

# The Role of YKL-40 and $\beta$ 2 Microglobulin as A Laboratory Biomarker in COVID-19

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## Abstract

**Background:** A cytokine storm and an aggressive immune response against the virus play a crucial role in enhancing the severity and fatality of sickness, according to recent studies. The YKL-40 and  $\beta$ 2 Microglobulin biomarkers are involved in the development of severe COVID-19 and may be used as early indicators of severity. **Aims:** The aim of this study is to compare asymptomatic, moderate, severe, and critical COVID-19 patients' serum levels of certain laboratory biomarkers (YKL-40,  $\beta$ 2 Microglobulin) to those of healthy controls. **Materials and Methods:** one hundred patients with positive RT-PCR COVID-19 results and a control group of 46 healthy participants with negative RT-PCR results. Patients were categorized as a four groups, critical, severe, moderate, or asymptomatic according to WHO standards. Enzyme-Linked Immune Sorbent Assay (ELISA) was used by (CV Human Reader HS REF 16670) to measure (YKL\_40,  $\beta$ 2 Microglobulin). **Results:** The mean levels of YKL-40 (550.9758),  $\beta$ 2 microglobulin (18.8349) among patients more than control (123.57) (9.88) groups, while the mean levels of YKL-40 and  $\beta$ 2 microglobulin respectively were higher among both critical (1266.89) (28.06) and sever (651.35) (20.13) of COVID-19 patients other than moderate (162.3) (16.49), asymptomatic (123.34)(10.64). **Conclusions:** The current study's findings revealed a significant difference in the level of (YKL-40,  $\beta$ 2 microglobulin) between patient groups (critical, severe, moderate, and asymptomatic) and the control group. We also discovered a strong correlation between the disease severity and high concentrations of biomarkers, aging, and chronic illnesses.

**Keywords:** YKL-40,  $\beta$ 2 microglobulin, COVID-19.

## 1. Introduction

A clinical illness known as coronavirus disease 2019 (COVID-19) is brought on by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus. In addition to respiratory and gastrointestinal symptoms, patients may also experience multiple organ failure, which can be fatal. The primary determinant of COVID-19 progression severity is the delicate balance between an efficient antiviral response and a impaired immunological response (1).

Most SARS-CoV-2 patients have mild illnesses and exhibit typical symptoms such fever, coughing, and exhaustion. (2). A cytokine storm, which is the term for the large production of pro-inflammatory cytokines that lead to immediate lung injury and a poor prognosis, can be brought on by SARS-CoV-2 infection (3).

Pro-inflammatory cytokine levels that are too high can result in shock, damage to the heart, liver, and renal tissues, respiratory failure, or failure of multiple organs (4). They also play a role in the severe pulmonary disease that results in significant neutrophil and macrophage infiltration, diffuse alveolar destruction with hyaline membrane development, and diffuse alveolar wall thickening. Additionally seen in the dead patients were spleen atrophy and lymph node necrosis, both of which are signs of immune-mediated destruction (5).

In severe and critical COVID-19, the number of inflammatory and non-inflammatory markers increased. Some of these indicators were utilized to

assess the severity and prognosis of pneumonia. It is well recognized that the generation of pro-inflammatory cytokines typically characterizes dysregulated innate and adaptive immune responses (6).

Many factors had used to support diagnosis, IL-6, and IL-10, which act as pro-inflammatory cytokines and promote diagnosis, monitoring treatment, and severity determination, can be used as predictors for quick diagnosis of individuals at higher risk of disease and assist doctors (7).

Numerous more parameters can also be easily obtained from routine blood and biochemical analysis (8). This study will look at certain indices of peripheral blood analysis and biochemical analysis, including (YKL-40,  $\beta$ 2microglobulin) in COVID-19 patients, to see if they have prognostic impact in patients with the disease and to provide more evidence for clinical diagnosis and treatment.

A chitin-binding protein called YKL-40 is higher in people with a variety of inflammatory diseases that include continuous conversion; YKL-40 is a highly phylogenetically conserved chitin-binding glycoprotein.

In this paper we tried to find out if we can by use these inflammatory markers to determine disease severity in Covid-19 patients and to support diagnosis of covid-19 patient in addition to the principal parameters to detect whether these indices from general laboratory testing have prognostic value in patient of Covid-19.

## 2. Materials and Methods

Study was carried out on 146 persons, split into two groups; 100 patients with positive RT-PCR COVID-19 test, and a Control group of 46 healthy persons with negative RT-PCR test. Patients also had divided into four groups; (critical, severe, moderate and asymptomatic) patients ranged in age from (15-84) years. Measurement of YKL-40 and  $\beta$ 2microglobulin was done by using Enzyme-Linked Immune Sorbent Assay (ELISA) done by CV Human Reader HS REF 16670. We collected (5-10 ml) of peripheral blood samples of (100) COVID-19 patients after real-time PCR test for nasopharyngeal swab, the samples were taken while they were suffering from an active illness.

