CORRELATION SERUM LEVEL OF BRADYKININ AND MEMBRANE ATTACK COMPLEX WITH COMPUTED TOMOGRAPHY FINDING IN PATIENTS WITH COVID-19

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ABSTRACT
Coronavirus is one of the main pathogens that primarily targets the human respiratory system. Previous outbreaks of coronaviruses (CoVs) include the severe acute respiratory syndrome (SARS)-CoV and the Middle East respiratory syndrome (MERS)-CoV which have been previously described as agents that are a great public health threat. Ninety patients who include (severe, moderate, mild) with coronaviruses (Covid-19). Coronaviruses was diagnosed by the computed tomography into sever moderate and mild according to the C.T score. The total CT is the entire of the individual lobar scores range from 0 (no involvement) to 25 (maximum involvement, when all the five lobes showed more than 75% involvement). The study show highly significant correlation between bradykinin and membrane attack complex with computed tomography scores in covid – 19 patients.

Keywords: Coronavirus, Bradykinin, Membrane Attack Complex, Computed tomography scores, Severe acute respiratory syndrome, Middle East respiratory syndrome

I. INTRODUCTION
Coronavirus is one of the main pathogens that primarily targets the human respiratory system. Previous outbreaks of coronaviruses (CoVs) include the severe acute respiratory syndrome (SARS)-CoV and the Middle East respiratory syndrome (MERS)-CoV that have been previously described as agent that are a great public health threat. In late December 2019, a group of people was revealed to hospitals with an primary diagnosis of pneumonia of an unknown causes. These people was epidemiologically related to a seafood and wet animal wholesale market in Wuhan, Hubei Province, China¹.

The coronavirus (CoVs) belong to the genus Coronavirus, the family Coronaviridae, and the order Nidovirales². They are envelope and has a non-segmented, single-strand, positive-sense ribonucleic acid as their nuclear material. On electron microscope, these viruses showing a properties of the presence of that similar to a crown (corona in Latin means crown) due to the appearance of club-shaped surface protein projections³. The coronavirus are pleomorphic, range from 80 and 160 nm in length, and have a small genome measuring 27-32 Kilobytes with a unique replication strategy³.

Transmission is generally transmitted through direct or indirect contact of mucous membranes (eyes, nose, or mouth) with infectious respiratory droplets or fomites. Transmission risks increase with period and proximity with the contacts/infected persons⁴.

The main pathogenesis of COVID-19 infection as a respiratory system target virus was severe pneumonia, RNAemia, merged with the occurrence of ground-glass opacities, and acute cardiac injury. Significant high blood level of cytokines and chemokines were noted in patients with COVID-19 infection that including IL1-β, IL7, IL8, IL9, IL10, basic FGF2, GCSF, GMCSF, IFNy, IP10, MCP1, MIP1α, MIP1β, PDGFB, TNFα, and VEGFA. Some of the critical cases that were admitted to the ICU shows high levels of pro-inflammatory...
cytokines involving IL2, IL7, IL10, GCSF, IP10, MCP1, MIP1α, and TNFα that are causes to developed illness severity.

Bradykinin [BK-(1-9)] is a peptide-hormone of the kallikrein-kinin system (KKS) that action was first described by an elegant study by "Rocha e Silva and coworkers in 1949". Bradykinin (BK), a non-peptide of sequence "Arg1-Pro2-Pro3-Gly4-Phe5-Ser6-Pro7-Phe8-Arg9" is a member of the kinins, a group of peptides pervasively product by the actions of kallikreins on circulated kininogens. Other members of the kinin family involve kallidin (KD) (Lys0-BK) and the metabolites of KD and "BK: desArg9 - BK and desArg9-KD".

Membrane attack complex is a multi-meric assembly of proteins containing of "C5b, C6, C7, C8 and multiples copies of C9", that forms the membrane spanning pore. Assembly of the MAC is the end production of a complex series of biochemical reaction in which started by the soluble complement proteins bound and undergo dramatic structural rearrangements to form a transmembrane pore. The result membrane attack complex pore is a hetero-oligomer formed by the irreversible, stepwise assembly of 7 different polypeptide chains: "C5b, C6, C7, C8 (a hetero-trimer comprised of C8α, C8β and C8γ) and C9", where 18 copies of C9 are required to completed the pore. The activation of complement lead to the generation of C5b via the cleavage of C5 by membrane-bound C5-convertase enzymes.

