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EVALUATION OF THROMBOCYTOPENIA, D-DIMER, INFLAMMATORY CRP, AND CBC MARKERS IN COVID-19 CASES, INCLUDING PATIENTS FROM IRAQ, USING A CASE-CONTROL METHODOLOGY

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ABSTRACT:

COVID-19 is a highly contagious viral illness caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It primarily affects the respiratory system but can also impact other significant organs. Its rapid spread has heightened interest in biomarkers for screening and early diagnosis. This study evaluated D-dimer, C-reactive protein (CRP), and complete blood count (CBC) levels in patients with COVID-19 compared to healthy individuals. A total of 50 healthy individuals and 50 COVID-19 patients, aged 20 to 65, were included in the study, excluding individuals with conditions such as leukemia, thalassemia, or pregnancy. Whole blood and plasma samples were collected for CBC and D-dimer assays and stored at 2-4°C. The COVID-19 patients had significantly higher levels of D-dimer, CRP, white blood cells (WBC), granulocytes, and granulocyte percentage as compared with the healthy individuals ($p<0.01$), lower levels of lymphocyte percentage, mean corpuscular volume (MCV), and mean corpuscular hemoglobin (MCH) ($p<0.01$), as shown. The severe COVID-19 cases often show elevated D-dimer levels, indicating a higher risk of thrombosis. Increased CRP levels correlate with more severe conditions and help assess inflammation severity. A CBC provides insights into blood components, like RBC and WBC, and platelets. During COVID-19, CBC results may reveal lymphopenia, a low lymphocyte count linked to increased severity. For the most accurate and current information, consult healthcare professionals, reliable health organizations, or recent scientific studies on COVID-19.

KEYWORDS: Complete blood count, C-reactive protein, D-dimer, COVID-19.

1. INTRODUCTION

COVID-19, caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), rapidly became a pandemic after emerging in Wuhan, China, in December 2019 (Zhou *et al*, 2020). SARS-CoV-2 infections can lead to a wide range of clinical symptoms, with some individuals remaining completely asymptomatic (Xie *et al*, 2020; Lippi & Favaloro, 2020). The disease can cause severe complications, including acute respiratory distress syndrome, coagulation dysfunction, and death. By November 2020, there had been 55 million infections globally, resulting in about 1.34 million fatalities (Sohrabi *et al*, 2020). Clinical signs can range from mild acute upper respiratory symptoms (fever, cough, and body aches) to multiorgan failure and catastrophic disease. Of these, almost 80% experienced mild symptoms, 13% had severe illness, and just 5% had critical symptoms that required to be admitted to the intensive care unit (ICU) (Tang *et al*, 2020). The human immune system is unfamiliar with this unique coronavirus, and no natural immune system had evolved to combat it. As a result, this could explain why SARS-CoV-2 spread so quickly throughout the world. Disease resistance and infection prevention rely heavily on the immune system (Calder, 2020).

The results of COVID-19 can be predicted by a number of various laboratory markers, such as high-sensitivity cardiac troponin, LDH, D-dimer levels, and CRP (Flower *et al*, 2021. Globally, as of 17 June 2022, the confirmed cases of COVID-19 were 535,863,950, with 6,314,972 estimated deaths, and the number of vaccine doses administered had reached 11,902,271,619 according to WHO. In Iraq, between 3 January 2020 and 22 June 2022, there were 2,333,443 confirmed cases of COVID-19, with 25,229 deaths reported to WHO. As of 20 June 2022, a total of 18,589 vaccination doses had been administered (WHO, 2022). The COVID-19 pandemic affected Iraqi Kurdistan in three waves: the first occurred from March to December 2020, the second from January to June 2021, and the third from July to December 2021 (Merza *et al*, 2021). Phylogenetic analysis revealed similarities between the viral genome in Kurdistan and isolates from USA, UK, Germany, Austria, Canada, Australia, Denmark, Poland, and Colorado, indicating multiple virus introductions. Further research could clarify its infectivity and virulence (Taher *et al*, 2023).

The increasing trends of COVID-19 in the two neighboring countries, Iran and Turkey, had alarming effects on Iraqi Kurdistan. The first cases were reported in Iraq and Iraqi Kurdistan on February 24, 2020 and March 1, 2020 respectively (Merza *et al*, 2020; Merza, *et al*, 2021). Saudi Arabia is one of

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the countries that battled the pandemic in its early phases (Khan *et al*, 2021). The first case of COVID-19 in the world was discovered in March 2020, and once the first wave of COVID-19 ended, 557,082 individuals had been infected with SARS-CoV-2, and 8878 deaths were reported at the end of 2021 (Sharma *et al.*, 2020). The second COVID-19 wave is in its early stages in Saudi Arabia, while the third wave had already begun in some countries. This rapid progression has been driven by emerging variants of the virus, which have required new preventive and corrective measures to combat the emergence of each variant (Otto *et al*, 2021).

