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Determination of Some Hematological, Biochemical Parameters and Vitamin D Receptor Gene Polymorphism in Kurdish Patients with COVID-19 in Erbil City.

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Abstract

Coronavirus infection a new infectious illness brought on by the SARS-COV-2 virus has infected people worldwide as of 2019, a covid-19 disease is associated with hematological and biochemical parameters changes. The present study aimed to evaluate the possible relationship between patient parameters and disease severity. A total of 200 nasopharyngeal swabs and whole blood specimens were collected from individuals suspected of CoV-2 and healthy volunteers as control of both sexes, grouped into four groups:50 patients for each mild, moderate, and severe patients and 50 healthy volunteers. The current study demonstrated that female 82(55%) was more frequently affected than male 68(45%). Hematological parameters including white blood cell count (WBC), granulocyte count, and Red blood cell distribution width (RDW%) (increased significantly p value$<$ 0.05, while Lymphocyte count decreased significantly when compared with a control group. Significant differences in hemoglobin concentration, packed cell volume, red blood cell count, and indices of red blood cell count were shown when compared with a control group in both sexes. Regarding biochemical parameters including serum vitamin D, ferritin, D-dimer, procalcitonin (PCT), and liver function tests, serum vitamin D decreased significantly, while serum ferritin, D-dimer, procalcitonin and liver enzymes increased significantly in the covid-19 patients group compared to the control group. According to vitamin D receptor, gene polymorphism in covid-19 patients genotype Bb was most likely associated and strongly related to getting infected with CoV-2 virus with all the three known stages of infection. Severity of CoV-2 was associated with leukocytosis, lymphopenia and biomarkers are the best predictors of severe CoV-2, with a strong relation of VDR gene polymorphism BsmI with the severity of CoV-2 patients.

1. Introduction:

The World Health Organization claims that the new Coronavirus (2019-novel) or severe acute respiratory syndrome 2 (SARS-CoV-2) virus is the cause of Coronavirus disease-19 (COVID-19), a contagious illness (CoV-2) [1] The original occurrence was found in Wuhan, Hubei Province, China, in December of 2019 [2], then it spread fast to all places, including Iraq [3]. At some point, the WHO proclaimed a CoV-2 pandemic, 2,465,545 coronavirus cases were recorded in Iraq in January 2023, and 25,375 people died as a consequence [4]. From no symptoms to mild upper respiratory signs to

severe pneumonia with acute respiratory distress syndrome and death, COVID-19 may exhibit a wide range of clinical indications. [5], [6]. Significant hematological alterations linked to a hypercoagulable condition may be seen in CoV-2. Clinicians can recognize and predict the course of the disease with the help of careful monitoring of all the CBC-associated hematological and biochemical indicators [7]. Based on several prospective studies that have revealed that lymphopenia may indicate prognosis in CoV-2 patients, a higher level of WBC count should be given more attention in the treatment of CoV-2 [8], [9]. Higher RDW and mortality in patients with CoV-2, particularly in those who were not hospitalized in the intensive care unit. It seems that in CoV-2 instances, high RDW may be used as a marker of mortality [10].

In addition to regulating phosphate and calcium homeostasis, vitamin D, also identified as active vitamin D3 (1,25(OH)2 D3 or calcitriol, is a fat-soluble steroid that serves a variety of other purposes [11].

Numerous studies on the connection between vitamin D and coronavirus illness have been published since 2020. The majority of studies report that calcidiol concentrations were lower in CoV-2 patients than in controls and that vitamin D deficiency/insufficiency increased the risk of developing CoV-2; additionally, individuals with severe CoV-2 had lower calcidiol levels than patients with nonsevere CoV-2. [12], [13].

Nevertheless, the data are quite inconsistent. Several meta-analyses showed that vitamin D significantly lowers CoV-2 severity [14], while another investigation found no relevance for vitamin D in the duration and prognosis of CoV-2 [15].

In people with CoV-2, a sufficient level of 25(OH)2 D3 may operate as a protective role and may be predictive of disease susceptibility and progression [16].

Ferritin is a potential biomarker for inflammation in CoV-2. However, several variables and the founder might obscure the serum ferritin level. In CoV-2, a high blood ferritin level was related to a more severe illness and a poor result. Thus, the level of serum ferritin may act as an essential predictive biomarker for CoV-2 diagnosis and selection [17].

Mehta et al. in (2020) identified an increase in the level of serum ferritin among CoV-2 patients with severe clinical severity Additionally, serum ferritin levels are correlated with the existence of cytokine storms in such cases and may be used to predict the severity of CoV-2 disease [18].

The fibrin breakdown products known as D-dimer are produced when plasmin cleaves cross-linked fibrin [19]. As a biomarker for fiber production and degradation, D-dimer is the main fibrin breakdown fragment. D-dimer levels are generally low in healthy individuals and high in conditions linked to thrombosis [20]. D-dimer is regarded as the best laboratory indicator for abnormalities of hemostasis related to CoV-2 [21]. Procalcitonin has been used to direct antibiotic prescription as a marker for bacterial infections [22], [23].

Additionally, it is higher in CoV-2 patients with severe conditions compared to those with non-severe disease, showing bacterial super-infection. In individuals with non-complicated CoV-2, PCT levels do not exceed the normal range, consequently serving as a potential signal for the development of a serious disease [24]. Liver enzymes (aspartate transferase (AST), alanine transferase ALT and (alkaline phosphatase (ALP), The high levels in CoV-2 individuals are caused by myositis rather than liver damage [25].

Severe or lethal CoV-2 infection has been linked to significant abnormalities in clinical biochemistry markers. Common results include elevated levels of ferritin, procalcitonin, and liver dysfunction indicators of tissue damage (rises of aminotransferase) [26]. In addition to hepatobiliary dysfunction, CoV-2 individuals may also have hepatocellular damage, as seen by elevated ALT and AST values, which indicate liver damage caused by the virus [27].

