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The Clinical Role of Inflammatory Chemokine RANTES (CCL5) in a Sample of COVID-19 Baghdad Province Patients

Zahra'a Abdul AL-Aziz Yousif [*,1], Jabbar S. Hassan[2] and Ghaith H. Hameed[3]

[1]Ibn Sina University of Medical and Pharmaceutical Sciences, Baghdad, Iraq.
[2] Department of Microbiology, College of Medicine, Al-Nahrain University, Baghdad, Iraq.
[3] Ministry of Health ,MRCP Respiratory Medicine, Imamein Kadhimein, Medical City Baghdad, Iraq.
***Correspondence author**
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Abstract

COVID-19 disease is a clinical syndrome caused by an envelope RNA virus, called SARS-COV-2., which causes infection with wildly clinical pictures. Through COVID-19 infection several components of humoral and cellular immune response have an important role in the progression of the infection**.** Chemokines are one of the inflammatory mediators that play an essential role in the immune pathogenesis of COVID-19. It is secreted by respiratory virus-infected cells in the upper respiratory tract, causing stimulation and recruitment of inflammatory cells such as neutrophils, NK, eosinophils, and macrophages from the bloodstream to the site of the infection. This study strives to determine the impact role of inflammatory mediator (CCL5) in a sample of COVID-19 Baghdad province patients. Blood samples collected from 180 individuals were enrolled in this study, 120 of them were patients infected with COVID-19 and verified by reverse transcriptase polymerase chain reaction (RT-PCR). The patients were categorized into two groups based on the severity of the disease, the severe group included 60 patients and the mild/moderate group included 60 patients also. Furthermore, 60 healthy individuals who were confirmed to be COVID-19-negative were enrolled in this study as a control group. The quantitative detection of CCL5 in human serum was done by the CCL5 Enzyme Linked Immune Sorbent Assay kit based on the principle of sandwich ELISA. This study showed that there were interesting highly significant differences ($p<0.001$) in the median serum level of CCL5 between all groups that participated in this study and there was a significant increase in the median level of CCL5 in control and mild-moderate groups versus severe patients' group (66.66 pg/ml, and 54.04 pg/ml vs. 38.41 pg/ml respectively). According to the results of this study, the low level of CCL5 associated with COVID-19 severity infection could be used as a predictor marker for severity. In contrast, the elevated level of CCL5 in control and mild-moderate suggested that this chemokine is likely associated with the resolution of inflammation and recovery.

Keywords: CCL5, Chemokine, COVID-19, RANTES, Sandwich ELISA

Introduction

COVID-19 disease is a clinical syndrome caused by an envelope RNA virus called SARS-COV-2. It is a beta–coronavirus, which like other coronaviruses, causes infection with wildly clinical pictures. It initially occurred in China, in December 2019, and then spread all over the world. The World Health Organization (WHO) declared a pandemic in March 2020 [1, 2] . SARS-COV-2 infection initiates in nasal epithelial cells of the upper respiratory tract, through binding with the specific viral receptor, angiotensin- convertase enzyme-2 (ACE2), then viral genome replication in these cells, causes stimulation of innate immune response, and triggering signaling pathway, which leads to expression of different pro-inflammatory cytokines, interferon types I and III (IFN α/β and λ), and different types of chemokines [1] **,** so the immune response of mucosal in the upper respiratory tract is crucial for the initial control of viral replication, clearance, and disease progression [3]**.** SARS-CoV-2 infection may be related to reduced induction of some innate immune pathways in the upper airway and causes dysregulated antiviral in the nasal epithelium cells, which seems to predict progression to severe and critical COVID-19 disease [4, 5]. For this, the protective immune response in the nasopharynx is very important in preventative, and therapeutic strategies against this viral infection [6, 7]**.** Chemokine is one of the inflammatory mediators that play an essential role in the immune pathogenesisCOVID-19 infectious disease. The respiratory virus-infected cells in the upper