This study aimed to evaluate serum level of bradykinin, membrane attack complex with computed tomography scoring in patients with coronaviruses (covid-19) and their correlation with each other.

II. MATERIALS AND METHOD

This study was approved by Karbala University of College of Medicine in October /2020. The type of the study is cross – sectional study. A total of 90 patients who were attending in Al – Hussein – medical city, Al – Hayat unit, in Karbala, Iraq. Were carried out of October 2020 to January 2021. Under the supervision of radiologists specialists were included in this study.

Ninety patients who include (severe , moderate , mild ) with coronaviruses (Covid–19). Coronaviruses was diagnosed by the computed tomography into severe moderate and mild according to the C.T score. The total CT is the entire the individual lobar scores ranging from 0 (no involvement) to 25 (maximum involvement, when all the five lobes showed more than 75% involvement). The demographic, clinical, laboratory, data are extracted from medical records using a standardized data collection form which included age, gender, smoker, family history, routine blood examinations (complete blood count), D-dimer, CR-Protein and serum ferritin, CT scan are done for all patients.

Inclusion criteria: All patients with positive covid19 according to the C.T.

Exclusion criteria: COVID -19 Patient on Steroid Treatment, others immoderate drugs, patient with autoimmune disease, diabetic patients, patients with inflammatory bowel disease, asthmatic patients, Patients with COPD, Hypertensive patients on ACE inhibitors drugs.

Ethical Issue: The information about each case collected from patients was taken with ethical considerations, so to get blood sample, we already informed patients and controls that we would use their blood for research purposes and most of them were cooperative and helpful. The permission had been taken from the director of AL-Hussein hospital.

Blood Sample Processing: Blood sample were collected by venipuncture from 90 patients, five millimeters of the venous blood was draw by disposable syringe under sterilization conditions and put it in gel tube then, allowed to clot; after that serum was separating by centrifugation 1500 rpm for 5 minute. The serum has been collected in plain tube then stored at -20c to be used for ELISA test to determine concentration of BK and MAC.

Statistical Analysis: Statistical analyses were performed using SPSS statistical package for Social Sciences (version 20.0 for windows, SPSS, Chicago, IL, USA). Data normality distribution was examined using Shapiro-Wilk test. Oxygen saturation, CRP, S. Ferritin, D-dimer, total lung involvement, BK and MAC were found to be not normally distributed. Quantitative data are represented as mean, standard deviation and range for normally distributed data or median, IQR (Interquartile range) for non-normally distributed data. Qualitative data are represented as count and percentage. Correlation test was done to test the relation of BK and MAC with other.
parameters. Mann-Whitney U test was used to test differences. ANOVA test or Kruskal-Wallis test were used to test differences according to data normality distribution P value of <0.05 was considered statistically significant.

III. RESULTS

One hundred inpatient cases were in this study, ninety inpatient cases were included in this study and distributed according severity to 44 severe, 29 moderate and 17 mild of Covid-19 according to computed tomography score. Demographic characteristics of the subjects are present in table (1). The ten excluded cases in this study were inpatient pregnant woman, inpatient under 12 years old, patient with negative computed tomography score and patients with medications.

Table (1): Demographic data of the studied groups

<table>
<thead>
<tr>
<th>Category</th>
<th>Count</th>
<th>Column N %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>56</td>
<td>62.2%</td>
</tr>
<tr>
<td>Female</td>
<td>34</td>
<td>37.8%</td>
</tr>
<tr>
<td>Smoker</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>45</td>
<td>50.0%</td>
</tr>
<tr>
<td>No</td>
<td>45</td>
<td>50.0%</td>
</tr>
<tr>
<td>Family History</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>9</td>
<td>10.0%</td>
</tr>
<tr>
<td>No</td>
<td>81</td>
<td>90.0%</td>
</tr>
<tr>
<td>Medical History</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0</td>
<td>0.0%</td>
</tr>
<tr>
<td>No</td>
<td>90</td>
<td>100.0%</td>
</tr>
<tr>
<td>URT signs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flue like</td>
<td>90</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

The table (1) displays the patient’s demographic characteristics in this status of the inpatient cases were included in this study which included 56 male and 34 female. A correlation was stated of each of the characteristics with the disease status. A highly significant correlation was found between the gender and upper respiratory tract sings. while smoker, medical history are not.