Coagulation indicators and D-dimer identification early on can help manage and control COVID-19 (Huang *et al*, 2021). Thus, in the context of a prothrombotic state, elevated D-dimer levels in COVID-19 patients may help in the early identification of individuals with major medical issues, pulmonary difficulties, and a high risk of venous thromboembolism. This would support early therapeutic strategy deployment and risk classification, both of which could lower COVID-19 morbidity and mortality (Khan *et al*, 2021). C-reactive protein (CRP), a plasma protein produced by hepatocytes, can be elevated by various inflammatory mediators, including IL-6. CRP is an acute-phase protein that serves as an early warning indication of infection or inflammation (Elbe & Buckland-Merrett, 2017). When clinical features are paired with biological markers like CRP, they become more understandable. As a result, CRP levels may be necessary for early detection and treatment of COVID-19-related diseases (Upadhyay *et al*, 2020). All patients receive a Complete Blood Count (CBC), a routine test that provides vital information that may aid in clinical care. This information includes the stage of inflammatory disease, etiology, anemia, and therapeutic response, presence of infection or inflammation, and diagnosis. Individuals who are more likely to have COVID-19 could be identified with the help of basic blood testing and clinical observations (Li *et al*, 2020).

The purpose of this study is to compare the levels of specific biomarkers through estimated D-dimer, CRP, and Complete Blood Count (CBC) levels between COVID-19 patients and healthy individuals to assess disease severity. Elevated D-dimer and CRP levels are associated with inflammation and coagulation abnormalities. Identifying CBC patterns can help understand the impact on blood parameters, potentially improving patient care and outcomes.

2. MATERIALS AND METHODS

Clients and Study Designs

This study took place from April to August 2022 at the private medical Jin Complex laboratory. Patients who visited the laboratory provided samples. Fifty COVID-19 patients and fifty healthy controls, ranging in age from 20 to 65, participated in the study. The positive samples were confirmed as COVID-19 using molecular diagnostic tools (PowerChek 2019-nCoV Real-time PCR Kit) according to the manufacturer's procedure. A medical expert identified the people who tested positive for the virus and had elevated CRP as COVID-19 patients.

Collection of samples

A nasopharyngeal swab was collected from 100 samples (50 COVID-19 patients and 50 non-COVID-19 samples). Ten milliliters of blood were collected from each subject using disposable syringes and vein punctures. Five milliliters were placed in an Ethylene diamine tetraacetic acid EDTA tube, three milliliters in buffered sodium citrate, and two milliliters in gel tubes. To perform CBC and D-dimer assays, whole blood and plasma samples were refrigerated at 2 to 4 °C post-collection. The gel tube samples were centrifuged at 3000 g for 10 minutes for CRP detection, and the resulting serum was stored at -20 °C until analysis.

Sample Analysis.

Using the ELFA technique (Enzyme Linked Fluorescent Assay) and a commercially available protocol, the D-dimer was evaluated using VIDAS D-DIMER Exclusion II (60 Tests) equipment for the immunoenzymatic assessment of fibrin degradation products (FbDP) in human plasma (sodium citrate) (Chen *et al*, 2020). CRP was quantified using Eurolyser Diagnostics GmbH Bayemstrabe II a 5020 in Austria. The concentration was determined kinetically by photometric detection of the antigen-antibody interaction between the sample's CRP and antibodies to human CRP attached to polystyrene particles at 546 nm or 700 nm. For the CBC profile, the Swelab AlfaDiluent and RFID Swelab AlfaLyse system (Spnga, Sweden) were used.

Statistical Analysis.

Statistical tests were considered significant at $p < 0.05$ and highly significant at $p < 0.01$, using a 95% confidence range. The independent samples students' t-test and descriptive statistics were tools used to analyze all the data in the Statistical Package for Social Sciences (SPSS) version 25 and RStudio version 4.3.3. The data were analyzed using descriptive statistics and the Independent Samples Students' t-test. To identify the most significant predictors, stepwise regression analysis was employed. This method was chosen to optimize model selection by including only those variables that significantly contributed to the model's predictive power. The results of the stepwise regression are presented in Table 3 of the Results section, where the mean and standard deviation of the results are also displayed. For each regression model, an Analysis of Variance (ANOVA) table was generated to assess the overall significance of the predictors. The ANOVA table includes the following key components.

Table 1: The ANOVA table was generated to assess the overall significance of the predictors.

SOURCE	DF	SS	MS	F	P-VALUE
FACTOR	m-1	SS (Between)	MSB	MSB/MSE	0.00
ERROR	n-m	SS (Error)	MSE		
TOTEL	n-1	SS (Total)			

SS: Sum of Squares; DF Degrees of Freedom; MSE Mean Square Error; F-statistic: Ratio of the regression mean square to the residual mean square, used to test the significance of the overall model. Factor DF: m−1, where m is the number of groups; Error DF: n−m, where n is the total number of observations; Total DF: n−1. Significance level (p-value): Indicates whether the observed F-statistic is statistically significant, helping to determine if the predictors have a significant impact on the dependent variable.

3. RESULTS

The gender distribution of the patients and control groups is shown in Figure 1. Male representation was 62%, higher than the female percentage, which was only 38%. The gender distribution among COVID-19 patients was 58% male and 42% female.