respiratory tract secreted different chemokines in an attempt to infectious controlling, by recruitment of different inflammatory immune cells; such as NK, macrophage, eosinophil, and neutrophils from the bloodstream to the site of tissue infection [8]**.** (CCL5) which is known as Regulated Normal T-lymphocyte Expression and Secreted; CCL5, C-C Motif Chemokine Ligand 5, is an immunity-powerful chemotactic marker, with activating properties for different immune cells, it is used as a surrogate marker for interferon activity to demonstrate the integrity of the downstream signal of interferon production via viral infected cells [9]**.** Also, it regulates normal T-lymphocyte expression, secreted upon activation, and promotes interaction between dendritic cells and T-lymphocytes, which have a crucial role in viral control. CCL5 is important for sustaining CD8 T cell response during a systemic viral infection [10]**.** It is expressed by several cell types; including epithelial cells, platelets, and T-lymphocyte cells. CD8T-cells also secreted this chemokine upon antigen stimulation as an antiviral function in HIV, by competing with the virus for chemokine receptor (CCR5) [11]**.** This study strives to determine the impact role of inflammatory mediator (CCL5) in a sample of COVID-19 Baghdad province patients.

Materials and Methods

Populations and study design

This case-control prospective study was carried out during the 4th COVID-19 wave. Samples collected through the period (January 2021 to May 2021), 180 individuals were enrolled in the study, with a variety of age groups and both sexes, the subjects included (60) individuals who participated as healthy control, RT-PCR COVID-19 negative, and (120) participants introduced as positive COVID-19 patients, were diagnosed by RT-PCR test from nasopharyngeal swabs, and symptomatic with fever, dyspnea, cough and tiredness. The patient's samples were collected from two hospitals in Baghdad, Dar AL-Salam and Imamein Kadhimein Medical City, which has frequently served as a major Quarantine center in Baghdad and its suburbs, samples were processed in the Departments of the Medical Microbiology /College of Medicine/ AL-Nahrain University. Patients group categorized into two groups based on the severity of COVID-19 according to guidelines issued by the Iraqi Ministry of Health [12], which included; a mild-moderate group and a severe group, each of which consisted of (60) individuals. All patients were subjected to laboratory tests which included; CBC tested by auto hematomary analyzer (Foshan concern Medical Equipment China) and biochemical tests (CRP was measured via turbidimetry, while ferritin was measured using the electro-chemiluminescence technique,(using Randox Daytona plus (Randox Laboratories Ltd., Crumlin, UK) and D-dimer was measured using the Enzyme-Linked Fluorescent Assay (ELFA) technique(Bio Mérieux, Marcy L'Etoile, France) [13]., Real-time reverse transcriptase –polymerase chain reaction (Abbott RealTi*m*e SARS-CoV-2 Amplification Reagent Kit) [14] all techniques were performed following the manufactures instruction , oxygen statement [15], these results were collected from the hospital records system among each patient included in this study. As well as the control group also tested these parameters**.**

Blood sample collection and handling

A venous blood sample (5ml) was taken via venipuncture, from each member involved in this study, and placed in a specific serum-separated gel tube to facilitate serum sorting then left at room temperature for 15 minutes and separated by centrifuge 4000 RPM for 15 minutes, then kept at (-20 C°) until they were tested (CCL5) using a commercially available Human CCL5 ELISA kit [16] as recommended by company protocol (Sunlong/China) Catalog number NO.:SL3288Hu

The inclusion criteria: mild-moderate cases and severe patients who confirmed positive Real-time reverse transcriptase –polymerase chain reaction (RT-PCR) [14] who were admitted to the hospital for several days about (3 to 10 days), smokers patients as unhealthy lifestyle, patients who have chronic diseases, patients with other co-infections. Control group which included RT-PCR COVID-19 negative peoples. The **exclusion criteria** included patients who were admitted to the hospital for a long period of more than 14 days, and patients with no or insufficient clinical data.

