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HIGH INTER INTERLEUKIN-18 LEVEL COULD BE ASSOCIATED WITH SEVERE DISEASE IN COVID-19 PATIENTS

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Abstract:

Coronavirus disease 2019, also known as COVID-19, is a new public health emergency that poses a threat to humanity .A strong immune response during viral infections, as well as a SARS-CoV-2, may be required for COVID-19 to be resolved. In severe individuals, however, chronic immune activation can develop to a hemophagocytosis-like condition, with uncontrollable cytokine production. IL-18 is produced by macrophages in the early stages of viral infections .In this study carried out on 100 samples of blood from COVID-19 patients and 20 control both sex (male &female) to determine IL-18 . In general, the Serum IL-18 levels were remarkably higher in COVID-19 patients compared to healthy individuals (control).
Furthermore, the infections were significantly higher in age group (70 >80 years old) years while IL-18 levels according to their gender IL-18 were found to be higher in men than women

Keywords: COVID-19, Interleukin-18,

INTRODUCTION

Coronavirus disease is a new public health crisis threatening the humans. This pandemic disease is caused by the novel betacoronavirus. COVID-19 has very important clinical features such as high rates of transmission, mild to moderate clinical manifestation with more serious radiological abnormalities seen in the elderly. Remarkably Coronaviruses enter cells through the ACE-2 receptor (Zhoug et al., 2020).

SARS-CoV-2 link to angioten Coronaviruses enter cells through the ACE-2 receptor. sin-converting enzyme 2 (ACE2) receptors to invade human cells, and these receptors are highly expressed in the intestinal epithelium (Ni, W. ,2020)

Coronaviruses are members of the Nidovirales order's Coronaviridae family (Su et al. 2016). There are four genera that have been identified: alpha , beta , gamma , and delta . (Perlman and Netland 2009). However, the Coronaviruses belongs to the genera of β- (Wu *et al.*, 2020)

Coronaviruses are single-stranded, positive sense RNA viruses with spike-like projections on their surface that give them a crown-like appearance under the electron microscope, hence the name coronavirus. Coronaviruses are enveloped, positive sense RNA viruses (26-32 kb in length) with a diameter ranging from 60 nm to 140 nm and a diameter ranging from 60 nm to 140 nm. (Richman *et al.*, 2016) .

Immune patterns are obviously linked to the progression of disease in patients infected with viruses, according to evidence. In severe and critical COVID-19 patients, SARS-CoV-2 has been demonstrated to disrupt normal immunological responses, resulting in a weakened immune system and uncontrolled inflammatory reactions, Lymphopenia, lymphocyte activation, dysfunction, granulocyte, monocyte abnormalities, high cytokine levels, and an increase in immunoglobulin G (IgG) are the main symptoms of the viral infection (Yang L., *et al.*, 2020).

Innate immune cells play an important role in antiviral immunity, inflammatory signaling, and cytokine generation. IL-1 and IL-18 are major mediators of the inflammatory response, and elevated levels of IL-1 and IL-18 in plasma have been linked to mortality or severity in COVID-19 patients (Hadjadj *et al.*, 2020).

IL-18 is produced by macrophages in the early stages of viral infections, and it stimulates the production of IL-6 and IFN-, both of which are important for viral host defense..(Lagunas-Rangel F.A *et al* .,2020). However, abnormal IL-18 production can also lead to serious pathological damage. The activity of IL-18 is balanced by IL-18 binding protein (IL-18BP) which is stimulated by IFN-γ, (Arend W.P et al 2008) . Moreover, high IL-18 concentrations in serum might serve as a biomarker to predict disease outcome.

Markedly high serum IL-18 levels have been related to severe disease and mortality in some viral infections characterized by cytokine storm such as Dengue virus

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and avian influenza (Valero N ., 2019). IL-18 is produced from immune cells, such as macrophages, DCs, Langerhans cells, and many nonimmune cells, such as chondrocytes ,osteoblasts, endothelial cells, keratinocytes, and intestinal epithelial cell.(H. P. Carroll, V et al .,2008). Upon viral infection, IL-18 release induces ferritin, explaining the frequently observed hyperferritinemia in viral infections (Slaats J., 2016) . Identification of the role of IL-18 will shed light on disease pathogenesis of COVID-19 which is also characterized by hyperferritinemia and cytokine .The concentrations of IL-18 levels are upregulated in the serum of COVID-19 patients (Rognes T *et al.*, 2016) . Intestinal infection by viruses can also increase the production of the proinflammatory cytokine IL-18,(Rognes T. *et al* .,2017).

METHODS

Blood sample were collected from 100 Covid -19 patients, and 20 control samples . All samples were placed in gel tube, and separated by centrifuge (4000xg for 15 minutes), and directly stored at -20 ºC to be analyzed later for IL-18.

