorescent technique with 2 chambers, A and B, each chamber takes 3stripsp. This device fully has an automated technique and high accuracy.

Statistical analysis.

Initially, all parameters were checked for normalcy (Kolmogorov-Smirnov and Shapiro-Wilk test). Mean and standard deviation (SD) were used for parameters that passed both tests (no significant difference). In contrast, median and range were used for parameters that failed both tests (significant difference), and Mann-Whitney tests were used to determine whether or not there was a significant difference between the medians (for comparison between two groups). The Pearson-Chi-square test or two-tailed Fisher exact probability was used to determine if there were significant variations in the other parameters' percentage frequencies (p). p-value ≤ 0.05 has been considered significant.

RESULTS

The study shows three significant differences ($p < 0.05$) between LDH, D dimer, ferritin parameters and study groups. The LDH, D dimer and ferritin parameters scored the highest mean value in Unvaccinated patients (442.46 ± 150.78 , 1016.16 ± 400.77 , and 290.61 ± 122.02) and the lowest mean value in vaccinated patients (232.95 ± 111.82 , 929.46 ± 340.54 , and 58.55 ± 25.80) respectively compared to healthy groups. The present study showed significant differences ($p < 0.05$) between CRP parameters and vaccine types. The CRP scored the highest mean value in patients with the Pfizer vaccine (214.65 ± 88.51) and the lowest mean value with AstraZeneca (125.36 ± 55.40). (Table 1).

(Yao et al., 2020) found that COVID-19 patients had higher levels of D dimer than healthy people, and these findings were consistent with the current study. Critically sick individuals with COVID-19 are more likely to suffer from coagulopathy. Microvascular thrombosis may be present in most fatalities, according to new autopsy findings²⁰. COVID-19 patients often show conspicuously higher D-dimers, which have been hypothesized to indicate an underlying thromboembolic load and related to increased mortality in these patients. This has been found in many cases¹⁹. D-dimer levels are now used to guide empiric therapeutic anticoagulation (AC) in treating COVID-19. There is a strong correlation between COVID-19 and increased D-dimer levels. Patients hospitalized for COVID-19 have higher D-dimer levels when their condition is more severe, which is a good predictor of death during the hospital stay (Yao et al., 2020).

		N	Mean	Std. Deviation	P-value
LDH	Un vaccinated	50	442.46	150.78	P<0.001*** LSD= 80.20
	Vaccinated	300	232.95	111.82	
	Healthy	50	195.20	23.23	
D_dimer	Un vaccinated	50	1016.16	400.77	P<0.01** LSD=372.11
	Vaccinated	300	929.46	340.54	
	Healthy	50	361.86	81.16	
Ferritin	Un vaccinated	50	290.61	122.02	P<0.001*** LSD=65.51
	Vaccinated	300	58.55	25.80	
	Healthy	50	92.12	45.89	
CRP	Un vaccinated	50	68.79	33.09	P<0.001*** LSD=41.30
	Vaccinated	300	189.41	80.34	
	Healthy	50	6.12	2.14	

Table 1. comparative LDH, D dimer, and ferritin within study groups using ANOVA (F test).

Relation of LDH, D dimer, CRP and ferritin parameters with the gender of study groups

The current study's result shows significant differences ($p < 0.05$) between the LDH, D dimer, and ferritin parameters and the gender of study groups. The LDH scored the highest mean value in unvaccinated females (448.50 ± 166.33) and least mean value in vaccinated males (192.01 ± 88.85), D dimer scored the highest mean value in vaccinated males (1115.36 ± 500.26), and the least mean value in healthy males (357.54 ± 83.25), ferritin scored highest mean value in unvaccinated males (382.95 ± 150.79), and least mean value in vaccinated females (53.19 ± 21.44) compared to other values (table 2).

According to the study, men were more likely than women to be admitted to the hospital in a serious condition. Death in hospitalized COVID-19 patients was predicted by age, severe illness upon admission, obesity, anemia, D-dimer, estimated glomerular filtration rate, lactate dehydrogenase, and creatine kinase²⁷. Many intermediate effect modifiers, such as anemia, elevated D-dimer, LDH, and CK, were also independently associated with the risk of death in COVID-19 patients. This suggests the need to consider several other parameters apart from gender to better estimate the prognosis of COVID-19 patients. Men with SARS-CoV-2 infection were shown to have a greater level of inflammation than females, which may explain why males had a poorer prognosis than females¹⁹.