Quantification of CCL5 serum level

CCL5 ELISA kit based on the principle of sandwich enzyme-linked immune-sorbent assay, was used for the quantitative detection of (CCL5) in human serum samples. The wells of the microtiter plate were captured with an antibody specific to (CCL5). The spectrophotometer measured optical density (O.D) at 450nm.

A Standard curve can be performed by plotting the optical density on the vertical (Y) axis for each standard versus the concentration on the horizontal (X) axis and then calculating each sample as shown in the Figure (1).

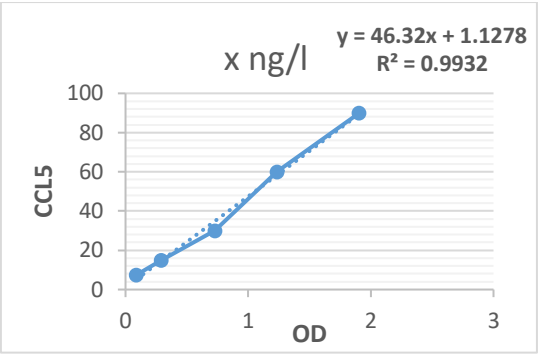

Figure 1. Standard curve of etermination (CCL5)

Statistical analysis

Statistical analysis of this data study was performed by using the Statistical Package for the Social Sciences (SPSS version 25, Chicago). Shapiro-Wilk test was used to detect the normality of data, which revealed the non-normal distribution presented as median, while normal distribution data was presented as mean. Mann-Whitney test is one of the non-parametric tests, used to detect the significant effect of markers. The chi-squared test used for the categorical variables was presented as number and percentage. A value less than 0.05 was considered a statistically significant effect. Receiver Operating Characteristic Curve (ROC) was applied to detect the disease outcome dependent on CCL5 level between the control group and both patients' groups (mild-moderate versus severe).

Results

General description of the studied population

The mean ages of patient groups (severe and mild-moderate) (60.90 years and 38.92 years) respectively, while the mean age of the healthy control group (30.50) years with a highly statistically significant ($p<0.001$**), the highest incidence of this disease infectious in the sixth decade and in the seventh decade. While there was no statistical significance among the sexes in the study groups was a ($P= 0.638$) as shown in Table (1) and. Figure (2).

Table 1. The demographic characteristic of the study population

Variables		Study groups			P value
		Control n= (60)	Mild/moderate n= (60)	Severe n= (60)	
Age (year)	Median	34.00	35.00	64.00	<0.001**
	Percentile 05	20.00	19.00	18.00	
	Percentile 95	45.00	73.00	85.00	
Age group	≤20 years	4 (6.7%)	8 (13.3%)	4 (6.7%)	<0.001**
	21-30 years	21 (35.0%)	15 (25.0%)	0 (0.0%)	
	31-40 years	25 (41.7%)	15 (25.0%)	4 (6.7%)	
	41-50 years	10 (16.7%)	7 (11.7%)	7 (11.7%)	
	51-60 years	0 (0.0%)	5 (8.3%)	9 (15.0%)	
	61-70 years	0 (0.0%)	6 (10.0%)	19 (31.7%)	
	>71 years	0 (0.0%)	4 (6.7%)	17 (28.3%)	
Sex	Female	40	35	38	0.638^{NS}
		66.7%	58.3%	63.3%	
	Male	20	25	22	
		33.3%	41.7%	36.7%	