Ethic approves

This study was approved by the Ethics Committee of Diyala Health Department / Training and Human Development Center / Research and Knowledge Management Division (No. 3266. Date 3/11/2021) and also by the Committee of the College of Science/University of Diyala. Written informed consents were also obtained from all participants prior to registration.

Quantitative determination of human interleukin (IL-18)

The concentration of IL-18 in the serum of Covid -19 patients were evaluated by enzyme linked immunosorbent assay (ELISA) according to Satış, H..et al 2021 .

RESULTS AND DISCUSSION

Descripted of study samples

This study performed from November- 2021 to January -2022. It has carried out by using (100 blood sample Covid -19 patients, 20 control)that were Baquba teaching hospital, from both sex with age range (15–80 years)

IL-18 concentration

As shown in Fig. 1, the average IL-18 concentration was significantly higher in all selected patients' sera compared to the control sera ($P \leq 0.001$).

The first patients group (15-25 years old) showed around 275.1± 110.7 (pg/ml) as a mean of IL-18 concentration . Whereas, the other group (26-36 years old) has 355.5 ± 79.12 (pg/ml) of IL-18 levels in their patients serum . Furthermore, the mean of IL-18 concentration was around 384.0 .0±57.95 (pg/ml) for the third age group (37- 47 years old). Furthermore, the measurements of the IL-18 was 379 .2±79.55 (pg/ml) for the patients that around 48-58 years old. In additionally, the age group(59-69 years old) presented 434.2 ±305.6 pg/ml as a mean of IL-18 in the sera of their infected participants. Finally, the higher concentration of IL-18 levels was measured in the sera of elderly patients (70 >80 years old) with 447 ± 191.1(pg/ml) . IL-18 might serve as an indicator of infection in COVID-19 patients. The result of current study comes in agreement with Kerget, B., et al 2021, the concentrations of IL-1Ra and IL-18 levels were found to be significantly higher in the non-survivors ($p < .001$), who observed a different pattern in serum interleukin 18 (IL-18) levels.

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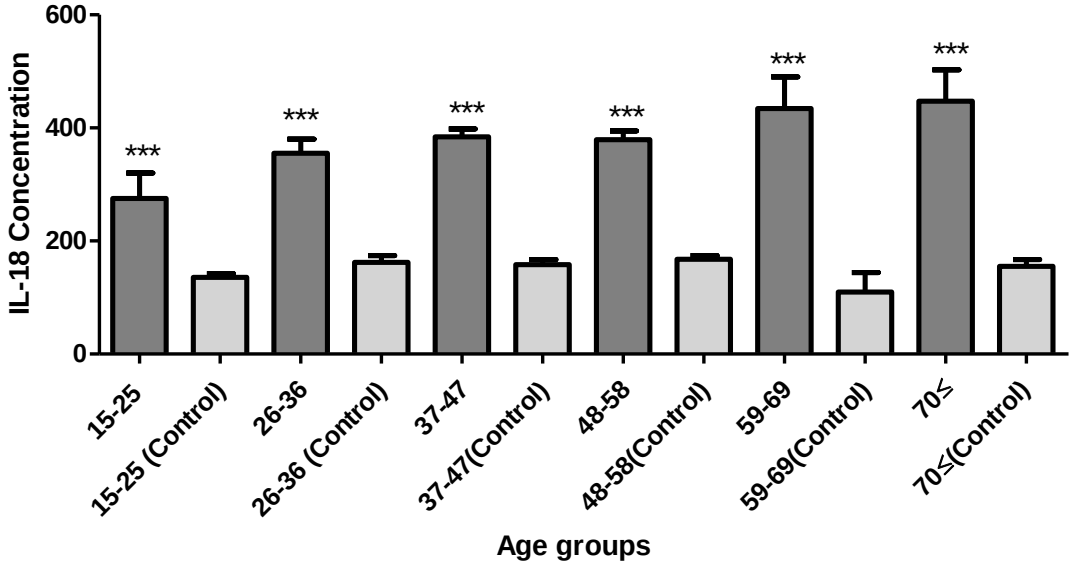

Fig 1: The mean values of IL -18 concentrations ((pg/ml) (according to the participants age groups)

According to fig 1,all control samples did not show significant differences s of IL-18 levels according to their gender. However