### 3. Results

One hundred adult patients of COVID-19 with positive RT-PCR COVID-19 test with age group ranging from (25 to 84) years were included in this study. The patients were selected from different Hospitals in Iraq. The mean ages of critical and severe COVID-19 patients were at the sixth decade

**Table 2: Distribution of studied groups according to genders.**

| Study Groups | N | Gender |        | Total  | P Value                         |
|--------------|---|--------|--------|--------|---------------------------------|
|              |   | Male   | Female |        |                                 |
| Critical     | N | 14     | 11     | 25     | Chi-square=7.27<br>p-value= 0.1 |
|              | % | 56.0%  | 44.0%  | 100.0% |                                 |
| Sever        | N | 13     | 12     | 25     |                                 |
|              | % | 52.0%  | 48.0%  | 100.0% |                                 |

The mean levels of YKL-40 in patients were (550.9758) more than control (127.6558) were highly significant, while the mean levels of YKL-40 were significantly higher among critical (1266.89) and sever (651.35) of COVID-19 patients more than moderate (126.3), asymptomatic (123.34) groups. These differences have  $p \leq 0.001$  as shown in figure (1).

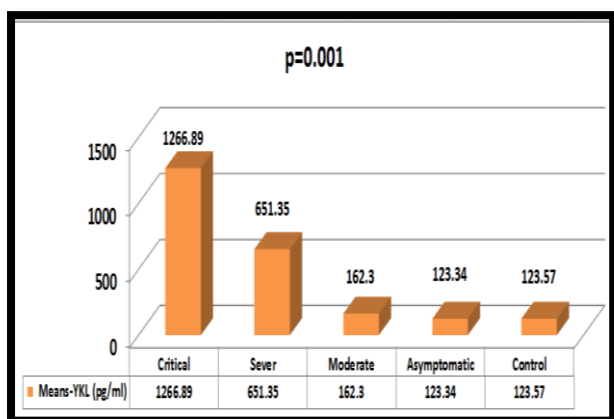


Figure 1: the levels of YKL-40 among COVID-19 patients and control group.

The mean levels of  $\beta$ 2microglobulin (18.8349) in patients more than control (9.8871), while the levels of  $\beta$ 2microglobulin in critical (28.06) and sever (20.13) of COVID-19 patients, more than the moderate (16.49), asymptomatic (10.64) cases of COVID-19 patients, these differences were highly significant ( $p \leq 0.001$ ) as shown in figure (2).

(61.12) (61.04) respectively, while the moderate and asymptomatic COVID-19 patients were at the fifth to third decade of ages (57.40) (38.56) respectively, in comparison with mean ages of control which recorded at the fourth decade of ages (43.97), these differences statistically were highly significant ( $p \leq 0.001$ ) as arranged in table (1).

**Table (1): Comparison the mean ages of studied group.**

| Study Groups        | Mean  | St.D | P value               |
|---------------------|-------|------|-----------------------|
| Critical (n=25)     | 64.12 | 2.49 | $\leq 0.001$<br>(H.S) |
| Sever (n=25)        | 61.04 | 2.45 |                       |
| Moderate (n=25)     | 57.40 | 2.23 |                       |
| Asymptomatic (n=25) | 38.56 | 1.97 |                       |
| Control (n=46)      | 43.97 | 2.84 |                       |
| Total               | 51.71 | 1.43 |                       |

The most cases of Covid-19 were males (66%) versus (34%) of females in all age groups of the patients and there is no Significant statically differences between male and female ( $p$ -value= 0.1) as shown in table (2).

| Group        | N | Gender |        | Total  | P Value      |
|--------------|---|--------|--------|--------|--------------|
|              |   | Male   | Female |        |              |
| Moderate     | N | 20     | 5      | 25     | $\leq 0.001$ |
|              | % | 80.0%  | 20.0%  | 100.0% |              |
| Asymptomatic | N | 19     | 6      | 25     |              |
|              | % | 76.0%  | 24.0%  | 100.0% |              |
| Control      | N | 33     | 13     | 46     |              |
|              | % | 71.7%  | 28.3%  | 100.0% |              |
| Total        | N | 99     | 47     | 146    |              |
|              | % | 67.8%  | 32.2%  | 100.0% |              |

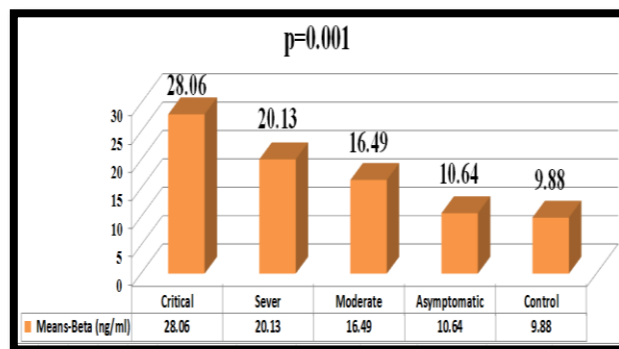


Figure (2): the levels  $\beta$ 2microglobulin among COVID-19 patients and control group.