Few studies have shown a link between CoV-2 patients' liver test abnormalities, disease severity, and fatality [26], [28]. Previous studies suggest that the signaling axis of VD/VDR may have beneficial effects on CoV-2 infection by modulating the renin-angiotensin-system(RAS), dampening the chemokines cytokines storm, and regulating the activity of various immune cell types, especially in the ARDS phenotype that is linked to the condition., [29], [30].

The function of Vitamin D is regulated by the VDR-gene [31]. The vitamin D receptor (VDR) is a well-known nuclear receptor (NR) that plays a role in DNA transcription [32], [33]. The vitamin D receptor (VDR) is a chromosomal protein that controls gene expression in response to vitamin D. It is a member of the steroid hormone receptor superfamily and is situated on chromosome 12q12-q14 [34]. The intronic region contains the BsmI polymorphism [31].

The discovery of genetic variants connected to varying susceptibility of people to CoV-2 infections and degree of unfavorable effects should aid current biomedical research programs to battle the virus. This may potentially lead to new opportunities for novel tailored therapies, risk-based population stratification, and the protection of those at greater risk [32], [33]. This study aimed to evaluate some hematological, and biochemical parameters and vitamin D receptor (BsmI) in the early diagnosis and covid-19 severity.

2. Materials and methods:

2.1 Participants:

Participants in the study comprised cases and controls who, using real-time reverse transcriptase-PCR and nucleic acid detection of sampling swabs from the oro-nasopharynx, respectively, tested positive and negative for CoV-2. These patients were admitted to three hospitals (West Erbil emergency, Lalav emergency, and Emarate hospital in Erbil city from August 2021 to February 2022. The patients were categorized into three groups. Age, gender, ethnicity, and related

comorbidities as well as the severity of the illness at the time of admission, as well as the laboratory results on the first day of hospitalization and later on throughout the hospital stay, were reported for each CoV-2 patient.

following interim advice from the WHO [35]. Based on the patient's clinical symptoms, they were divided into 3 groups: group 1: 50 asymptomatic subjects, (male and female) based on the lack of clinical symptoms and the lack of hospitalization or ventilation need; group 2: 50 moderate patients (male and female) with a varied range of symptoms, including fever, dry cough, sore throat, shortness of breath, diarrhea, headache, and group 3:50 subjects (male and female) with a severe condition. For severe cases of respiratory impairment, non-invasive ventilation is needed, with ages ranging between (21-75 years), and 50 healthy control (male and female) with ages ranging between (23-70 years).

2.2 Blood samples:

Each participant's blood was taken for testing around 5 ml of venous blood, the blood samples were immediately poured into two different laboratory tubes. Two ml of the blood was in the EDTA test tube and the rest of the three ml of the whole blood was collected in a serum-separating gel tube for 30 minutes to coagulate. The samples were centrifuged at 5000 RPM for 5 minutes to collect serum, for routine blood count tests and biochemical analyses such as the levels of vitamin D, ferritin, D-dimer, PCT, and liver function tests. Hematological parameters were performed by using an automated hematology analyzer (Medonic mserries, sweden), And the biochemical tests (vitamin D and Procalcitonin) analyses by using the enzyme-linked immunosorbent assay (ELISA), and ferritin, D-dimer, and liver function tests are determined by Cobas 411- Roche (Germany). The results were analyzed using Graph Pad Prism version 9 and Med Calc version 18. Mean and S.E was calculated by the Kruskal Wallis test, p value < 0.05 was considered significant. The optimal cut-off values for vitamin D, Ferritin, D-dimer, procalcitonin, and liver function tests were determined by Receiver Operator Characteristic (ROC) Curve Analysis.

2.3 Gene polymorphisms genotyping of VDR by ARMS-PCR:

Each Kurdish participant's peripheral blood was taken and DNA extraction was done using the BetaPrep Genomic DNA Extraction Kit (Beta Bayern GMbH, Germany), following the advice provided by the manufacturer. DNA quality, concentration, and purity were assessed using the NanoDropND-1000 Spectrophotometer. (Thermo Scientific (U.S.A)) and respective gel electrophoresis. ARMS-PCR was used to genotype the target SNPs.

2.4 DNA extraction:

Each individual collected two ml of total intravenous blood, which was collected in (EDTA) tubes and used to extract DNA. We looked at one polymorphism in the VDR gene, [BsmI (B/b)]. Genotyping was based on whether one or both reactions amplified an allele specifically. The ARMS-PCR assay used Specific and control primer sequences, as well as their specificities and mixes, which were: BsmI/B $5^{'}$ AGCCTGAGTACTGGGAATGT $3^{'}$, BsmI/b $5^{'}$ AGCCTGAGTACTGGGAATGC $3^{'}$, and BsmI/C $5^{'}$ GGGAGGGAGTTAGGCACC $3^{'}$ 12 μL of DNA genome, 15 μL of a mixture of reactions combining control and particular primer mixtures, 200 μM of each deoxynucleotide-triphosphate (dNTP), 19 ammonium sulfate-based PCR buffer, 1.5–2.5 mM Mg Cl2, and 0.6 unit Taq DNA polymerase made up the optimal PCR process conditions. An Eppendorf gradient Master cycler PCR system was used to intensify the reaction. The system began by heating the sample to 94 °C for two minutes, then performed ten cycles of 10 s at 94 °C, 60 s at 65 °C, and 20 cycles of 10 s at 94 °C, 50 s at 61 °C, and 30 s at 72 °C. A 2 percent agarose gel stained with a red safe stain was used to evaluate the PCR results. Primer mixtures may be dried and pre-aliquoted in PCR plates or string tubes for quick performance and to prevent pipetting mistakes, and then sample genomic DNA, PCR master-mix, and Taq polymerase were added.