The level of IL-18 of males was significantly ($p<0.001$) higher (430 pg/ml) in patients than their control. Similarly with female patients who presented a significant high mean of IL-18 (372 pg/ml) as compare with the control. Furthermore, there is a significant difference of IL-18 means ($p<0.001$) between both patients groups (Fig 4). The result of current study comes in agreement with Satış, H., et al 2021 (The serum levels of IL-6 and IL-18 were found to be higher in men than women), and Takahashi, T et al 2020 (Male patients had higher plasma levels of innate immune cytokines IL-18 the female patients) .and Takahashi, T., and Iwasaki, A. 2021.(IL-18, are increased in male patients compared with female patients in the early phase of COVID-19)

The higher level of IgG antibody, which could help against SARS-CoV-2, was observed higher in female patients compared with males , and more immune-related genes were located on X-chromosome (Takahashi,2020)

Inflammation is a well-coordinated response against viral or bacterial infection induced by the generation of pro-inflammatory cytokines (Satış,2021). COVID-19 is characterized by the inflammatory response regulated by the stimulation of the nucleotide-binding oligomerization domain (NOD)- leucine-rich repeats (LRR)- and pyrin domain-containing protein 3 (NLRP3) inflammasome. The activated NLRP3 inflammasome leads to the release of interleukin-18 (IL-18) and IL-1β and pyroptotic cell apoptosis (Gedefaw,2021).

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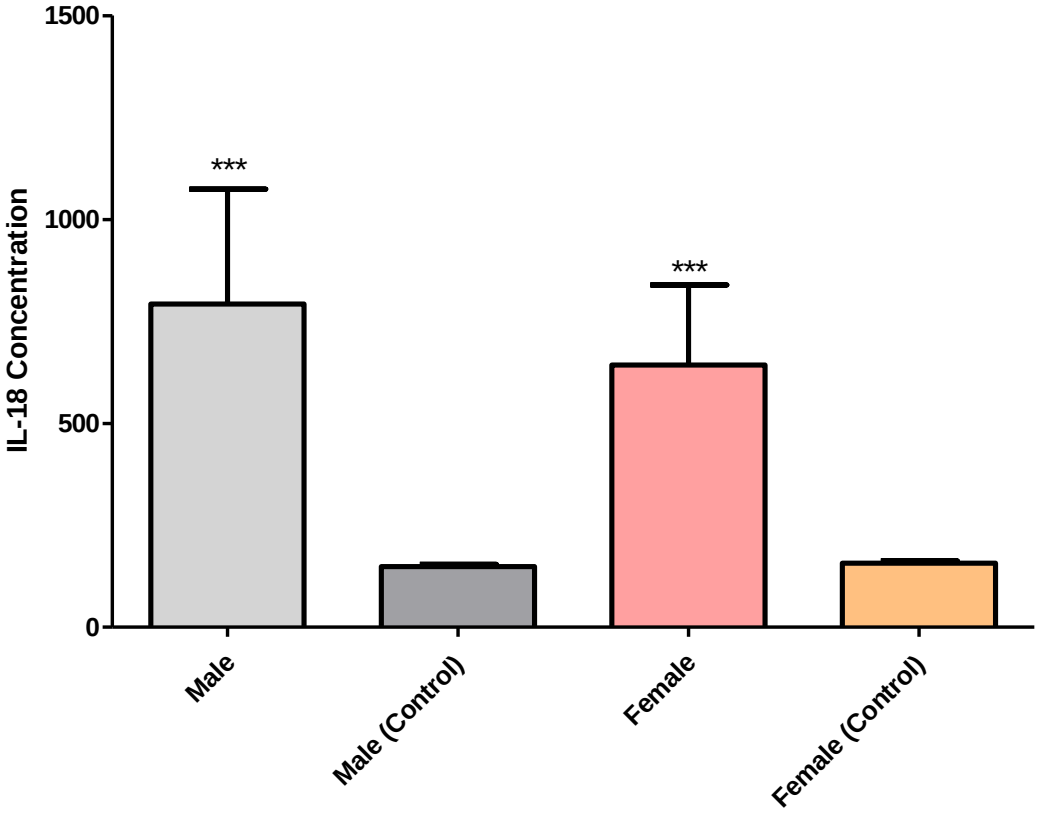

Figure 2: The comparison of IL-18 concentration in the plasma between participants (according to the gender). One-way Anovo with Dunnett's multi-comparison post-hoc test comparing all the data within and between the columns; *** p<0.001 .

In conclusion according to the results of the present study. The serum concentrations of IL-18 correlate markers and reflect disease severity. Results of the present study shed light on role of IL-18 on COVID-19 pathogenesis and might provide an evidence for the clinical trials on IL-18 antagonists for the treatment of severe COVID-19 patients IL-18 levels according to their age, the infections were significantly higher in age group between(70 >80 years old) ,while IL-18 levels according to their gender IL-18 were found to be higher in men than women.

Conflict of interest statement

The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, and in the decision to publish the results.

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