### 4. Discussion

In this study investigation of the COVID-19 patients showed most cases are among men, this may be because men are more likely to engage in risky behaviors such as working in low-skilled jobs that require them to remain active, go outside of the home, and interact with others even during the containment phase. Men also typically leave their homes, sit with others, remove their masks when drinking or smoking, and engage in other social activities (9).

Male and female sex hormone levels and types may vary, which may affect a person's vulnerability to COVID-19 infection (10). This study found that patients the sixth decade. This finding may be explained by the fact that patients in this age range are more likely to have other predisposing diseases,

such as diabetes mellitus, hypertension, liver dysfunction, or kidney failure (11). People between the ages of 56 and 80 had the highest infection rate (43%). In contrast to the findings of a study conducted in Italy, this one found the opposite patients older than 70 were more likely to contract infections and die overall (12).

High blood YKL 40 levels have been linked to an increased risk of death from a variety of conditions, including cardiovascular disease, YKL 40 levels has been linked to an increased risk of asthma, bronchial hyper responsiveness according to earlier research, Macrophages, neutrophils, chondrocytes, endothelial cells, and vascular smooth muscle all secrete YKL-40 it is linked to a poor prognosis, IL-6, TNF-, and CRP were measures of systemic inflammation that were linked with YKL-40 levels,

## References

Iwamura APD, Tavares da Silva MR, Hümmelgen AL, Soeiro Pereira PV, Falcai A, Grumach AS, et al. Immunity and inflammatory biomarkers in COVID-19: a systematic review. *Reviews in Medical Virology*. 2021;31(4):e2199.

Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *The lancet*. 2020;395(10223):497-506.

Cao X. COVID-19: immunopathology and its implications for therapy. *Nature reviews immunology*. 2020;20(5):269-70.

Fara A, Mitrev Z, Rosalia RA, Assas BM. Cytokine storm and COVID-19: a chronicle of pro-inflammatory cytokines. *Open biology*. 2020;10(9):200160.

Kilpatrick LE, Dass C, Wang H, Criner GJ. Acute respiratory distress syndrome (ARDS). *Essentials of Clinical Pulmonology*: CRC Press; 2018. p. 640-9.

Henry BM, De Oliveira MHS, Benoit S, Plebani M, Lippi G. Hematologic, biochemical and immune biomarker abnormalities associated with severe illness and mortality in coronavirus disease 2019 (COVID-19): a meta-analysis. *Clinical Chemistry and Laboratory Medicine (CCLM)*. 2020;58(7):1021-8.

Scheller J, Chalaris A, Schmidt-Arras D, Rose-John S. The pro-and anti-inflammatory properties of the cytokine interleukin 6. *Biochimica et Biophysica Acta (BBA)-Molecular Cell Research*. 2011;1813(5):878-88.

Wells PM, Doores KJ, Couvreur S, Nunez RM, Seow J, Graham C, et al. Estimates of the rate of infection and asymptomatic COVID-19 disease in a population

which would be a risk factor for mortality (13).

When antigen-presenting cells die as a result, "damage-associated molecular patterns" (DAMPs) are released from the cells, which trigger an innate and adaptive immune response that could be harmful to the host if regulatory mechanisms malfunction the trimeric MHC class I complex engages the T-cell receptor, causing the chain to separate from Beta2-microglobulin before being internalized and destroyed (14).

Conclusion: The levels of YKL-40,  $\beta$ 2microglobulin were significantly higher in patients and the levels of markers are increased in sever and critical significantly than moderate and asymptomatic while the count of lymphocyte was significantly lower in critical and sever Covid-19 patients.

sample from SE England. *Journal of Infection*. 2020;81(6):931-6.

Wan Y, Shang J, Graham R, Baric RS, Li F. Receptor recognition by the novel coronavirus from Wuhan: an analysis based on decade-long structural studies of SARS coronavirus. *Journal of virology*. 2020;94(7):e00127-20.

Parohan M, Yaghoubi S, Seraji A, Javanbakht MH, Sarraf P, Djalali M. Risk factors for mortality in patients with Coronavirus disease 2019 (COVID-19) infection: a systematic review and meta-analysis of observational studies. *The Aging Male*. 2020;23(5):1416-24.

Zhang Y, Xiao M, Zhang S, Xia P, Cao W, Jiang W, et al. Coagulopathy and antiphospholipid antibodies in patients with Covid-19. *New England Journal of Medicine*. 2020;382(17):e38.

Zhang Y, Xiao M, Zhang S, Xia P, Cao W, Jiang W, et al. Coagulopathy and antiphospholipid antibodies in patients with Covid-19. *New England Journal of Medicine*. 2020;382(17):e38.

DelaRosa O, Pawelec G, Peralbo E, Wikby A, Mariani E, Mocchegiani E, et al. Immunological biomarkers of ageing in man: changes in both innate and adaptive immunity are associated with health and longevity. *Biogerontology*. 2006;7(5):471-81.

Hermansen M-L, Hummelshøj L, Lundsgaard D, Hornum L, Keller P, Fleckner J, et al. Increased serum  $\beta$ 2-microglobulin is associated with clinical and immunological markers of disease activity in systemic lupus erythematosus patients. *Lupus*. 2012;21(10):1098-104.