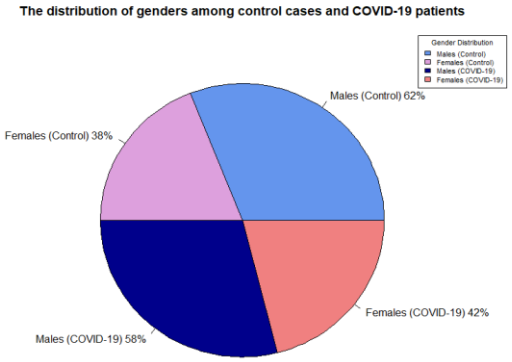

Figure 1: The pie chart above illustrates the gender distribution among control cases and COVID-19 patients

The descriptive statistics provide a comprehensive overview of the variables analyzed in the study. The table compares several hematological parameters between two groups, patients and a control group (likely healthy individuals), with a corresponding p-value indicating the statistical significance of the differences, so an explanation of the key elements: The measured blood components parameters are D-dimer (ng/ml): Indicates clot formation and breakdown with patients having 1164.34±944.64 and the control group having 157.32±81.81 with a P-value of 0.001 (Significant difference), while the CRP (C-reactive protein) (mg/l): A marker of in patients is 42.98±28.42 and in the control group is 2.584±1.78, with a P-value of 0.001 (Significant difference). About Platelets (10^9/l): Cells involved in blood clotting: patients have 237.52±71.11 and the control group has 256.32±70.37, with a P-value of 0.147 (Not significant). The WBC (10^9/l): Indicator of the immune response. Patients have 10.06±3.99 and the control group has 7.42±1.76, with a P-value of 0.001 (Significant difference). The Granulocyte (10^9/l) in patients is 7.15±3.7, and in the control group is 4.48±1.4, with a P-value of 0.001. The Granulocyte (%) in patients is 68.7±11.67%, and in the control group is 57.07±9.38%, with a P-value of 0.001. The Lymphocyte (10^9/l) patients have 2.22±0.79, and the control group has 2.43±0.61, with a P-value of 0.041. Lymphocyte (%): The percentage of total WBC lymphocytes in patients is 25.19±10.67%, and in the control group is 33.49±9.28%, with a P-value of 0.001. About the RBC (10^{12}/l): patients have 4.81±0.63, and the control group has 4.63±0.46, with a P-value of 0.174 (Not significant). The Hemoglobin (HB) (g/dl) Protein in RBCs that carries oxygen in patients is 12.48±1.94, and in the control group, it is 12.69±1.44, with a P-value of 0.255 (Not significant). Hematocrit (HTC) (%) in patients is 40.2±6.22, and in the control group is 41.53±4.81, with a P-value of 0.108 (Not significant). The MCV Patients have 83.98±7.73 and the control group has 89.82±4.83, with a P-value of 0.001 (Significant difference). The MCH in patients is 26.12±2.64 and in the control group, it is 27.5±1.66, with a P-value of 0.001 (Significant difference). MCHC in patients is 31.07±1.07 and in the control group, it is 30.29±1.45, with a P-value of 0.022 (Slightly significant) the P-values were $P < 0.05$: So, the significant differences (marked with * or **) and $P \geq 0.05$: Not significant (NS)

Significant differences exist in markers like D-dimer, CRP, WBC, granulocytes, and some RBC indices (MCV, MCH, and MCHC). Non-significant differences include platelets, RBC, hemoglobin, and hematocrit. The patient group generally shows signs of increased inflammation (elevated D-dimer, CRP, and WBC) compared to the control group.

The skewness is positive (1.041), suggesting a tendency towards higher counts. The granulocyte's mean is 6.287 with a significant positive skew (3.84), indicating a distribution with high values. This variable RBC shows extreme positive skewness (9.182) and kurtosis (90.669), suggesting outliers at higher values. The concentration of HB and HCT both variables show slight negative skewness and moderate kurtosis, indicating relatively symmetrical distributions, but with some outliers. Finally, the MCV, MCH, and MCHC. These metrics have relatively low skewness and moderate kurtosis, indicating near-normal distributions. Based on the above results and Table 2, it is evident that the data does not meet normal assumptions. To address this, we will implement various transformation techniques to achieve a more normal distribution. The selected transformations are detailed in Table 3.

Table 2: shows the statistics of the parameters evaluated for patients with the COVID-19 and the control group.

Hematological parameters	Patients	Control	*P*-value
D-dimer (ng/ml)	1164.34±944.64	157.32±81.81	0.001**
CRP (mg/l)	42.98±28.42	2.584±1.78	0.001**
Platelets (10^9/l)	237.52±71.11	256.32±70.37	0.147 (NS)
WBC (10^9/l)	10.06±3.99	7.42±1.76	0.001**
Granulocyte (10^9/l)	7.15±3.7	4.48±1.4	0.001**
Granulocyte (%)	68.7±11.67	57.07±9.38	0.001**
Lymphocyte (10^9/l)	2.22±0.79	2.43±0.61	0.041*
Lymphocyte (%)	25.19±10.67	33.49±9.28	0.001**
RBC (10^{12}/l)	4.81±0.63	4.63±0.46	0.174 (NS)
HB (g/dl)	12.48±1.94	12.69±1.44	0.255 (NS)
HTC (%)	40.2±6.22	41.53±4.81	0.108 (NS)
MCV (fl)	83.98±7.73	89.82±4.83	0.001**
MCH (pg)	26.12±2.64	27.5±1.66	0.001**
MCHC (g/dl)	31.07±1.07	30.29±1.45	0.022**

Table 3 below displays the chosen transformations for each variable, along with their skewness and kurtosis values. Figure 2 shows the correlation matrix, reveals both strong and weak relationships among the transformed variables, with notable patterns of high positive and negative correlations that could guide further analysis or modeling.

