YKL-40 Serum Level in COVID-19 Patients Having Skin Manifestations

Azza G. Farag  
*Dermatology, Andrology and STDs department, Faculty of Medicine- Menoufia University, Egypt*

Eman A. Badr  
*Medical Biochemistry and Molecular Biology department, Faculty of Medicine- Menoufia University, Egypt*

Eman A. Tayel  
*Dermatology, Andrology and STDs department, Al-Qabbary General Hospital- Alexandria, Egypt, emantayel1991@gmail.com*

Eman N. Elshafey  
*Dermatology, Andrology and STDs department, Faculty of Medicine- Menoufia University, Egypt*

Follow this and additional works at: https://www.menoufia-med-j.com/journal

Part of the Medicine and Health Sciences Commons

**Recommended Citation**

DOI: https://doi.org/10.59204/2314-6788.1009

This Original Study is brought to you for free and open access by Menoufia Medical Journal. It has been accepted for inclusion in Menoufia Medical Journal by an authorized editor of Menoufia Medical Journal. For more information, please contact menoufiamedicaljournal@yahoo.com.
ORIGINAL STUDY

YKL-40 Serum Level in Coronavirus Disease 2019 Patients Having Skin Manifestations

Azza G. Faraga, Eman A. Badr, Eman A. Tayel, Eman N. Elshafey

Departments of Dermatology, Andrology and STDs, Faculty of Medicine, Menoufia University, Menoufia, Egypt

Department of Medical Biochemistry and Molecular Biology, Faculty of Medicine, Menoufia University, Menoufia, Egypt

Departments of Dermatology, Andrology and STDs, Al-Qabbary General Hospital, Alexandria, Egypt

Abstract

Objectives: To measure the level of YKL-40 in coronavirus disease 2019 (COVID-19) patients with and without skin lesions in El-Bagour Hospital.

Background: The outbreak of COVID-19, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, has emerged in China in December 2019 and rapidly spread to more than 196 countries worldwide.

Patients and methods: A case–control study was conducted on a total of 180 patients including 60 COVID-19 patients with skin manifestations and 60 COVID-19 patients without skin manifestations besides 60 age-matched and sex-matched healthy individuals as a control group. The patients were those attending El-Bagour Hospital COVID-19 isolation from March 2020 to March 2021. Diagnosis of COVID-19 was done clinically and by laboratory investigations, confirmed by PCR.

Results: The mean levels of YKL-40 were significantly higher in COVID-19 patients than in controls (66.47 ± 66.52 vs. 17.25 ± 3.16 ng/ml). The mean levels of YKL-40 were significantly higher in COVID-19 patients with cutaneous manifestations than those without cutaneous manifestations (94.85 ± 84.50 vs. 38.09 ± 12.12 ng/ml).

Conclusion: The mean level of YKL-40 was significantly higher in COVID-19 patients, especially severe cases than the controls and in COVID-19 patients with cutaneous manifestations than those without cutaneous manifestations.

Keywords: Coronavirus disease 2019, Skin lesions, YKL-40

1. Introduction

Coronavirus is a big family that can damage the respiratory system. Previous epidemic or the pandemic of coronavirus were severe acute respiratory syndrome (SARS) in 2002 and Middle East respiratory syndrome (MERS) in 2012. Since December 8, 2019, a novel kind of coronavirus pneumonia was reported. Coronavirus disease 2019 (COVID-19) is a single-stranded RNA virus from the coronaviridae family, which originates in bats, and can infect humans with a 2–14 days incubation period [1].

Common symptoms include fever, cough, fatigue, dyspnea, and hypogeusia/hyposmia. Among extrapulmonary signs associated with COVID-19, dermatological manifestations have been increasingly reported in the last few months [2]; skin eruptions occurring concomitant with SARS-CoV-2 infection have been described, with six main clinical patterns: urticarial rash, confluent maculopapular rash, papulovesicular exanthema, chilblain-like acral pattern, livedo reticularis pattern, and purpuric vasculitis pattern. Maculopapular eruption is the most common pattern described ranging from 23 to 47% of cases [3].

An abnormally strong inflammatory response known as a ‘cytokine storm’ may play an important role in the pathophysiology of COVID-19 [4].

Measuring serum levels of proinflammatory cytokines may have several potential applications in the management of COVID-19, including risk assessment, monitoring of disease progression,
determination of prognosis, selection of therapy, and prediction of response to treatment [5].

One of those markers is YKL-40, also known as chitinase-3-like protein-1 (CHI3L1). The name YKL-40 is derived from the three N-terminal amino acids present on the secreted form and its molecular mass. YKL-40 is expressed and secreted by various cell types including macrophages, chondrocytes, fibroblast-like synovial cells, vascular smooth muscle cells, and hepatic stellate cells. It has a pro-mitogenic action on pulmonary fibroblasts, increases the activity of macrophages, and is associated with inflammatory disorders. In interstitial lung disease, YKL-40 has been described to be associated with the severity of lung disease and risk of death [6]. This work aimed to measure the level of YKL-40 in COVID patients with and without skin lesions.

In COVID patients with central nervous system damage or confusion or agitation, there are increased levels of YKL-40 in the patient's plasma and brain [7]. YKL-40 could be of interest as a specific biomarker of severe COVID-19 infection [6].

The aim of the study was to measure the level of YKL-40 in COVID patients with and without skin lesions.