3. Results:

A total of 150 patients with CoV-2 and 50 control (healthy persons) were included in the current study. According to the hematological parameters, Table 1 demonstrated that the white blood cells count(WBC) in female patients with CoV-2 increased significantly in the mild, moderate, and severe groups as a value (8.96±0.770), (12.93±1.007) and (14.30±1.332) with P value < 0.0001) respectively when compared with the control group as value (7.37±0.387). Lymphocyte count decreased high significantly between CoV-2 groups and control group (mild 0.97±0.099, moderate 0.86±0.087, severe 0.087±0.086) and control group (2.24±0.104) with P value < 0.0001. About granular counts, the same table showed that the severe group increased high significantly (13.13±1.249) when
compared with mild (7.33±0.659), moderate (11.29±0.919), and control group (4.32±0.288) with P value < 0.0001.

Hemoglobin concentration decreased significantly in mild, moderate, and severe as a value (13.20±0.251, 11.94±0.315, 11.17±0.236 with P value < 0.0001) respectively when compared with the control group as value (13.13±0.270).

And Packed cell volume (PCV) also decreased high significantly in CoV-2 groups as a value (mild 38.82±0.964, moderate 36.24±1.014 and severe 32.03±0.691) when compared with a control group (37.25±0.918) with P value $<$ 0.0001.

Red blood cell count (RBC) increased significantly in mild as a value of (4.68±0.110) and decrease significantly in moderate and severe as a value (of 4.31±0.136, 4.02±0.103)

Table 1. Mean ±SE of some hematological parameters in CoV-2 patients and control group in females.

Category of COVID-19 cases					
Parameters	Control n =29	Mild n=29	Moderate n=27	Sever n=26	P. Value
WBC (10^9/l)	7.37±0.387 a	8.96±0.770 ab	12.93±1.007 c	14.30±1.332 d	0.0001
LYM (10^9/l)	2.24±0.104 a	0.97±0.099 b	0.86±0.087 bc	0.87±0.086 bcd	0.0001
GRAN (10^9/l)	4.32±0.288 a	7.33±0.659 ab	11.29±0.919 c	13.13±1.249 cd	0.0001
Hb (g/dl)	13.13±0.270 a	13.20±0.251 ab	11.94± 0.315 c	11.17±0.236 d	0.0001
PCV (%)	37.25±0.918 a	38.82±0.964 ab	36.24±1.014 ac	32.03±0.691 d	0.0001
RBC (10^12/l)	4.61±0.116 a	4.68±0.110 ab	4.31±0.136 ac	4.02±0.103 cd	0.005
MCV (fl)	81.13±1.294 a	84.30±0.926 ab	83.21±1.898 ac	79.96±1.428 acd	0.042
MCH (pg)	29.20±0.685	28.34±0.338	27.30±0.614	28.07±0.566	ns
MCHC (g/dl)	35.06±0.141 a	33.16±0.357 b	32.83±0.217 bc	34.88±0.277 ad	0.0001
RDW% (%)	12.81±0.321 a	13.27±0.257 b	13.67±0.292 c	13.73±0.271 cd	0.0014

respectively when compared with the control group as a value (4.61±0.116) with P value < 0.005.

Mean Corpuscular Volume (MCV) increased significantly from 81.13±1.294 in the control group to 84.30±0.926 in the mild group, then decreased significantly from 83.21±1.898 in the moderate group to 79.96±1.428 in the severe group with P value < 0.042. Mean Corpuscular hemoglobin (MCH) level decreased non-significantly in mild and moderate as values (28.34±0.338 and 27.30±0.614) respectively in the severe group raised to control group by (29.07±0.566 to 29.20±0.685).

A significant decrease was demonstrated in the mild and moderate group for Mean Corpuscular hemoglobin concentration (MCHC) by (33.16±0.357 and 32.83±0.217) with an increase in the severe group by (34.88±0.277) when compared with the control group by (35.06±0.141) with P value < 0.0001. Red-blood-cell Distribution Width (RDW%) increased significantly in CoV-2 patient groups of CoV-2 patients as a value (of 13.27±0.257 in mild, 13.67±0.292 in moderate, 13.73±0.271 in severe) when compared with the control group (12.81±0.321) with P value 0.0014.

Table 2 showed that the (WBC) in male CoV-2 patients increased significantly in mild, moderate, and severe groups as a value (11.28±1.293, 12.98±1.056, and15.39±1.445 with P value < 0.0001 respectively when compared with the control group as value (6.86±0.415). Lymphocyte decreased (LYM) high significantly between CoV-2 groups and control group (mild 1.003±0.091, moderate 1.02±0.137, severe 0.846±0.114) and control group (2.053±0.138) with P value < 0.0001.

About granular counts (GRAN) showed that the severe group increased significantly (14.30±1.348) when compared with mild (8.19±1.109), moderate (11.05±0.949), and control group (4.043±0.296) with P value < 0.0001. Hemoglobin concentration decreased significantly in mild, moderate, and severe as a value (of 14.21±0.290, 13.41±0.272, and 12.76 ±0.330 with P value < 0.0001) respectively when compared with the control group value (14.96±0.174), and PCV also decreased high significantly in CoV-2 groups as a value (mild 41.19±0.952, moderate 40.37 ± 0.785 and sever 37.03 ± 0.987) when compared with a control group (42.15±1.079 with < 0.005 P value. Red blood cell count significantly decreased in the three groups of CoV-2 patients (5.07±0.294 in mild, 4.82±0.138 in moderate, and 4.43±0.117 in severe when compared with the control group as a value (6.04±0.785) with P value < 0.0001.Red-blood-cell.Mean Corpuscular Volume (MCV) increased in the mild group by (85.64±5.116) then decreased non-significantly in the moderate and severe groups with values (of 84.81±1.703 and 82.99±1.131) when compared with the control group as a value (84.49±0.701).