Regarding to the family history for the patient with covid-19, the Ninety inpatient cases were found (90%) of patients without family history for covid-19 and (10%) with state of family history of the disease.

A smoking was found as implicated as trigger for the disease in the covid-19 patient groups.

The table (2) shows the mean of age, PCV, Hb, WBCs and platelets in patient with covid-19. Were the mean of age 48.86 with minimum 19 years and maximum 88 years explains the relationship between the injury's forgetfulness of 19 years and over. The mean of PCV and Hb are 38.70, 12.81 show normal range with covid-19 while the white blood cells and platelets show high percentage with covid-19.

Table (2): Hematological parameter of the studied sample

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean</th>
<th>Standard Deviation</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Year)</td>
<td>48.86</td>
<td>15.73</td>
<td>19.00</td>
<td>88.00</td>
</tr>
<tr>
<td>PCV (%)</td>
<td>38.70</td>
<td>4.72</td>
<td>29.00</td>
<td>50.00</td>
</tr>
<tr>
<td>Hb (G/DL)</td>
<td>12.81</td>
<td>1.62</td>
<td>9.00</td>
<td>16.50</td>
</tr>
<tr>
<td>WBC(X10^9/L)</td>
<td>9.29</td>
<td>5.15</td>
<td>3.20</td>
<td>23.00</td>
</tr>
</tbody>
</table>
The table 3 shows the median of demographic characteristics of parameter investigations with covid-19. The oxygen saturation median 90% with minimum 70% and maximum 95% the results showed that the oxygen rate is lower in a severe injury. The CRP and other investigations S. ferritin, D- dimer shows high level in the severe infection with covid-19.

Regarding to the total lung involvement, bradykinin and membrane attack complex was implicated as trigger for sever infection.

Table 3: Demographic characteristics of the parameter investigations in the studied sample:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Median</th>
<th>Minimum</th>
<th>Maximum</th>
<th>IQR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxygen saturation (%)</td>
<td>90.00</td>
<td>70.00</td>
<td>95.00</td>
<td>4.00</td>
</tr>
<tr>
<td>CRP (ng/ml)</td>
<td>40.00</td>
<td>4.00</td>
<td>830.00</td>
<td>48.50</td>
</tr>
<tr>
<td>s. Ferritin (ng/ml)</td>
<td>775.00</td>
<td>109.00</td>
<td>3264.00</td>
<td>317.00</td>
</tr>
<tr>
<td>D. dimer (ng/ml)</td>
<td>792.00</td>
<td>110.00</td>
<td>4759.00</td>
<td>283.00</td>
</tr>
<tr>
<td>Total lung involvement (score )</td>
<td>15.00</td>
<td>1.00</td>
<td>24.00</td>
<td>9.00</td>
</tr>
<tr>
<td>BK (ng/ml )</td>
<td>11.48</td>
<td>1.00</td>
<td>33.00</td>
<td>11.83</td>
</tr>
<tr>
<td>MAC (ng/ml )</td>
<td>670.93</td>
<td>1.00</td>
<td>2426.77</td>
<td>622.51</td>
</tr>
</tbody>
</table>

The table 4 shows the correlation between bradykinin, membrane attack complex with total lung involvement. There was a positive correlation between BK and MAC (P<0.005). and there was a positive correlation between total lung involvement with BK and MAC (P<0.005).

Table 4: Correlation of BK, MAC with total lung involvement Correlations

<table>
<thead>
<tr>
<th>Parameters</th>
<th>BK</th>
<th>MAC</th>
</tr>
</thead>
<tbody>
<tr>
<td>BK</td>
<td>Pearson Correlation</td>
<td>0.470**</td>
</tr>
</tbody>
</table>
There was a positive correlation between BK and MAC ($r=0.470, P<0.005^*$).