Table 3: Summarizing the best transformation for each variable based on skewness and kurtosis from the two sets of results:

Variable	Best Transformation	Skewness	Kurtosis
D-dimer ng/m	Ddimer_boxcox	0.21	-1.22
CRP mg/l	CRP log	0.29	-1.29
Platelet $10^9/l$	Platelet_sqrt	-0.96	3.40
WBC $10^9/l$	WBC_log	0.31	-0.42
Gran $10^9/l$	Gran_sqrt	0.90	1.15
Gran100	Gran100_log	-0.75	18.04
Lym	Lym_log	0.29	0.92
Lym100	Lym100_inv	1.32	1.64

Figure 2 below shows significant linear correlations between the transformed variables that are highlighted in the correlation matrix. There is a significant positive relationship (r = 0.77) between D-dimer and CRP levels between D-dimer_boxcox and CRP_log. Similarly, there appears to be a link between granulocyte levels and WBC, as evidenced by the strong correlation (r = 0.72) between WBC_log and Gran_sqrt. Hb100_sqr and HCT_sqr exhibit a nearly perfect correlation (r = 0.97) that is indicative of their polynomial transformations. On the other hand, there is a slight negative connection (r = -0.15) between D-dimer_boxcox and Gran100_inv, and a negative correlation (r = -0.52) between Lym_log and Lym100_inv. A number of variables show low correlations, and strong p-values support the strength of these associations, especially for CRP log and D-dimer_boxcox ($p < 0.0001$)

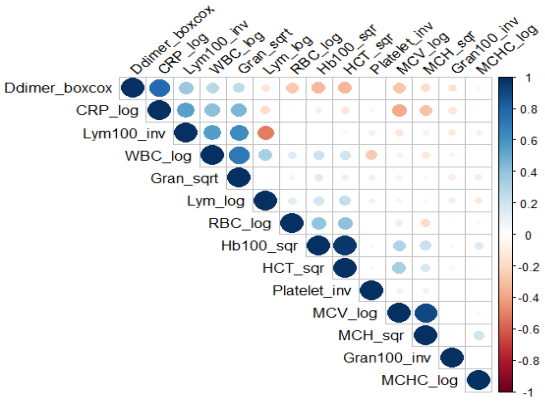

Figure 2: Correlation Matrix of Transformed Variables

. Table 4 below shows the stepwise regression analysis and shows that the model accounts for approximately 75.7% of the variance in the response variable, with an adjusted R-squared of 74.1%. Significant predictors include D-dimer_boxcox (p = 0.00312), CRP_log (p < 2e-16), WBC_log (p = 0.02549), and MCH_sqr (p = 0.00707), indicating their significant impact on the outcome. HB100_sqr is marginally significant (p = 0.08365), but Gran_sqrt is not statistically significant (p = 0.15839). The residual standard error is 20.37, which represents the average deviation between the observed values and the model's predictions. The model has a firm fit, but further refinement could improve prediction accuracy by examining more interactions or non-linear relationships. Expressing the stepwise regression model in equation form based on the provided coefficients: According to Table 4, the final model, which represents the best combination of predictors identified through the stepwise regression process for predicting c, is expressed as follows:

COVID19 Severity=132.78−99.85×Ddimer_boxcox+29.78×CRP_log+20.59×WBC_log−6.59×Gran_sqrt−0.09×Hb100_sqr+0.044×MCH_sqr

Where: COVID-19 Severity dependent variable

And Ddimer boxcox, CRP_log,WBC_log ,Gran_sqrt, Hb100_sqr, MCH_sqr are dependent variables.

The above equation reflects the optimal model derived from the stepwise regression, incorporating the most significant predictors to explain the variability in COVID-19 severity.

Table 4: Overview of the Stepwise Regression Model.

Residuals:				
Min	1Q	Median	3Q	Max
-38.208	-12.747	-3.465	10.92	93.355
Coefficients:	Estimate	Std. Error	t value	Pr(>|t|)
(Intercept)	132.78294	71.13870	1.867	0.06508.
Ddimer_boxcox	-99.85124	32.91491	-3.034	0.00312 **
CRP_log	29.77760	2.66606	11.169	< 2e-16 ***
WBC_log	20.59175	9.07087	2.270	0.02549 *
Gran_sqrt	-6.59474	4.63821	-1.422	0.15839
HB100_sqr	-0.09402	0.05377	-1.748	0.08365.
MCH_sqr	0.04428	0.01608	2.754	0.00707 **

Significant codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Residual standard error: 20.37 on 94 degrees of freedom
Multiple R-squared: 0.7569, Adjusted R-squared: 0.7413
F-statistic: 48.77 on 6 and 94 DF, p-value: < 2.2e-16
Figure 3 below shows the relationship between the fitted values from the model and the current values of D-dimer_boxcox. This will help in visually assessing how well the model predicts the actual data. The geom_smooth line should ideally show how well the predicted values align with the actual values, indicating the model's fit.