Mean Corpuscular hemoglobin (MCH) levels increased non-significantly in mild, moderate, and severe with values (of 29.00±0.392, 28.24±0.602 and 28.70±0.416) when compared with the control group as a value (27.76±0.33). Sever group showed a significant increase in (MCHC) level with (34.47±0.337) when compared with the control, mild, and the moderate group as a value (33.72±0.262, 33.79±0.248, and 33.28±0.157) with P value < 0.003.RDW% level raised in three groups of CoV-2 patients as a value (13.20±0.301, 13.46±0.193 and 14.07±0.436) respectively when compared with the control group (12.15±0.86) with p-value < 0.0001.

4. Biochemical tests in CoV-2:

Statistical analysis of the current study showed that vitamin D was decreased significantly in all CoV-2 patient groups (5.470±0.259, 8.724±1.119, 6.793±0.232) when compared

Table 2. Mean ±SE of some hematological parameters in CoV-2 patients and control group in males.

Category of COVID-19 cases					
Parameters	Control n =29 n =29	Mild n=29 n=29	Moderate n=27 n=27	Sever n=26 n=26	P. Value
WBC (10^9/l)	7.37±0.387 a	8.96±0.770 ab	12.93±1.007 c	14.30±1.332 d	0.0001
LYM (10^9/l)	2.053±0.138 a	1.003±0.091 b	1.02±0.137 bc	0.846±0.114 bcd	0.0001
GRAN (10^9/l)	4.043±0.296 a	8.19±1.109 b	11.05±0.949 c	14.30±1.348 d	0.0001
Hb (g/dl)	14.96±0.174 a	14.21±0.290 ab	13.41±0.272 c	12.76±0.330 d	0.0001
PCV (%)	42.15±1.079 a	41.19±0.952 ab	40.37±0.785 ac	37.03±0.987 d	0.0005
RBC (10^12/l)	6.04±0.785 a	5.07±0.294 ab	4.82±0.138 c	4.43±0.117 cd	0.0001
MCV (fl)	84.49±0.701	85.64±5.116	84.81±1.703	82.99±1.131	ns
MCH (pg)	27.76±0.338	29.00±0.392	28.24±0.602	28.70±0.416	ns
MCHC (g/dl)	33.72±0.262 a	33.79±0.248 ab	33.28±0.157 abc	34.47±0.337 d	0.0039
RDW% (%)	12.15±0.86 a	13.20±0.301 b	13.46±0.193 bc	14.07±0.436 d	0.0001

with the control group (14.27±2.651) and non-significant between mild to moderate and moderate to the severe group then ROC curve analysis identified that best value of cut-off of vitamin D for predicting severity in CoV-2 patients was $\leq$ 7.59 ng/ml (sensitivity = 81.3%; specificity = 46.0%; AUC = 0.646) with P value < 0.001 (Figure 1 A & B).

Ferritin levels were high significant increase between (mild, moderate, and severe) (1039 ± 94.94, 1171 ± 88.11, 1441 ± 84.19) respectively compared to the control group (105.7±9.622), but there was a non-significant between mild to moderate and moderate to the severe group. that was shown in Figure 2 A, ROC curve analysis identified that the best cut-off values of ferritin for predicting severity in CoV-2 patients was $>$ 300.1 ng/ml (sensitivity = 90.0%; specificity = 100.0%; AUC 0.973) with P value < 0.0001(Figure 2 B).

D-dimer is the most significant marker of CoV-2 patients, our results showed that increased high significantly from 0.319±0.029 in the control group to (2.104±0.252 in mild, 6.918±0.344 in moderate,14.67±1.279 in sever group) with P value < 0.0001, and ROC curve analysis identified that the best cut-off value was $>$ 0.69 µg/ml (sensitivity = 100.0%; specificity= 96.0%; AUC = 0.997). (Figure 3 A B).

Serum Procalcitonin level is one of the important biomarkers of CoV-2 patients, PCT was high significantly increased in all three groups (9.459±0.649 in mild, 15.02±1.672 moderate, 20.14±1.310 in severe) respectively compared to control group (6.936±0.217) but there was no significant difference between the moderate and severe group. (Figure 4 B) showed the ROC curve analysis identified that the best cut-off value of PCT for manipulative severity in covid-19 patients was $>$ 8.32 pg/ml (sensitivity =70.0%; specificity = 92.0%; AUC=0.802) with P value < 0.0001. As shown in (Figure 5 A,B,C & D) the values of liver function tests were increased high significantly in CoV-2 patients in all groups when compared with control healthy group, AST values were (38.41±2.377 in mild, 45.13±3.669 in moderate, 52.65±3.587 in sever) and control group value was (23.96±2.103) and ROC curve analysis identified that the best cut-off value of AST for predicting severity in CoV-2 patients was $>$ 22 U/L (sensitivity = 92.0%; specificity= 70.0%; AUC= 0.880) with P value < 0.0001,and ALT values were (39.91±0.688 in mild, 40.89±4.059 in moderate, 69.26±20.90 in sever) and control group (20.75±0.989), and ROC curve analysis identified that the best cut-off value of ALT for predicting severity in CoV-2 patients was $>$ 34 U/L (sensitivity= 49.3%; specificity = 100.0%; AUC= 0.770) with P value < 0.0001, and ALP values were (199.9±13.42 in mild, 270.20±17.92 in moderate, and 174.6±25.46 in sever) increased significantly when compared with control group (108.20±12.36) with p value < 0.0001, and ROC curve analysis identified that the best cut-off value of ALP for predicting severity in covid-19 patients was $>$ 67 U/L (sensitivity = 90.0; specificity = 62.0; AUC = 0.781). Regarding the genotypes of the participants in the studied groups in this research, the SNP of the gene of vitD (Bsm) the high producer BB genotype was non significantly higher in severe Covid19 patients than control Odd ratio (OR): 0.62, C.I: 0.20 to 2.03 and considered as a protective factor against the disease. Whereas the Bb genotype for the same group of patients was 1.7 folded than the control, OR: 1.71, C.I: 0.55 to 5.93 and this genotype might be the risk factor for the disease. While the low producing bb genotype of the patients was no correlations with the disease, OR: 1, C.I: 0.34 to 2.96. According to allele frequency the B allele was more frequent in the control group while the b allele frequency was found in patients. Allele b was 1.23 folded susceptible to get the