chi-squared test ; NS: non-significant , **: highly statistically significant

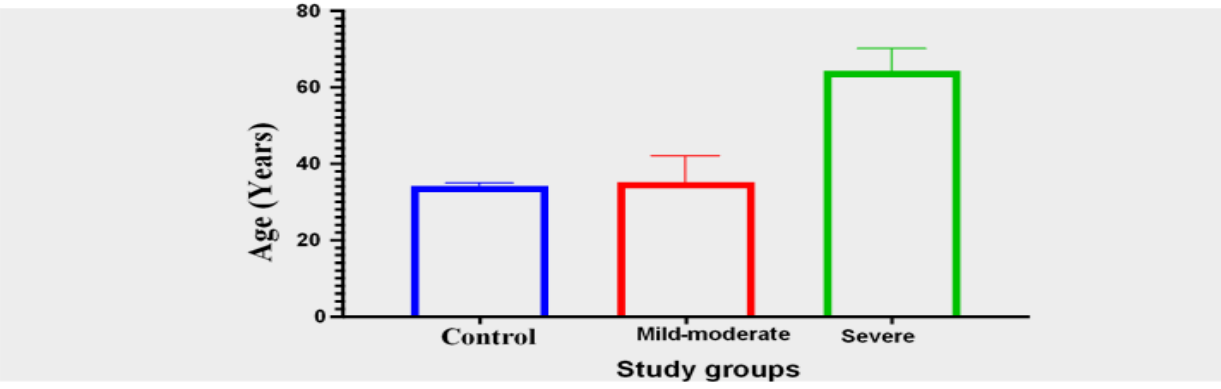

Figure 2. The age demographic characteristic of the study population

Estimation of serum (CCL5) level in the study population

This study showed that there were interesting highly significant differences in median serum level of (CCL5) between the control group and both patients' groups mild-moderate versus severe (66.66 pg/ml and 54.04 pg/ml vs 38.41 pg/ml) respectively, with highly statistically significant differences as shown in Table (2) and Figure (3).

Table 2. Serum level of (CCL5) with odds ratio among study Populations

Variables		Study groups			P value
		Control N=60	Mild/Moderate N=60	Severe N=60	
CCL5 (pg/ml)	Median	66.66	54.04	38.41	<0.001**
	Percentile 05	54.44	26.37	22.43	
	Percentile 95	87.18	110.56	432.48	
P value	Vs control		0.038*	<0.001**	<0.001**
	Vs none severe			<0.001**	
CCL5	<60 (pg/ml)	12	32	54	<0.001**
	Count	20%	53.3%	90%	
	≥60 (pg/ml)	48	28	6	
	Count	80%	46.7%	10%	
Odds ratio (95 CI)			2.32 (1.45 to 3.96)	4.89 (3.01 to 8.35)	