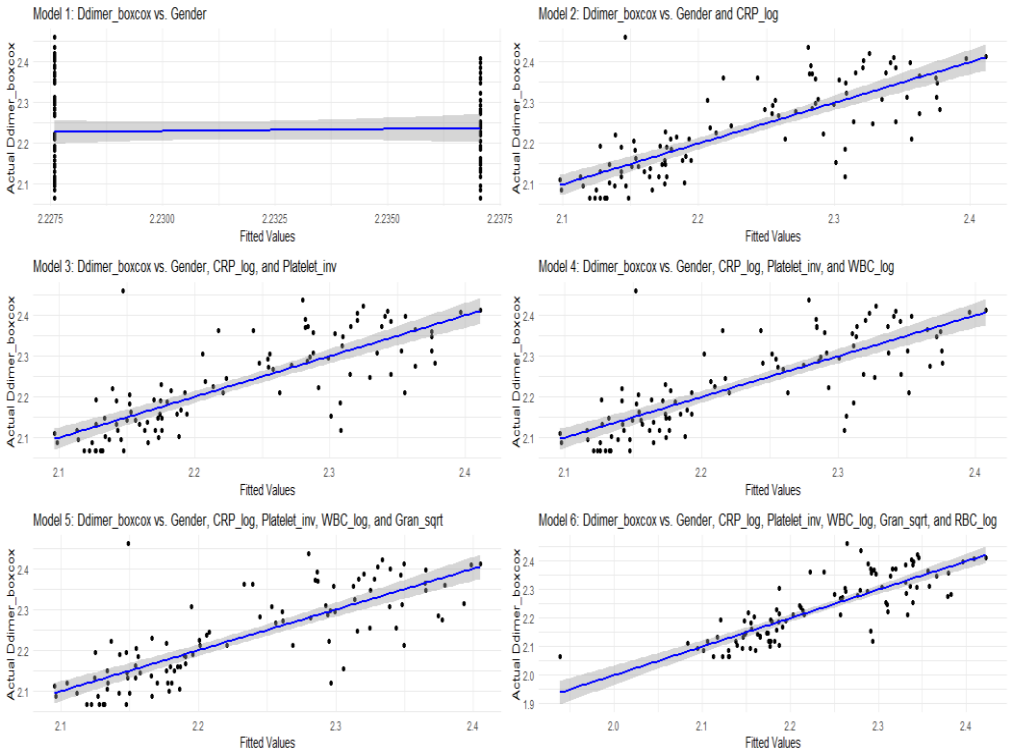

Figure 3: Fitted vs. Actual Values of D-dimer_boxcox from Stepwise Regression Model The following is shown by the stepwise regression model's ANOVA results in Table 5The ANOVA results for the stepwise regression model indicate the following:

D-dimer_boxcox and CRP_log are highly significant predictors of the response variable CRP_log with p< < 2.2e-16 ***. Both variables exhibit large F-values, suggesting strong effects on the response. MCH_sqr is also significant with p=0.007066, indicating that its contribution to explaining the variability in CRP_1 is noteworthy, though less prominent compared to D-dimer_boxcox and CRP_log. WBC_log, Gran_sqrt, and HB100_sqr do not show significant effects, with p-values above 0.05. These variables do not significantly contribute to explaining CRP_1 in the context of this model. The residuals account for a significant portion of the variance, suggesting that while the model explains a considerable amount of variability, there are still unexplained factors influencing CRP_1.

Table 5: Analysis of Variance for Stepwise Regression Model

Variable	Df	Sum Sq	Mean Sq	F value	Pr(>F)
Ddimer_boxcox	1	54308	54308	130.8980	< 2.2e-16 ***
CRP_log	1	62378	62378	150.3498	< 2.2e-16 ***
WBC_log	1	809	809	1.9496	0.165921
Gran_sqrt	1	344	344	0.8285	0.365046
Hb100_sqr	1	410	410	0.9892	0.322497
MCH_sqr	1	3147	3147	7.5852	0.007066 **
Residuals	94	38999	414		

Significance Codes: 0 '' 0.001 '' 0.01 '' 0.05 '.' 0.1 '' 1

4. DISCUSSION

D-dimer is a fibrin decomposition product that consists of several cross-linked D domains and/or E domains from the original fibrinogen molecule, and its formation is only theoretically conceivable when both the hemostasis and fibrinolysis pathways are engaged. In the early stages of COVID-19 illness, our study found from the data in Table 2 that D-dimer in patients was increased compared to the control, which means it is statistically significant (p = 0.001). This data was in agreement with that of (Rostami & Mansouritorghabeh, 2020). Regarding the specific relationship between D-dimer levels and COVID-19, severe COVID-19 can lead to a hypercoagulable state, which increases the risk of blood clot formation. Recent findings show that D-dimer elevations are common in patients with SARS-CoV-2infection (especially in those with

thrombosis), that its value predicts the clinical severity (up to death) of COVID-19, and that it remains more frequently elevated in COVID-19 patients with post-discharge clinical sequelae (Lippi *et al*, 2023). CRP levels were statistically significantly elevated (p = 0.001), in patients compared to the control group, so by comparing our findings with those of other researchers, we found that high levels of CRP in the blood (Ali, 2020). Other studies have shown that higher CRP levels are associated with a more severe course of COVID-19.

In the context of COVID-19, CRP levels can be elevated, particularly in severe cases or individuals with complications such as pneumonia (Abdelhadi & Kassem, 2021), and this may be an increase in CRP produced by the liver in response to inflammation, infection, and tissue damage. CRP elevations in the blood can be utilized as a biomarker of inflammation since they signify an acute-phase response (xu *et al*, 2020). This is most likely because the immune system responds to viral infections more forcefully by producing a variety of immunological chemicals. In COVID-19 patients, excessive CRP production above normal limits may result in organ failure. CBC results can help providers assess overall health, detect infections or abnormalities, and monitor response to treatment. CBC results in individuals infected with COVID-19 may show specific changes that indicate the presence of the infection or its impact on the body. These changes may include alterations in WBC counts, among the different subtypes of WBCs, such as lymphocytes, neutrophils, and monocytes. COVID-19 can cause Lymphopenia (decreased lymphocyte count) and Neutrophilia (increased neutrophil count) in some cases as happened with our patients' results, although individual variations exist (Petrone *et al*, 2021). However, many studies have investigated the trends of lymphocyte count during the progression of the disease in COVID-19 patients. It was found that lymphocytes declined over time in non-survivors and increased in survivors in the early hospitalization stage. Within 10 days after admission, the difference in lymphocyte counts between the two groups increased by 0.0731 × 109/L per day (Chen *et al*, 2023).