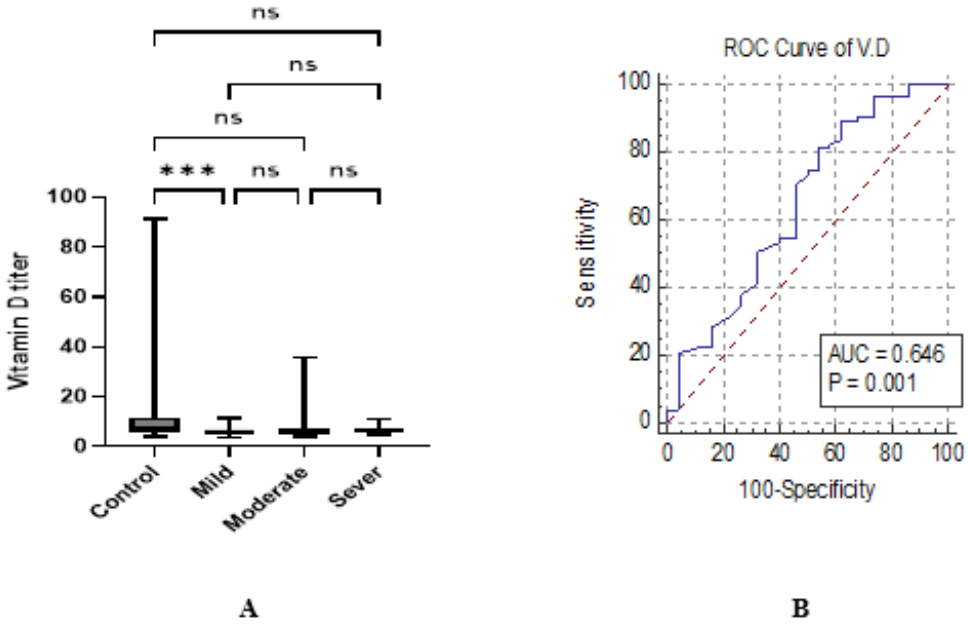

Figure 1. A: Comparison of Vitamin D levels in patients and the control group.
B: The area under the curve value shows vitamin D as a biomarker of the patient group.

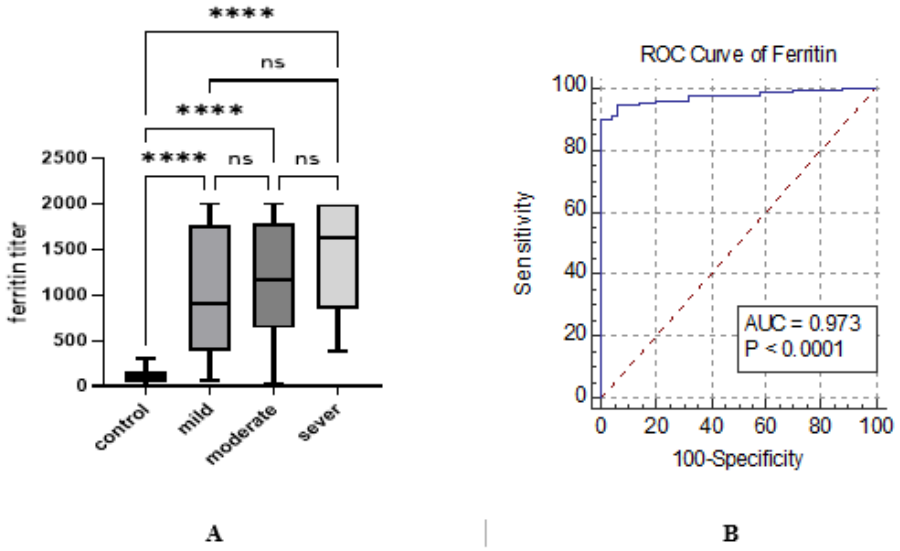

Figure 2. A: Comparison of ferritin levels in patients and the control group
B: The area under the curve value show ferritin as a biomarker of the patients' group.

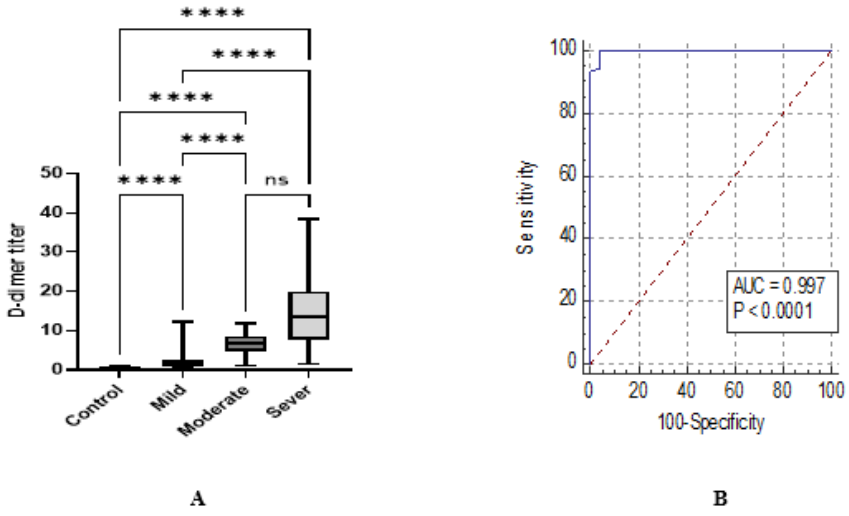

Figure 3. A: Comparison of D-dimer levels in patients and the control group.
B: The area under the curve value shows D-dimer as a biomarker of the patient group.