There was a positive correlation between total lung involvement with BK and MAC ($r=0.928, P<0.005^*$; $r=0.535, P<0.005^*$ respectively).

The table (5): shows the Effect of lung involvement regions on oxygen saturation, CRP, s. ferritin, D. dimer, BK and MAC. There was a significant difference in oxygen saturation ($P=0.009$), CRP ($P<0.005$), s. ferritin ($P<0.005$), D. dimer ($P<0.005$), BK ($P<0.005$) and MAC ($P<0.005$) according to lung involvement regions. Kruskal-Wallis test. To study the lung involvement regions on the studied parameters, Tables (3.10).

### Table (5): Effect of lung involvement regions on oxygen saturation, CRP, s. ferritin, D. dimer, BK and MAC

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Mild N=17</th>
<th>Moderate N=29</th>
<th>Severe N=44</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median</td>
<td>IQR</td>
<td>Median</td>
</tr>
<tr>
<td>O$_2$Sat %</td>
<td>92.00</td>
<td>1.00</td>
<td>90.00</td>
</tr>
<tr>
<td>CRP ng/ml</td>
<td>16.00</td>
<td>18.00</td>
<td>54.00</td>
</tr>
<tr>
<td>S.ferritin ng/ml</td>
<td>434.00</td>
<td>198.00</td>
<td>785.00</td>
</tr>
<tr>
<td>D.dimer ng/ml</td>
<td>512.00</td>
<td>303.00</td>
<td>830.00</td>
</tr>
<tr>
<td>BK ng/ml</td>
<td>3.78</td>
<td>3.50</td>
<td>9.06</td>
</tr>
<tr>
<td>MAC ng/ml</td>
<td>205.43</td>
<td>55.00</td>
<td>600.74</td>
</tr>
</tbody>
</table>

### IV. DISCUSSION

Coronavirus is an enveloped positive-sense RNA virus, which is describing by club-like spikes projection from its surface. Although coronavirus is common related with acute respiratory tract infections in humans, its has ability to infected multiples host species and a different of illnesses makes it a complex pathogen$^{19}$. The recurrent interactions of wild animals with humans make them a common source of zoonotic infections. Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) and Middle Eastern Respiratory Syndrome Coronavirus (MERS-CoV) are zoonotic pathogens that can cause severe respiratory illnesses in humans$^{11}$. The SARS-CoV-2 virion with a genome size of 29.9 kb, possesses a nucleocapsid composed of genomic RNA and phosphorylated nucleocapsid (N) protein. The nucleocapsid is inhumed inside phospholipid bilayers and wrapped by two...
different kinds of spike proteins: "The spike glycoprotein trimmer (S) that exists in all CoVs, and the hemagglutinin-esterase (HE) only shared among some CoVs. The membrane (M) protein and the envelope (E) protein are located among the S proteins in the viral envelope¹².

The age was considered as an significant effector in the occurrence of the disease severity. Study showed the age of the sample was found to be highly significant when correlated with the disease severity. While the gender was found to be significant to the state of the disease.

The general mean of age groups was 48.86, as in the table (3.2). The elder patients (above 60 years old) present the high risk to Covid-19, even more than having any comorbidity. On the other hand, it seems that younger adult patients (30-39 years old) present some safeguard. The severity of COVID-19 correlated significantly with older age¹³. The possible reason for the association between infection-related mortality, particularly viral infections with age, may be due to impaired cellular immune function and a longer duration of inflammation in the elderly¹⁴.

Where the gender was also found to be significant in the disease severity table (3.1). Men tended to develop more serious cases than women, according to the clinical classification of severity. The present study view that a male dominance in the incidence of COVID-19 has been noted, similarly to that of SARS-CoV, indicating males are more susceptible to SARS-CoV-2 infection than females¹⁵.

Another study that show females are, in general, more like to be infect by SARS-CoV-2, especially in some specific age groups. The infection of SARS-CoV-2 appear firstly through the angiotensin-converting enzyme 2 receptor, which act as a gateway for the virus’s entry into tissues¹⁶.