The granulocyte count, particularly neutrophils, is often elevated in COVID-19, reflecting an intense inflammatory and immune response. This study and our findings confirm significantly higher granulocyte levels in patients compared to controls, aligning with other research indicating that elevated granulocytes are a hallmark of severe COVID-19 and are associated with poor (Li *et al*, 2023). Thromboembolic problems and systemic inflammation are associated with higher COVID-19 death rates. Neutrophilia is involved in the necrotic inflammatory response and is a sign of venous thrombosis. Although protective, neutrophil extracellular traps can have adverse effects when an infection is present. Cytokine storms, which result in acute respiratory distress syndrome (ARDS) and severe inflammatory response syndrome (SIRS), can be caused by improper phagocytosis and excessive extracellular trap formation. The immune system's homeostasis and inflammatory reactions depend heavily on lymphocytes. Research indicates that individuals with elevated WBC levels and reduced levels of lymphocytes, monocytes, basophils, and eosinophils may be prone to inflammation. In COVID-19 patients, eosinophils are helpful and reduce neutrophil-induced inflammation (Qin *et al*, 2020).

Hemoglobin and hematocrit levels reflect the oxygen-carrying capacity of the blood. In COVID-19, these levels may be influenced by inflammatory processes and comorbidities. The lack of significant differences between patients and controls is similar to our results from the data in Table 2, which suggests that they might not vary as markedly as other hematologic parameters in response to COVID-19 (Li *et al*., 2020). Anemia is not a common finding in patients suffering from COVID-19. Other different results indicate lower hemoglobin-related parameters and a reduced RBC volume in the COVID groups compared to control subjects, thus supporting recent data (Bros *et al*, 2023). RBC counts can be affected by COVID-19 through mechanisms such as inflammation-induced anemia or hemoconcentration due to dehydration. Although RBC counts were lower in patients compared to controls, the lack of statistical significance (p-value = 0.174) from our findings suggest that RBC count alone may not be a strong indicator of COVID-19 severity (Henry *et al*, 2020).

This variability could be due to the complex interplay of factors such as the body's inflammatory response and pre-existing conditions, while RBC deformability has been reported to be reduced after SARS-CoV-2 infection in critically ill patients, but also in patients showing a relatively mild disease course (Bros *et al*, 2023). This study showed that low MCV and MCH were both with (p = 0.001) significantly associated with the severity of the illness. So, a comprehensive analysis of the RBC parameters would be helpful for early identification and better management of severe COVID-19 disease. A significantly higher level of MCHC (p-value = 0.022) was observed with our data results shown n table 2, where similarly lower levels of MCHC are reported to be associated with disease severity and mortality in COVID-19 of this study (Mao *et al*, 2021). However, in a previous study, significantly higher MCHC levels were found in COVID-19 survivors regardless of the post-COVID-19 symptoms compared to healthy subjects (Gameil *et al* 2021). While other different results of COVID-19 cases were found to have significantly lower levels of Hb concentration MCH, MCHC, and MCV in comparison with negative patients, this result is quite similar to that of previously reported studies (Elkhalifa *et al*, 2022). Platelet counts in COVID-19 can vary, with some studies reporting thrombocytopenia and others showing normal or even elevated counts. In this study, the mean platelet count was lower in patients compared to controls, which is consistent with findings that thrombocytopenia is common in severe COVID-19 cases (Lippi *et al*, 2020). However, the lack of significant difference (p-value = 0.147) suggests that platelet count alone might not be a reliable marker for disease severity in all cases. A detailed understanding of immune responses following SARS-CoV2 infection will enable better treatment and diagnostic procedures, as well as the development of successful vaccines that will help to control the global COVID-19 pandemic. In this regard, it is essential to better understand the presence of neutralizing anti-SARS-CoV-2 serum antibodies in the population, as they potentially prevent (re)infection and might be a treatment option (Abdullah *et al*, 2023). Our research has significant limitations. First, COVID-19 patients' BMI and treatments were not taken into account. Second, the research exclusively covered patients from the Duhok City region.

CONCLUSION

The study highlights the significant elevation of D-dimer and CRP levels in COVID-19 patients compared to controls, indicating a hypercoagulable state and inflammatory response that correlate with disease severity. Elevated D-dimer is associated with worse outcomes and thrombosis, while CRP

serves as a biomarker of inflammation, particularly in severe cases. Hematological findings reveal changes in white blood cell counts, including lymphopenia and neutrophilia, which reflect the immune response to the virus. Although red blood cell parameters showed variability, low MCV and MCH were linked to illness severity. Thrombocytopenia was noted, but without significant differences in platelet counts. Overall, understanding these hematological and inflammatory markers can aid in the management of COVID-19.

REFERENCES

Abdelhadi, A., & Kassem, A. (2021). Candida pneumonia with lung abscess as a complication of severe COVID-19 pneumonia. International medical case reports journal, 853-861. doi: https://doi.org/10.2147/IMCRJ.S342054.