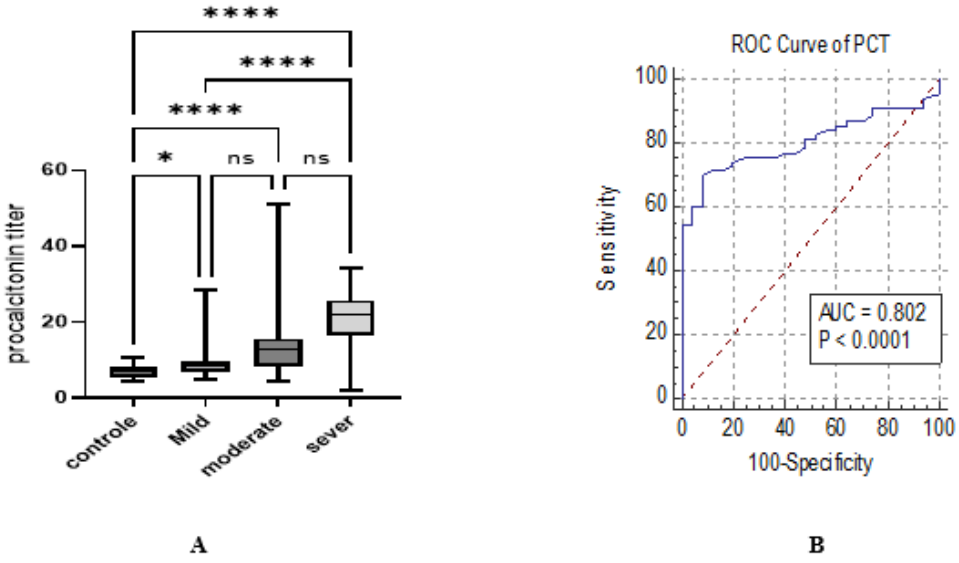

Figure 4. A: Comparison of PCT levels in patients and the control group.
B: The area under the curve value show PCT as a biomarker of the patients' group.

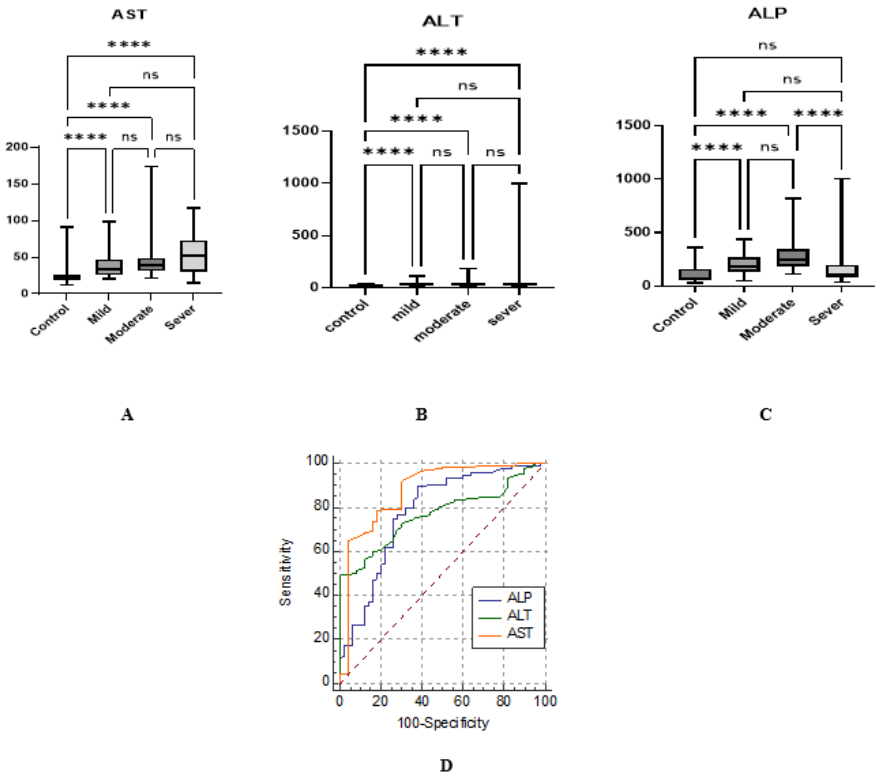

Figure 5. A, B, and C: Comparison of tests of liver function level in patients of covid-19 and control group B: The area under the curve value show liver function tests as a biomarker of the patients' group.

disease severely. The second group of patients was moderate CoV-2 patients. The BB genotype was protected for the disease when compared with the control, OR: 0.5, C.I: 0.17 to 1.49. The intermediate genotype Bb was 1.41 folded in patients than control, OR: 1.41, C.I: 0.44 to 4.93, this genotype is a risk factor for moderate infection with the virus. Low producer's bb genotype was also regarded as a slighter risk for the disease, OR: 1.38, C.I: 0.52 to 3.69. In this patients group the B allele was also more frequent than the control with 0.63 of susceptibility to get the moderate infection. Where the b allele was 1.58 the fold higher in patients than control. The last studied group of patients had a mild infection with CoV-2 virus. The BB genotype was almost as same as the control with the OR: 1.09, C.I: 0.40 to 3.05, this genotype was suspected to get the disease. While the Bb genotype was most probably associated to get the CoV-2 disease with almost 3.5 folded than controls, OR: 3.41, C.I: 1.12 to 11.44. The low producing bb genotype was protected against mild infection by the Covid19 virus, OR:0.24, C.I: 0.08 to 0.74. Unlike the other patient group in the mild infection of CoV-2 the B allele was more frequent (1.58) fold in patients than control and the b allele was protective factor for this type of infection with only 0.5 rate of infection. Genotype BB was a protected against severe and moderate infection. While the bb genotype was a protective genotype for mild infection with the CoV-2 virus. Allele B was mostly found in control in comparison with severe and moderate infection. While in the mild infection the B allele was increased when compared to control. Table 3

5. Discussion:

Globally, the number of CoV-2 patients and CoV-2 -related death rates are both rising quickly. The pandemic's quick spread places a heavier load on hospitals. The severity of CoV-2 symptoms varies from moderate to serious [1] The 2019 coronavirus disease (CoV-2) is accompanied by hematological abnormalities of varying degrees of severity and multi-system consequences [36].