The current literature suggests that men tend to have a higher risk of severe infection and mortality related to COVID-19. Regard to gender, we observe a large expansion of male patients, but the mortality risk was not different, and this may be in part elucidated by the stronger effect of older age in population.

The age difference of the subjects between literature and the current Study have many explanations including one prominent explanation is that the sample was selected from a public health hospital that is designated for adults. One other reason is that the patients may be referred to private hospitals and/or clinics for diagnosis and treatment and not public health hospitals, the reporting of the disease may be associated with the active status as seen in our results, explaining the elevated threshold of the age groups of patients.

Regarding to the smoker and family history, The smoker implicated as trigger for the disease in the covid-19 patient groups. In the study table (1). The smoking is a risk factor for progression of COVID-19, with smokers having 1.91 times the odds of progression in COVID-19 severity than never smokers. Smoking Considering risk of severe disease indicate that there is a significant association between COVID-19 and current or ever smoking. Smoking is associated with increased disease severity in COVID-19¹⁷,¹⁸.

Smoking is correlation with up-regulation of ACE2, the receptor for the SARS-CoV-2 virus in the lungs, with up-regulation in epithelial cells and downregulation in alveolar type 2 cells. The status is further complexed by the probability that internalization of ACE2 due to viral infection leads to opposite ACE inhibitor activity and high angiotensin II levels, participate to endothelial damage and the coagulopathy and micro thrombosis seen in severe coronavirus. Smoking itself causes vascular endothelial damage, a notable feature in the pathophysiology of severe COVID-19.

Regarding to the family history of the patients the study showed there is no significance with Covid-19 table (1). As the most of the literature wasn’t found family history of covid-19, the family history was found to be of no significance when correlated with the disease.

Predominantly, in the context of a global pandemic, accurately recording the smoking and family history is likely to be of low priority for clinicians whose focus is stabilizing severely and critically ill patients.

Regarding to the hematological parameter of the studied sample the result of white blood cells shown in table (2). Henry et al. also completed in COVID-19 positive patients that patients with critical and fatal illness had significant elevated white blood cells, compared to non-severe disease²⁰. Huang et al. reported that the percentage of severe COVID-19 patients who had increased WBC counts was significantly higher than non-severe
counterparts (54% vs 19%), further highlighting the fact that the extent of deviation from normal white blood cell counts correlates with disease severity⁵.

We found that the WBC counts of COVID-19 patients were significantly higher in the severe cases as compared to the non-severe group at discharge. Monitoring the patients' WBC counts during hospitalization also disclosed a simple method of predicting COVID-19 prognosis²¹.

Regarding the platelets the results show different significant as in table (2). The low of thrombocytes was correlated with poor respiratory function in severity ill patients. Thrombocytes directed react with viral pathogens through the pathogen recognition receptors such as "protease-activated receptor 4 (PAR4) and glycoprotein IIIa (GPIIIa)", and this interact can lead to thrombocytes activating, that is associated with lung inflammation as well as the severity of viral infections, lung injury and death²².

There are many reasons why the thrombocytes of COVID-19 patients reduced in the first stages. On the one hand, virus infection involved lung tissues damaged, resulting in activation, aggregation, and entrapment of the thrombocytes. This led to thrombosis at the lung injury site, which raised the consumption of platelet. On the other hand, overripe megakaryocytes may liberated platelets in the lungs. Therefore, when the damage lungs causes pulmonary fibrosis and pathological changes, production of platelet might be affected²³.

Regarding to the hemoglobin the results show different significant as in table (2). Hemoglobin levels in COVID-19 positive patients was found to be significant higher than in survival patients. While no significant difference was observe among woman, higher hemoglobin levels was seen in non-survival male patients. It's likely that these results are also affected by many reasons, such as the existence of comorbidities or anemia, and habits such as cigarette smoking. The patient files used for this study did not involve a detail patients history, and thus, their effects on hemoglobin level was not account for. Also, the normal hemoglobin level in the woman population is lower than that of men²⁴.