Mann-Whitney test; **: highly statistically significant at level 0.001

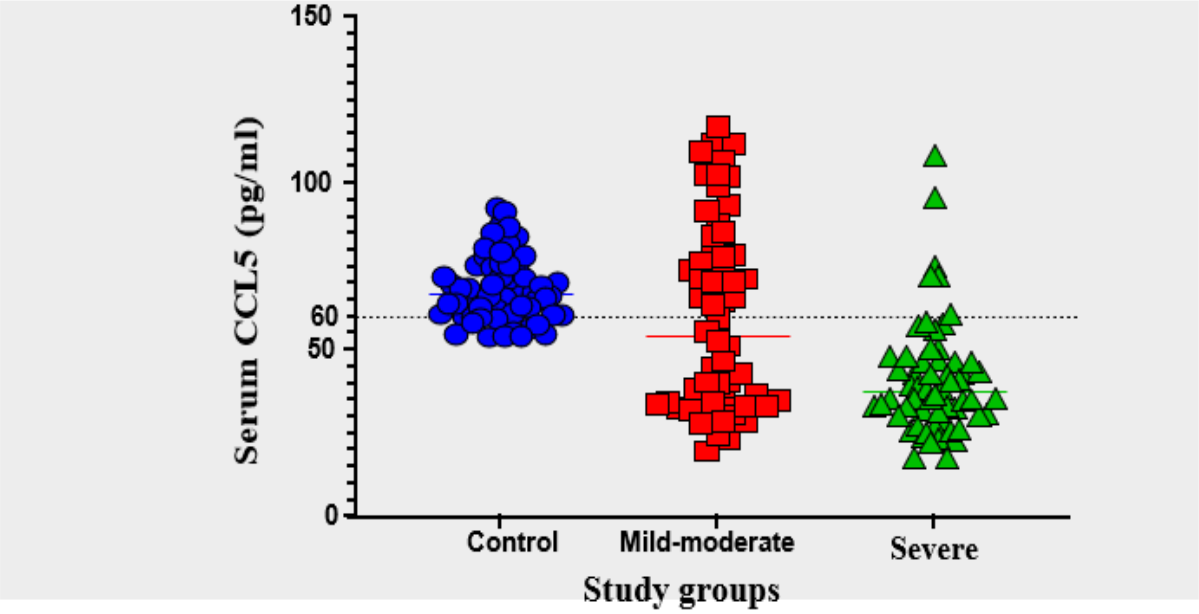

Figure 3. Serum level of CCL5 among population groups stud

The receiver operating characteristic (ROC) curve was applied to detect the disease outcome dependent on CCL5 level among all groups enrolled in this study; by applying optimal cut-off obtained by the receiver operating curve (ROC) analysis 60 (pg/ml) about severity illness, area under the ROC curve (AUC) 0.768, which entitles a highly significant (p<0.001), threshold of accuracy for (CCL5) in the distinguished of disease outcome in groups study, significant correlation between level of (CCL5) in the severe form patients group (OR= 4.89, CI= 3.01-8,35) compared to those with the control group; and so were results of mild-moderate group patients (OR=2.32, CI=1,45-3,96) were (p–value =<0.001) as shown in Figure (4).

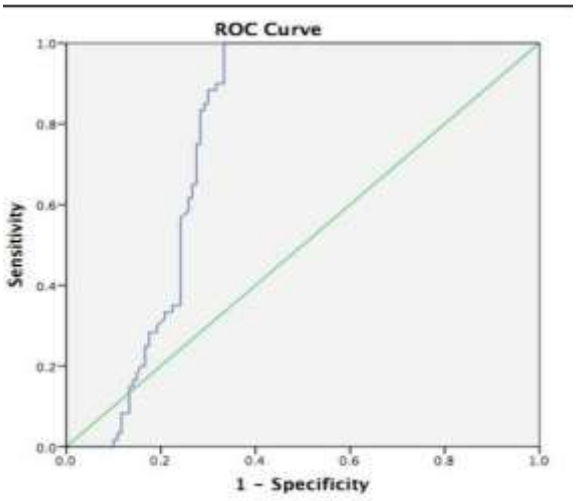

Figure 4. ROC of CCL5 among study groups. Areas under the curves (AUC) are 0.768 , *P*<0.001 CI = 0.698-0.837, Cutoff= 60 (pg/ml) Sensitivity= 78%, Specificity=80%.

Discussion

There is some limitations about this study which included, the difficulty of obtaining medical information for the largest number of patients as a result of the medical quarantine conditions, taken by most isolation hospitals, as well as the fact that this study included patients in a limited number of hospitals and in the capital Baghdad only, since the number of people participating in this study was 180 individuals.

COVID-19 is one of the crucial public health problems, it has ramifications for a large number of morbidity and mortality. Different studies reported that severe COVID-19 infections were frequently associated with advanced age. In study, the severity impact of COVID-19 was significantly higher in ages older than 60 years, these findings agreed with previous studies from Iraq [17, 18], and studies from other countries in the world [19, 20]. This finding may be explained by age–related disease comorbidities such as cardiovascular, diabetic, and other chronic diseases, moreover, pre-existing conditions such as smoking, obesity, and other unhealthy lifestyles which are most common in elderly patients can exacerbate the risk of severity associated with age above 60 years [21] , most patients participants in this study suffere from diabetic as comorbidity disease and smoking as unhealthy lifestyle. While concerning sex, the present study revealed there wasn't a considerable difference among the study groups of patients (mild-moderate and severe), this finding agreed with the previous Iraq study [18].