As shown in table 1 in the current study the White blood cell count appears as leukocytosis, lymphopenia, and agranulocytosis, these results are in agreement with [37], which discovered that lymphopenia, greater leukocyte counts, and lower lymphocyte counts in severe patients have been identified as indicators of outcome in CoV-2 patients. Since lymphocytes include ACE2 receptors, the viral invasion theory is now the most popular explanation for lymphopenia [38], [39].

The virus may penetrate bone marrow cells, directly assault lymphocytes and induce apoptosis, or it may destroy the spleen or lymph nodes. Reduced lymphocyte proliferation

Table 3. Genotypes and allele frequencies of vitamin D receptors in CoV-2.

Genotypes	OR	C.I	X^2	P value
SEVERE				
BB	0.62	0.20 to 2.03	0.79	0.42
Bb	1.71	0.55 to 5.93	0.84	0.41
bb	1	0.34 to 2.96	1	1
B	0.82	0.41 to 1.61	0.338	0.341
b	1.23	0.62 to 2.42	0.338	0.341
MODERATE				
BB	0.5	0.17 to 1.49	1.64	0.15
Bb	1.41	0.44 to 4.93	0.32	0.39
bb	1.38	0.52 to 3.69	0.34	0.42
B	0.63	0.32 to 1.25	1.68	0.13
b	1.58	0.80 to 3.14	1.68	0.13
MILD				
BB	1.09	0.40 to 3.05	0.02	0.53
Bb	3.41	1.12 to 11.44	4.81	0.02
bb	0.24	0.08 to 0.74	6.9	0.01
B	1.84	0.93 to 3.63	3.24	0.05
b	0.54	0.28 to 1.08	3.24	0.05

might result from increased levels of lactic acid in COVID-19 [40]. Active research is being done on the relationship between early hematological parameter alterations and illness outcomes [41]. In CoV-2, increased leukocyte counts were linked to higher mortality [41]. After the course of CoV-2, anemia may develop as a result of direct CoV-2 infection, iatrogenic blood loss during admission, or abnormal iron metabolism. [42].

Serum vitamin D in the current study decreased in all covid-19 groups, its consistent with Alshahawey and colleagues,2020, which found that A potential problem for CoV-2 was alleged to be a vitamin D deficiency. Could interact with the angiotensin-converting enzyme-2 receptor (ACE2), one of which acts as the virus's entrance site and has its (S) protein spike, to function as an inhibitor for the virus' entry [41].

In CoV-2, it is interestingly found that vitamin D deficiency is related to higher risks for CoV-2 infection [43]. Various studies, mostly observational, have sought to demonstrate whether there is truly a relationship between 25(OH)D3 levels and the acquisition and/or severity of the disease. Hypovitaminosis D is widespread worldwide, so the prevention of COVID-19 through vitamin D supplementation is being considered a possible therapeutic strategy that is easy to implement [44] Acute respiratory illness syndrome and Systemic inflammatory response syndromes (SIRS) are two features of CoV-2 that, in terms of severe symptoms, hyperferritinemia syndromes. [16]. The combination of elevated serum ferritin levels and an existing hyperinflammation that ultimately results in multi-organ failure is the common factor linking hyperferritinemia syndrome with the aforementioned problems [5], [45].

Our study's findings concur with others who discovered that the level of D-dimer is the most reliable marker for determining the severity of CoV-2illness. [46]. A severe inflammatory reaction brought on by CoV-2 infection starts off the coagulation cascade [47]. In CoV-2 patients, stimulation of the coagulation system is linked to a hypercoagulable condition and poor clinical outcomes, including mortality occurrence of defective coagulation in CoV-2 patients, highlights the urgent need for therapeutic therapy and laboratory monitoring that are hemostasis-focused [48]. According to certain research, people with CoV-2 may be treated with empiric complete anticoagulation or have a workup for venous thromboembolism (VTE) if their D-dimer levels are two to four times higher than the typical cut-off number [49]. It has been discovered that D-dimer levels are related to thrombosis development and patient death in CoV-2 patients [[50], [51], [52]. To treat individuals with CoV-2, some advice suggests that coagulation indicators, such as D-dimer levels, be tested first [53].

In C-cells in the follicular region of the thyroid gland, procalcitonin (PCT), a glycoprotein lacking hormonal action, is the precursor of calcitonin [54]. Bacterial infections raise PCT levels, but viral infections have relatively low PCT levels [55]. Recently, multiple investigations found an inverse relationship between high PCT and CoV-2 severity [56]. In patients with CoV-2, PCT seems to be an accurate indicator for making predictions and adjusting treatment therapy [57]. However, mounting evidence indicates that even in the absence of bacterial infection, a severe respiratory illness is linked to an increase in PCT level [58]. Recent research found that CoV-2 prognostication is aided by moderately raised procalcitonin levels. When a patient is admitted, a high PCT level might signify an inflammatory reaction, which would then cause an immunological hyperactivation and cytokine storm. In individuals with severe CoV-2, bacterial superinfection is extremely challenging to evaluate [59]. The severity of the condition was linked to the malfunctioning liver enzyme, the abnormal liver function test results in CoV-2 might theoretically be due to direct virus-induced cytopathies [60]. The presence of CoV-2 particles without membrane-bound vesicles in the cytoplasm of hepatocytes from CoV-2 patients with abnormal liver function test results offered evidence for direct hepatic infection [61]. Some studies found that abnormal liver function tests, particularly elevated AST and ALT, are associated with increased disease severity and mortality whereas other studies did not find an association with mortality, disease progression, ICU admission, or length of hospital stay [62]. The liver is the organ most frequently affected following lung loss, according to several studies, as the number of CoV-2