Regarding to the demographic characteristics of the parameter investigations in the studied sample as in the table (3). Studies that show the CRP marker was found to be significant elevated in the first phases of the infection for severe COVID-19 patients. CRP has been correlated with disease evolution and is an first predictor for severe COVID-19. CRP of critical patients was significant greater than those of mild patients. The level of C-reactive protein in elder patients is significant higher than that in the younger and middle-aged group, which is similar to MERS-CoV²⁵ ²⁶²⁷.

The role of CRP in illness pathology may include host protection and inflammation. In response to inflammatory outset, CRP bound to pathogens and promotes their removal by phagocytic cells, function as the primary line of innate host defense. In addition, CRP can reveal anti-inflammatory effect by inhibiting neutrophil chemotaxis. However, by up-regulating expression of adhesion molecules and pro-inflammatory IL-1, IL-6, IL-8, and TNF-α, CRP can also exert pro-inflammatory effects. Dialectical result of serum CRP levels was observed in patients with acute lung injury (ALI) or acute respiratory distress syndrome (ARDS)²⁸.

The serum ferritin increased levels in patients with severe and very severe Covid-19. Another study it was found that individuals with severe and very severe coronaviruses exhibited elevated serum ferritin levels, being serum ferritin in the very severe COVID-19 group significant higher than in the severe COVID-19 group²⁹ ³º.

The clinical picture of the severity cases of COVID-19 similar to macrophage activating syndrome, which is common related with high level of ferritin or even a cytokine storm. H-chain of the ferritin could be paramount in activating macrophages to raise the secretion of inflammatory cytokines observed in COVID-19 patients³¹.

The D-dimer level is elevated in patients of all age groups with COVID-19. In patients with COVID-19, the increase D-dimer level in these patients may be due to inflammatory responses to virus infections, dysfunction of endothelial cells that rising thrombin production. Hypoxia causes coagulation disorders by elevated both viscosity and the transcription factor-dependent signaling pathway³².

Regarding to the correlation of BK, MAC with total lung involvement. This study focused on the BK and MAC, measured them in comparison with Covid – 19 patents groups, where BK and MAC was found to be of significance in that correlation.
MAC: We investigated the serum levels of sC5b-9 as markers of complement activation in patients with COVID-19, the table (4) shows the levels of MAC in groups of patients.

Several studies that show the serum levels of MAC was significant higher in the patients with moderate illness and those with severe and significant high in the patients with critical disease than in those with moderate illness. MAC level was elevated in patients with mild, moderate or severe illness.

Complement activation, formation of C5b-9 or membrane attack complex (MAC) or terminal complement complex (TCC) is important to be evaluated. In their study have shown that C5b-9 was significant higher in COVID-19 patients with moderate illness than healthy controls and those with critical disease than healthy control, and also C5b-9 was significant high in patients with critical illness than those with moderate disease. Thus, C5b-9 levels probably are an index of severity of disease as C5b-9 also has a role in neutrophils activation and inflammation that leads to endothelial damage.

Complement activation contributes to the induction and amplification of the inflammatory process as a resulting of the ability of C5a and MAC to recruited phagocytic cells in the lungs and other infecting organs, activated endothelial cells, and stimulate vascular permeability.

Consequently, measurement complement activation products particular MAC may providing a sensitive and useful biomarker of COVID-19 severity and activity.

BK: The serum levels of BK as marker in patient with Covid – 19 , the table (4) results reveal that there was differences in bradykinin level among the covid-19 patient groups.

Many studies that shows the levels of BK are elevated. Bradykinin is a high strong non-peptide vasoactive, capable of enlarge venules through the liberation of nitric oxide (NO) and elevating vascular permeability through its action on B1 and B2 receptors. The Angiotensin-Converting Enzyme 2, also known as Kininase II, is one of those accountable for degrading kinins, including bradykinin SARS-CoV-2 binds to ACE 2 receptors to enter the cells.

The ACE 2 receptor is mainly found in endothelial cells. The action of SARS-CoV-2 could result in endothelialitis, which would lead to thrombocytes overactivation, aggregation, and retention, thereby determin the generation of microthrombi in the damaged the site Research has therefore indicated that COVID-19, in addition to possibly developing a Severe Acute Respiratory Syndrome (SARS).