The innate immune system stimulation by RNAs viral, evoke signaling pathways leading to the expression of interferon type I and III (IFN-α, ß and δ), pro-inflammatory chemokines such as (C-C motif) ligand 5 (CCL5) and C-X-C motif chemokine ligand 10 (CCL10), and cytokines such as (IL-6 and TNF- α) , which causes recruitment of the inflammatory immune cells to the site of infection [22]. The findings of the present study indicate that the (CCL5) levels in sera of control and mild-moderate cases were increased compared to COVID-19 severe cases. This result is consistent with the study done by (Montalvo *et al*) [23] who attributed such result to that; during the onset of SARS-CoV-2 infection the resident cells in upper respiratory epithelium reduced their capacity of (CCL5) production in response to stimulation with IFN- γ production, while in asymptomatic patients (CCL5) expression was sufficient to attenuate the inflammatory effect of IFN- γ, and renew an optimum influx of mononuclear cell, with virucidal activity which consider the most important source for the cytokines production such as IFN- γ , that act synergistically to minimize the inflammatory injury of respiratory mucosa. In addition, (CCL5) expression in alveolar epithelial cells is dependent on synergies of Tumor Necrosis Factor-Alpha and Interferon-Gamma induction, TNF- α induces translocation of NFκB and IFN regulatory factor 3 which triggers CCL5 expression by binding to its promoter region. Furthermore, Liao MF, *et al* reported that increased serum levels of chemokine (CCL5) in non-severe cases (mild-moderate) compared with severe and progression cases in the early COVID-19 stage, and attributed this to it being produced by virus-specific CD-8 +T cells, this is maintained with the highest percentage of total lymphocyte cell counts in non-severe cases (mild-moderate) at all time and implies a protective role for such marker in this cases to resolve the infection, and clear the virus before lung inflammation take place [24]. This hypothesis is supported by the finding of the current study which shows significantly elevated (CCL5) in control and mild-moderate groups of patients. The result also suggested that CCL5 is likely to be associated with the resolution of inflammation, and it plays a protective role in disease progression and recovery possibly through the effect in the activation of cytotoxic T cells, and the production of chemokines upon antigen presentation [12]. On the other hand, the current results contradict the results in Iraqi by Hussein HA in addition with broad studies by Patterson *et al* and Li. S. *et al* reported the (CCL5) level is elevated along with IL-6 in severe patients than in non-sever, and causes deterioration of patients' healthy state due to its role in the induction and activation of inflammatory cells [25, 26, 13]. The discrepancy results regarding the role of CCL5 in COVID-19 disease pathogenesis can be illustrated by differences in the populations studied, the methods used for detection, and the timing of measurement of this marker.

Conclusion

The results of this study concluded that the lower level of (CCL5) associated with COVID-19 severity infection, and ICU admission so could be used as a predictive marker for disease progression, while the elevated level of it in control and non-severe cases suggested this chemokine is likely to be associated with the resolution of inflammation and disease recovery.

Acknowledgments

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Conflict of Interest

The authors declare that they have no competing interests.

Funding

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Ethics Statements

This project was granted ethical approval by guidelines of the Iraqi Ministry of Health and Institutional Review Board (IRB) at the College of Medicine of Al-Nahrain University. (NO: 20211058).

Author's Contribution

The authors confirm contribution to the paper as follows: contributed in methodology, resources, data curation, and formal analysis: Zahra'a Abdul AL-Aziz Yousif ; original data draft conceptualization and supervision: Jabbar S. Hassan ; Investigation and writing draft preparation: Ghaith Hamid Hameed. All authors reviewed the results and approved the final version of the manuscript.

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الدور السريري للكيموكين الالتهابي (رانتز) في مجموعة من مرضى كوفيد -١٩ العراقيين

زهراء عبد العزيز يوسف[١]، جبار سلمان حسان[٢]و غيث حامد حميد[٣]

[١] جامعة ابن سينا للعلوم الطبية والصيدلانية ، بغداد ، العراق.

[٢] فرع الاحياء المجهرية- كلية الطب ،جامعة النهرين، بغداد، العراق.