The D-dimer test is a useful non-invasive triage diagnostic²⁸ for patients with suspected venous thromboembolism. AstraZeneca vaccination participants who were female were more likely to have D-dimer elevation than those who were male. According to AstraZeneca vaccination data from more than 20 countries, most cases of uncommon blood clotting problems in women under 55 have been resolved²⁹. "Vaccination-induced immune thrombotic thrombocytopenia"

(VITT) is the name given to this unusual occurrence of the AstraZeneca vaccine, which is pathologically similar to heparin-induced thrombocytopenia (HIT) ³⁰. Detection of both the NLR and CRP increased diagnostic performance for COVID-19 when used in conjunction ³¹. correlated higher CRP readings with COPD and poorer lung function in both men and women, and these results were consistent with the current findings. In males, the study found a higher link between systemic inflammation and a decrease in lung function than in women, which is consistent with previous findings.

		Groups						P-value
		Unvaccinated		vaccinated		Healthy		
		Mean	SD	Mean	SD	Mean	SD	
LDH	Male	435.36	144.85	192.01	88.85	193.75	25.68	P<0.001*** LSD= 75.20
	Female	448.50	166.33	281.00	100.05	196.54	21.16	
D_dimer	Male	1028.30	500.68	1115.36	500.26	357.54	83.25	P<0.01** LSD=261.11
	Female	1005.82	399.90	711.22	191.99	365.85	80.63	
Ferritin	Male	382.95	150.79	63.12	29.83	89.58	48.02	P<0.001*** LSD=64.44
	Female	211.96	100.50	53.19	21.44	94.46	44.65	
CRP	Male	67.01	33.85	234.94	100.90	6.17	2.46	P<0.001*** LSD=40.22

Table 2. comparative LDH, D dimer, and ferritin within the gender of study groups using ANOVA (F test).

According to the study, men were more likely than women to be admitted to the hospital in a serious condition. Death in hospitalized COVID-19 patients was predicted by age, severe illness upon admission, obesity, anemia, D-dimer, estimated glomerular filtration rate, lactate dehydrogenase, and creatine kinase ²⁷. Many intermediate effect modifiers, such as anemia, elevated D-dimer, LDH, and CK, were also independently associated with the risk of death in COVID-19 patients. This suggests the need to consider several other parameters apart from gender to better estimate the prognosis of COVID-19 patients. Men with SARS-CoV-2 infection were shown to have a greater level of inflammation than females, which may explain why males had a poorer prognosis than females ¹⁹.

The D-dimer test is a useful non-invasive triage diagnostic ²⁸ for patients with suspected venous thromboembolism. AstraZeneca vaccination participants who were female were more likely to have D-dimer elevation than those who were male. According to AstraZeneca vaccination data from more than 20 countries, most cases of uncommon blood clotting problems in women under 55 have been resolved ²⁹. "Vaccination-induced immune thrombotic thrombocytopenia" (VITT) is the name given to this unusual occurrence of the AstraZeneca vaccine, which is pathologically similar to heparin-induced thrombocytopenia (HIT) ³⁰. Detection of both the NLR and CRP increased diagnostic performance for COVID-19 when used in conjunction ³¹. correlated higher CRP readings with COPD and poorer lung function in both men and women, and these results were consistent with the current findings. In males, the study found a higher link

between systemic inflammation and a decrease in lung function than in women, which is consistent with previous findings.

Relation of LDH, D dimer, and ferritin parameters with vaccine types

The present study showed significant differences ($p < 0.05$) between LDH and D dimer parameters and vaccine types. The LDH scored the highest mean value in patients with the Sinopharm vaccine (332.87 ± 150.94) and the lowest with Pfizer (189.11 ± 90.69). The D dimer scored the highest mean value in patients with the Pfizer vaccine (1183.20 ± 400.01) and the lowest mean value with Sinopharm (584.34 ± 200.60). Finally, ferritin showed no significant differences ($p > 0.05$) among vaccine types (table 3).

		N	Mean	SD	P-value
LDH	Sinopharm	100	332.87	150.94	P<0.05* LSD=100.12
	Pfizer	100	189.11	90.69	
	AstraZeneca	100	195.02	88.23	
D_dimer	Sinopharm	100	584.34	200.60	P<0.05* LSD=355.26
	Pfizer	100	1183.20	400.01	
	AstraZeneca	100	565.81	266.78	
Ferritin	Sinopharm	100	44.34	21.20	P>0.05
	Pfizer	100	64.25	30.72	
	AstraZeneca	100	66.55	31.66	
CRP	Sinopharm	100	166.25	80.34	P<0.05* LSD=41.12
	Pfizer	100	214.65	88.51	
	AstraZeneca	100	125.36	55.40	

Table 3. comparative LDH, D dimer, and ferritin within vaccine types using ANOVA (F test).