We found that the changes in the levels of person components and activating products of the complement and kallikrein/kinin systems wascorrelated with survival/death, organ function, and scores of diseases severity. The kallikrein/kinin system was correlated with organ failure, reflected by injury to received mechanical ventilation, involving that the lungs, kidneys and heart was influence. Logistic regression analysis of prekallikrein strongly proposed that the correlation with death was due to is respiratory failure.

This study focusing on the correlation between total lung involvement with BK and MAC as diagnostic markers for severity Covid – 19 patient groups. the results showing strong correlation between BK and MAC, there was a significant correlation between BK and MAC (P<0.005), and there is correlation between total lung involvement and BK, MAC in the patients with moderate and severe Covid – 19, there was a positive correlation between total lung involvement with BK and MAC (P<0.005) as in table (4).

Regarding to the effect of lung involvement regions on oxygen saturation, CRP, S. ferritin, D. dimer, BK and MAC, The study show highly significant correlation between lung involvement regions and CRP, D. dimer and serum ferritin (P<0.005) as the table (5).

Several studies that show the levels of serum CRP in the CT imaging score ≥ 11 group were higher compared with the < 11 group. The CRP showed significant positive correlation with the severity of pneumonia quantified on initial CT score.

We found that CRP increase significant at the primary stage in severe COVID-19 patients; while still non-significant variation in the CT scores was found between the severe and mild patients clusters. CRP was an first biomarker for predicting the severity of COVID-19 with good performance. These results proposed that CRP could be used to initial identified patients who might become severely diseases and before the CT finding.
Many studies were found CT imaging score 11 group had dramatically elevated level of the D-dimer in the blood. Another studies show moderate correlation between CT score D – dimer. The D-dimer levels was significantly higher in severe patients, and the level of D – dimer increase was proportionate with the aggravation degree of chest CT lesions.

The pathological picture of COVID-19 involve diffuse alveolar destruction with cellular fibromyxoid exudates, desquamation of pneumatocytes and hyaline membrane generation, pulmonary edema with hyaline membrane generation, and interstitial mononuclear inflammatory infiltrates, predominant by lymphocytes, which greatly resemble those seen in SARS and MERS coronavirus infection. The observe D-dimer elevation signify a hyperfibrinolysis status and elevated inflammatory burden induced in SARS-COV-2 infection.

Regarding to the serum ferritin levels there was a statistical highly significant between elevated serum levels of ferritin in correlation with CT stages, where ferritin was elevated in 18.4% in the mild, 63% in the moderate, and 100% in the critical stages. Patients with critical COVID-19 pneumonia show highly serum levels of ferritin than the non-severe patients using a multivariate logistic regression analysis showing that the serum ferritin level was an independent risk factor for disease severity.

Ferritin has been well described as an acute phase reactant, as well as a moderator from immune dysregulation in critical coronaviruses. Therefore, ferritin may be not only a marker of the inflammatory milieu but also an active player in the "cytokine storm" scenario that characterizes severe coronavirus. Complex feedback mechanism between ferritin and cytokine in the control of pro-inflammatory and anti-inflammatory mediators might exist as cytokines can stimulate ferritin expression, but ferritin can induce the expression of pro- and anti-inflammatory cytokines as well. In this regard, it has been speculated that COVID-19 with pulmonary involvement may be included within the spectrum of hyperferritinemnic syndrome.

Ferritin level was observe to be highly in the CT-positive patient group and have moderate positive correlation with CT severity. This status indicated that serum levels of ferritin is closely related to the radiological severity as well as the clinical severity of the subjects. In a similar line, the high level of serum D-dimer in the CT-positive group and its positive correlation with CT severity, though not high like ferritin, indicate that the serum D-dimer level is associated with clinical and radiological severity.

The study focusing on the correlation between lung involvement regions on BK and MAC and found highly significant correlation between lung involvement regions on BK and MAC and oxygen saturation (P<0.005), as the table (5).

V. CONCLUSION

In this study the bradykinin and membrane attack complex candidate as a biomarkers to evaluate the severity of covid -19

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