patients increases. [63], [64]. Even in the severe CoV-2 group, liver enzyme elevations are typically low to moderate, and the pattern of aberrant liver biochemistries was characterized by modest increases in hepatocyte-related enzymes, such as ALT and AST. Additionally, the majority of CoV-2 patients had ALP values that were normal, which suggests the most prevalent cause of liver damage is not a direct cytopathogenic impact of the CoV-2 virus [28], [65]. According to vitamin D receptor gene polymorphism, our result showed genotype BB was protected against severe and moderate infection. While the bb genotype was a protective genotype for mild infection with the CoV-2 virus. [66] reported that the main allele "B" has a protective effect whereas the minor allele "b" functions as a susceptibility factor to CoV-2 severity. Additionally, genetic design genotypic distributions showed that individuals with the "BB" genotype had a lower probability of developing CoV-2 that is more severe than those with the combined "bb + Bb" genotype. In contrast to coupled "BB + Bb" genotypes, "Bb" symptomatic heterozygotes showed greater susceptibility to CoV-2. Independently correlated with CoV-2 severity and patient survival are VDR polymorphisms [35].

6. Conclusion:

Leukocytosis and Lymphopenia were the most common hematological abnormalities in CoV-2 patients and were significantly associated with disease severity. Evaluation of vitamin D, ferritin, D-dimer, and procalcitonin could provide prognostic biomarkers in covid-19 patients and liver enzymes of patients affected significantly specially in alanine transaminase and alkaline phosphatase. In the comparison of the three genotypes of VitD (Bsm) gene SNP the intermediate genotype Bb was most likely associated and strongly related to getting infected with CoV-2 virus with all three known stages of infection. However, more extensive studies are needed to determine the impact of polymorphisms on CoV-2 and explain the underlying cause.

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Declarations:

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تحديد بعض المعلمات الدموية والبيولوجية و تعدد الاشكال الجينية لمستقبلات فيتامين د في مرضى الاكراد $COVID-19$ في مدينة أربيل

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الخلاصة

مرض فيروس كورونا الذي بدأ عام 2019 هو مرض معد جديد يسببه $SARS-COV-2$ وقد أثر على الفرد على مستوى العالم ، و هو مرتبط بتغيرات المعايير الدموية والكيموحيوية. كان الهدف من هذه الدراسة هو تقييم العلاقة المحتملة بين المعايير الدموية والكيموحيوية وشدة المرض. اذ تم جمع ما مجموعه 200 مسحة من البلعوم الأنفي وعينات دم كاملة من الأفراد المشتبه في إصابتهم ب $Cov-2$ والمتطوعين الأصحاء كعنصر تحكم من الجنسين مقسمة الي أربع مجموعات 50 مريضا لكل مجموعة خفيف ومعتدل وشديد و 50 متطوعا سليما. أظهرت الدراسة الحالية أن الإناث 82 (55%) تأثرن بشكل متكرر أكثر من الذكور 68 (50%)زادت المعايير الدموية بما في ذلك عدد خلايا الدم البيض وعدد المحببات وعرض كريات الدم الحمر ($RDW\%$) بشكل ملحوظ $p<0.05$ ،بينما انخفض عدد الخلايا الليمفاوية بشكل ملحوظ عند مقارنته بمجموعة التحكم. ظهرت فروق معنوية في تركيز خضاب الدم وحجم خلايا الدم المتراصة وعدد كريات الدم الحمر ومؤشراته عند مقارنة كلا الجنسين بمجموعة التحكم .فيما يتعلق بالمعايير الكيموالحيوية بما في ذلك فيتامين د في المصل، والفيريتين، و $D-dimer$ البروكالسيتونين، واختبارات وظائف الكبد، انخفض فيتامين د، في حين زاد فيريتين، و $D-dimer$ ،والبروكالسيتونين ، وإنزيمات الكبد بشكل ملحوظ في مجموعة مرضى $CoV-2$ مقارنة بمجموعة التحكم. وفقا لمستقبلات فيتامين د، فإن تعدد الأشكال الجينية في النمط الجيني Bb لمرضى $CoV-2$ كان على الأرجح مرتبطا وبشدة بالإصابة بفيروس $CoV-2$ مع جميع مراحل العدوى الثلاث. نستنتج من الدراسة الحالية بأن شدة $CoV-2$ ارتبطت بزيادة عدد الخلايا البيض،وقلة اللمفاويات والمؤشرات الحيوية هي أفضل المتنبئين ب $Cov-2$ الشديد، مع ارتباط قوي بتعدد الشكل الجيني $BsmI$ مع شدة مرض $CoV-2$.

الكلمات الدالة: $SARS-CoV-2$ ؛ عوامل دموية؛ فيتامين د؛ بروكالسيتونين؛ مستقبلات فيتامين د .*BsmI*.

التمويل: لايوجد.

بيان توفر البيانات: جميع البيانات الداعمة لنتائج الدراسة المقدمة يمكن طلبها من المؤلف المسؤول.

اقرارات:

تضارب المصالح: يقر المؤلفون أنه ليس لديهم تضارب في المصالح.

الموافقة الأخلاقية: لم يتم نشر المخطوطة أو تقديمها لمجلة أخرى، كما أنها ليست قيد المراجعة.