Abdullah, Z. M., Goreal, A. A., & Abdo, J. M. (2023). Impact of SARS-CoV-2 RNA titer on the level of IgG antibodies in recovered patients with COVID-19 disease. The Journal of Infection in Developing Countries, 17(04), 432-438. https://doi.org/10.3855/jidc.17372

Ali, N. (2020). Elevated levels of C-reactive protein may be an early marker to predict the risk for the severity of COVID-19. *Journal of medical virology*, *92*(11), 2409. doi: https://doi.org/10.1002/jmv.26097

Bros, J., Ibershoff, L., Zollmann, E., Zacher, J., Tomschi, F., Predel, H. G. & Grau, M. (2023). Changes in Hematological and Hemorheological Parameters Following Mild COVID-19: A 4-Month Follow-Up Study. *Hematology reports*, *15*(4), 543-554. https://doi.org/10.3390/hematolrep15040057

Calder, P. C. (2020). Nutrition, immunity and COVID-19. *BMJ nutrition, prevention & health*, *3*(1), 74. https://doi.org/10.1136%2Fbmjnph-2020-000085

Chen, G., Zhao, X., Chen, X., & Liu, C. (2023). Early decrease in blood lymphocyte count is associated with poor prognosis in COVID-19 patients: a retrospective cohort study. *BMC Pulmonary Medicine*, *23*(1), 453. https://doi.org/10.1186/s12890-023-02767-z

Chen, W., Zheng, K. I., Liu, S., Yan, Z., Xu, C., & Qiao, Z. (2020). Plasma CRP level is positively associated with the severity of COVID-19. *Annals of clinical microbiology and antimicrobials*, *19*, 1-7. https://doi.org/10.1186/s12941-020-00362-2

Elbe, S., & Buckland-Merrett, G. (2017). Data, disease and diplomacy: GISAID's innovative contribution to global health. *Global challenges*, *1*(1), 33-46. https://doi.org/10.1002/jcp.30367

Elkhalifa, A. M., Elderdery, A. Y., Al Bataj, I. A., Tamomh, A. G., Alyami, M. M., Almakrami, H. A., ... & Mok, P. L. (2022). [Retracted] Hematological Findings among COVID-19 Patients Attending King Khalid Hospital at Najran, Kingdom of Saudi Arabia. *BioMed Research International*, *2022*(1), 4620037. https://doi.org/10.1155%2F2022%2F4620037

Flower, T. G., Buffalo, C. Z., Hooy, R. M., Allaire, M., Ren, X., & Hurley, J. H. (2021). Structure of SARS-CoV-2 ORF8, a rapidly evolving immune evasion protein. *Proceedings of the National Academy of Sciences*, *118*(2), e2021785118. https://doi.org/10.1073/pnas.2021785118

Gameil, M. A., Marzouk, R. E., Elsebaie, A. H., & Rozaik, S. E. (2021). Long-term clinical and biochemical residue after COVID-19 recovery. *Egyptian liver journal*, *11*, 1-8. https://doi.org/10.1186/s43066-021-00144-1

Henry, B. M., et al. (2020). Hematologic abnormalities in patients with COVID-19: A review. *American Journal of Hematology*, 95(7), 773 783. https://doi.org/10.1515/cclm-2020-0369

Huang, H., Zhu, Y., Niu, Z., Zhou, L., & Sun, Q. (2021). SARS-CoV-2 N501Y variants of concern and their potential transmission by mouse. *Cell Death & Differentiation*, *28*(10), 2840-2842. https://doi.org/10.1038/s41418-021-00846-4

Khan, A., Alsofayan, Y., Alahmari, A., Alowais, J., Algwizani, A., Alserehi, H., & Jokhdar, H. (2021). COVID-19 in Saudi Arabia: the national health response. *Eastern Mediterranean Health Journal*, *27*(11), 1114-1124. https://doi.org/10.26719/emhj.21.048

Khan, A., Zia, T., Suleman, M., Khan, T., Ali, S. S., Abbasi, A. A., ... & Wei, D. Q. (2021). Higher infectivity of the SARS-CoV-2 new variants is associated with K417N/T, E484K, and N501Y mutants: an insight from structural data. *Journal of cellular physiology*, *236*(10), 7045-7057. https://doi.org/10.1002/jcp.30367

Li, J., Zhang, K., Zhang, Y., Gu, Z., & Huang, C. (2023). Neutrophils in COVID-19: recent insights and advances. *Virology journal*, *20*(1), 169. https://doi.org/10.1186/s12985-023-02116-w

Li, Q., Cao, Y., Chen, L., Wu, D., Yu, J., Wang, H., & Hu, Y. (2020). Hematological features of persons with COVID-19. *Leukemia*, *34*(8),2163-2172. https://doi.org/10.1038%2Fs41375-020-0910-1

Li, Q., Guan, X., Wu, P., Wang, X., Zhou, L., Tong, Y., & Feng, Z. (2020). Early transmission dynamics in Wuhan, China, of novel coronavirus–infected pneumonia. *New England journal of medicine*, *382*(13), 1199-1207. DOI: https://doi.org/10.1056/NEJMoa2001316.