[٣] وزارة الصحة ،مدينة الامامين الكاظميين الطبية،مستشفى الكاظمية-بغداد ، العراق.

الخلاصة

مرض كوفيد -١٩ هو متلازمة سريرية يسببها فيروس الحمض النووي الريبزي المغلف المسمى (سارس-كوفيد-٢). وهو فيروس كورونا نوع بيتا، يشبهه الفايروسات التاجية الاخرى حيث يسبب عدوى سريرية شديدة الاصابة. تعد الكيموكينات احدى وسطاء الالتهابات التي تلعب دورا اساسيا في المناعه الامراضية لكوفيد-١٩ . يتم افراز الكيموكاينات من قبل الخلايا المصابة بالفايروس في الجزء العلوي من قناة الجهاز التنفسي ،مما يسبب تجنيد وتحفيز الخلايا الألتهابية مثل الخلايا العدلة ، القاتلة الطبيعية ، الحمضة والبلعمية من مجرى الدم الى مكان الأصابة . تسعى هذه الدراسة الى دراسة و تحديد دور تأثير الوسيط الألتهابي كيموكاين (الرانتيز) في المرضى المصابين بكوفيد-١٩ في العراق .تم جمع عينات دم من

١٨٠ فرد ، حيث كان ١٢٠ فردا منهم مصابين بكوفيد-١٩ وتم التاكد من اصاباتهم عن طريق تفاعل البلمره المتسلسل العكسي ، تم تقسيم المرضى الى مجموعتيين اعتمادا على شدة المرض، مرضى المجموعة الشديدة والتي ضمت ٦٠ مريضا ،و المجموعة المتوسطة والخفيفة والتي ضمت ٦٠ مريضا ايضا.علاوة على ذلك كان هناك ٦٠ فردا من الأصحاء تم اشتراكهم في هذه الدراسة كمجموعة سيطرة حيث تم التاكد من عدم اصابتهم بكوفيد-١٩. تم قياس تركيز الرانتز كيموكين في مصل الدم بواسطة تقنية فحص الأنزيم المناعي المرتبط .اظهرت نتائج هذه الدراسة فرقا معنويا عاليا(٠,٠٠١) في متوسط مستوى الكيموكين (الرانتز) في المصل بين جميع المجموعات التي شاركت في هذه الدراسة وكانت هناك زيادة كبيرة في مستوى الرانتز في تقسيم المرضى الى مجموعتيين اعتمادا على شدة المرض، مرضى المجموعة الشديدة والتي ضمت ٦٠ مريضا ،و المجموعة المتوسطة والخفيفة والتي ضمت ٦٠ مريضا ايضا. اظهرت نتائج هذه الدراسة فرقا معنويا عاليا(٠,٠٠١) في متوسط مستوى الكيموكين (الرانتز) في المصل بين جميع المجموعات التي شاركت في هذه الدراسة حيث كانت هناك زيادة كبيرة في مستوى الرانتز في مجموعة السيطرة والمجموعة المتوسطة -الخفيفة الاصابة مقارنه بالمجموعة الشديدة الاصابة (٦٦,٦٦ بيكوغرام-مل , ٥٤,٠٤ بيكوغرام-مل مقابل٣٨,٤١ بيكوغرام- مل على التوالي) . وفقا لهذه النتائج يمكن استخدام مستوى الرانتز المنخفض كمؤشرا مرتبطا بخطورة عدوى الكوفيد-١٩ وعلامة تنبؤيه لشدة المرض، بينما يشير المستوى المرتفع في مجموعة السيطره او الاصابة الخفيفة –المتوسطة الى ان المستوى المرتفع لهذه الكيموكاينات يرتبط مع تخفيف الالتهاب والشفاء .

الكلمات المفتاحية: رابطة كيموكين ٥، الكيموكين ،مرض كورونا فايروس-١٩ ، الرانتز ، فحص الانزيم المناعي المرتبط