The results of this study demonstrate that LDH levels were much lower in patients who received vaccines from Pfizer and AstraZeneca than those who received vaccines from Sinopharm. Researchers found that those who had received messenger RNA vaccinations had longer postvaccination intervals (median, 30.5 days) to breakthrough infection and lower white blood cell counts and lactate dehydrogenase levels when they arrived at the hospital with coronavirus illness 2019.³⁴ After receiving the first dose of the Pfizer vaccine, a 79-year-old female with a warm form of autoimmune hemolytic anemia developed an LDH, which necessitated increasing her steroid dose (to 5 mg day prednisone) and stabilizing her condition following the second dose. After the first dose of the Moderna vaccine, a 73-year-old man with the warm type of autoimmune hemolytic anemia, off-therapy, experienced a recurrence one week later and required prednisone 0.5 mg/kg every day³⁵.

Sinopharm and AstraZeneca vaccines were shown to have the greatest impact on D dimer levels, whereas the Pfizer vaccination had the least effect. Based on

clinical presentation (thrombosis) and laboratory evidence (poor platelets and high levels of D dimer), researchers recently reported the first instance of VITT following an inactivated SARS-CoV-2 vaccination, which has been linked to the development of thrombocytopenia. Additionally, the patient's symptoms and thrombocytopenia returned to normal within two weeks of no heparin anticoagulation³⁶. Patients with suspected vaccine-induced prothrombotic immune thrombocytopenia (VIPIT) may benefit from early non-heparin anticoagulation and high-dose intravenous immunoglobulin (IVIG) therapy, according to study data³⁷.

DISCUSSION

Patients with COVID-19 had lower levels of LDH, D dimer, and ferritin after immunization than in healthy groups, according to the results of this study. When pyruvate is oxidized to lactate by lactate dehydrogenase (LDH), it is an intracellular enzyme that participates in anaerobic glycolysis¹⁶. Blood LDH is frequently measured in a variety of clinical settings. Serum LDH levels have been linked to poor prognosis in various illnesses, including cancer and inflammation¹⁷. Patients with severe COVID-19 have higher serum LDH levels, according to research to date¹⁸. They also matched the current study, finding that LDH levels in COVID-19 patients were higher than in the general population.¹⁹ found that patients with COVID-19 who had high levels of serum LDH upon admission were more likely to die in the hospital. In COVID-19, admission D-dimer levels and trends were linked to outcomes; nevertheless, their predictive performance is limited²¹. There are several mechanisms by which ferritin contributes to the cytokine storm, including its direct immunosuppressive and proinflammatory effects in conditions of high hyperferritinemia²². COVID-19 fatalities have been linked to cytokine storm syndrome, and it has been claimed that illness severity is linked to cytokine storm syndrome. The serum ferritin levels of many people with diabetes are high²³. COVID-19 is recognized to increase the risk of significant side effects for certain patients¹⁹. Predicting the deterioration of COVID-19 patients was made easier by the presence of ferritin²⁰. Infection with COVID-19 may be aided by iron depletion due to iron metabolism. On the other hand, patients undergoing surgery and other frequent phlogistic procedures appear to have self-limited iron changes. Ferritin may be useful as a marker for COVID infection, according to new research²⁴. Study after study has shown that individuals with severe and fatal COVID-19 had higher levels of inflammatory biomarkers, including ESR, CRP, serum ferritin, IL-6, procalcitonin, and the IL-2R receptor in their bloodstream. According to Chinese research, 60.7% of COVID-19 patients had high C-reactive protein levels²⁵. A rise in CRP levels has been linked to a worsening of COVID-19 infection symptoms, such as the development of ARDS⁸. It was revealed that CRP levels rose with illness severity as the median level in mg/dL was 5.35, 7.40, and 10.95 for mild, moderate, and severe COVID-19 patients in Italy hospitalized in hospital²⁶.

According to³², this suggests a gender difference in the processes of lung function loss. Chronic obstructive pulmonary disease (COPD) patients had higher NLR values than healthy control participants of similar age and sex; these levels rose further during acute COPD exacerbations as opposed to periods of stability³³.

CONCLUSION

The vaccine type plays a major role in regulating inflammatory markers in patients with COVID-19.

There is a positive and negative correlation between biochemical and inflammatory markers in patients with COVID-19.

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