Lippi, G., & Favaloro, E. J. (2020). D-dimer is associated with severity of coronavirus disease 2019: a pooled analysis. *Thrombosis and haemostasis*, *120*(05), 876-878. DOI: https://doi.org/10.1055/s-0040-1709650

Lippi, G., Mullier, F., & Favaloro, E. J. (2023). D-dimer: old dogmas, new (COVID-19) tricks. *Clinical Chemistry and Laboratory Medicine (CCLM)*, *61*(5), 841-850. https://doi.org/10.1515/cclm-2022-0633

Lippi, G., Plebani, M., & Henry, B. M. (2020). Thrombocytopenia is associated with severe coronavirus disease 2019 (COVID-19) infections: a meta-analysis. *Clinica chimica acta*, *506*, 145-148. https://doi.org/1 https://doi.org/10.1016/j.cca.2020.03.022

Mao, J., Dai, R., Du, R. C., Zhu, Y., Shui, L. P., & Luo, X. H. (2021). Hematologic changes predict clinical outcome in recovered patients with COVID-19. *Annals of hematology*, *100*(3), 675-689. https://doi.org/10.1007/s00277-021-04426-x

Merza, M. A., Al Mezori, A. A. H., Mohammed, H. M., & Abdulah, D. M. (2020). COVID-19 outbreak in Iraqi Kurdistan: The first report characterizing epidemiological, clinical, laboratory, and radiological findings of the disease. *Diabetes & Metabolic Syndrome: Clinical Research & Reviews*, *14*(4), 547-554. https://doi.org/10.1016/j.dsx.2020.04.047

Merza, M. A., Aswad, S. M., Sulaiman, H. M., Abdulah, D. M., Rasheed, W. S., & Taib, N. I. (2021). Clinical and epidemiological characteristics and outcomes of Coronavirus disease-19 patients in a large longitudinal study. *International journal of health sciences*, *15*(4), 29. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8265303/

Otto, S. P., Day, T., Arino, J., Colijn, C., Dushoff, J., Li, M., & Ogden, N. H. (2021). The origins and potential future of SARS-CoV-2 variants of concern in the evolving COVID-19 pandemic. *Current Biology*, *31*(14), R918-R929. https://doi.org/10.1016/j.cub.2021.06.049

Petrone, L., Petruccioli, E., Vanini, V., Cuzzi, G., Fard, S. N., Alonzi, T., & Goletti, D. (2021). A whole blood test to measure SARS-CoV-2-specific response in COVID-19

patients. *Clinical microbiology and infection*, *27*(2), 286-e7.doi: https://doi.org/10.1016/j.cmi.2020.09.051.

Qin, C., Zhou, L., Hu, Z., Zhang, S., Yang, S., Tao, Y., ... & Tian, D. S. (2020). Dysregulation of immune response in patients with coronavirus 2019 (COVID-19) in Wuhan, China. *Clinical infectious diseases*, *71*(15), 762-768. https://doi.org/10.1093/cid/ciaa248.

Rostami, M., & Mansouritorghabeh, H. (2020). D-dimer level in COVID-19 infection: a systematic review. *Expert review of hematology*, *13*(11), 1265-1275. https://doi.org/10.1080/17474086.2020.1831383

Sharma, A., Tiwari, S., Deb, M. K., & Marty, J. L. (2020). Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2): a global pandemic and treatment strategies. *International journal of antimicrobial agents*, *56*(2), 106054. https://doi.org/10.1016/j.ijantimicag.2020.106054

Sohrabi, C., Alsafi, Z., O'neill, N., Khan, M., Kerwan, A., Al-Jabir, A., & Agha, R. (2020). World Health Organization declares global emergency: A review of the 2019 novel coronavirus (COVID-19). *International journal of surgery*, *76*, 71-76. https://doi.org/10.1016/j.ijsu.2020.02.034

Taher, S. M., Abdo, J. M., & Merza, M. A. (2023). Whole Genome Sequence Analysis of SARS-COV-2 Isolated from COVID-19 Patients in Duhok Province, Iraq. https://doi.org/10.20944/preprints202304.0961.v1

Tang, N., Li, D., Wang, X., & Sun, Z. (2020). Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *Journal of thrombosis and haemostasis*, *18*(4), 844-847. https://doi.org/10.1111/jth.14768

Upadhyay, J., Tiwari, N., & Ansari, M. N. (2020). Role of inflammatory markers in corona virus disease (COVID-19) patients: a review. *Experimental Biology and Medicine*, *245*(15), 1368-1375. https://doi.org/10.1177/1535370220939477

World Health Organization (2022) WHO health emergency dashboard who (covid-19) homepage. Available: https://www.who.int/emergencies/diseases/novel-coronavirus-2019 Accessed: 20 June 2022.

Xie, J., Tong, Z., Guan, X., Du, B., & Qiu, H. (2020). Clinical characteristics of patients who died of coronavirus disease 2019 in China. *JAMA network open*, *3*(4), e205619-e205619. doi: https://doi.org/10.1001/jamanetworkopen.2020.5619

Xu, X., Chen, P., Wang, J., Feng, J., Zhou, H., Li, X., ... & Hao, P. (2020). Evolution of the novel coronavirus from the ongoing Wuhan outbreak and modeling of its spike protein for risk of human transmission. *Science China Life Sciences*, *63*, 457-460. https://doi.org/10.1007/s11427-020-1637-5 Zhou, P., Yang, X. L., Wang, X. G., Hu, B., Zhang, L., Zhang, W., & Shi, Z. L. (2020). A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature*, *579*(7798), 270-273. https://doi.org/10.1038/s41586-020-2012-7