2. Patients and methods

This case-control study was conducted on a total number of 180 patients, including 60 COVID-19 patients with skin manifestations and 60 COVID-19 patients without skin manifestations besides 60 age-matched and sex-matched healthy individuals as a control group. The patients were those attending El-Bagour Hospital COVID-19 isolation during the COVID-19 pandemic from March 2020 to March 2021. The data of these patients were gathered from the records. Diagnosis of COVID-19 was done clinically and by laboratory investigations, confirmed by PCR. Before beginning this study, the Ethics Committee of Menoufia University's Faculty of Medicine approved it. In addition, an official permission letter was obtained and sent to the Ministry of Health's undersecretary in Menoufia as well as the administrators at El-Bagour Hospital.

Full history was taken from the patients including personal history (age, sex, residence, occupation, and special habits of medical importance) and present history including questions regarding any skin lesion and its onset (before or after 4 days of COVID-19), course (progressive, regressive, or stationary), duration, site, the extent of any skin lesion as well as any associated symptoms such as pruritus, pain, and burning. History of contact with any positive COVID-19 patient and history of previous treatment or skin diseases, for example psoriasis, were also taken. Assessment of vital signs and general examinations including blood pressure, pulsation, respiratory rate, heart rate, and temperature was done.

A complete dermatological examination as regards to skin, hair, nails, and the mucous membrane was performed. Skin lesions were evaluated regarding the site, size, shape, presence of scales, and presence of scratch marks. Examination of the hair was done to detect any hair fall, presence of scales in the scalp, or erythema in the scalp. A nail examination was performed to assess if there was loss of luster, nail pitting, pigmentation, or striations. Laboratory findings as the PCR nasopharyngeal swab was assessed to confirm the diagnosis of COVID-19. Complete blood count (hemoglobin, white blood cell count, red blood cell count, and platelets), C-reactive protein (CRP), lactate dehydrogenase (LDH), and D-dimer were performed.

Sample collections: every patient was instructed overnight fasting; 3 ml of venous blood was collected aseptically and put in a plain tube, and was allowed to stand at 37 °C for 45 min to clot. The serum was obtained and separated into aliquots and kept in −80 °C.

Quantitative detection of human YKL-40 was done by the ELISA technique using Human Chitinase-3-like protein-1 (YKL-40) (catalog No: BYEK2803) (Chongqing Biospes Co. Ltd, Room 27-2, Building 7, No. 15, Paradise Walk Chongqing, Jiangebei China) [8,9].

A suggested COVID-19 severity score named ABCD score was used. This score was based on many parameters including the age of the patient (<50 years and >50 years), blood tests (leukopenia, lymphocytopenia, CRP level, LDH level, and D-dimer), chest radiograph and computed tomography scan, comorbidities, and dyspnea. The risk score was developed using these variables with a minimum score of 0 and a maximum score of 14. The score was subcategorized into three groups: mild (0–4), moderate (4–8), and severe (>8). Higher scores indicate increased severity and demands for intensive care. Chest radiograph, computed tomography, and Reporting and Data System (CORES) were used for image evaluation and assessment of pulmonary involvement of COVID-19 [10,11].

This work was approved by the Medical Ethics Committee of the Faculty of Medicine at Menoufia University. Informed written consent was obtained from all participants included in this study.
2.1. Statistical analysis

Results were collected, tabulated, and statistically analyzed using the IBM personal computer and Statistical Package for the Social Sciences (SPSS) software package version 20.0. (2013; IBM Corp., Armonk, New York, USA).

Descriptive statistics: for example, percentage, median and range, mean, and SD. Analytic statistics: for example, \( \chi^2 \) test; for categorical variables, to compare between different groups. Mann–Whitney test for abnormally distributed quantitative variables, to compare between two studied groups. Analysis of variance test: for normally distributed quantitative variables, to compare between more than two groups, and post-hoc (Tukey) for pairwise comparisons. Kruskal–Wallis test for abnormally distributed quantitative variables, to compare between more than two studied groups, and post-hoc (Dunn’s multiple comparisons test) for pairwise comparisons. A \( P \) value of less than or equal to 0.05 was considered statistically significant.

3. Results

Personal and clinical data of the studied groups: baseline characteristic data and laboratory investigations of the studied groups (Tables 1 and 2).

In this study, we reported COVID-19 skin lesions as follows: The most common skin lesions were pityriasis rosea (66.7%) followed by livedo or necrosis (53.3%) maculopapules, erythema, and pruritus in about half of the patients (51.7%) (Fig. 1).

In our study, the mean levels of YKL-40 was significantly higher in all the COVID patients than in the controls. The mean levels of YKL-40 were significantly higher in group I than in group II and the controls (Table 3).

From this study, YKL-40 serum level was an excellent marker for the prediction of COVID-19 patients with skin lesions from COVID-19 patients without skin lesions. There was no significant relationship between YKL-40 serum levels and any type of skin lesions in COVID-19 patients with skin manifestations.

The mean levels of YKL-40 were significantly higher in severe than moderate cases in each of group I and group II skin lesions (Table 4).

4. Discussion

Although COVID-19 is best known for causing fever and respiratory symptoms, it has been reported to be associated also with different extrapulmonary manifestations, including dermatological signs [12].

There are six clinical patterns of COVID-19-associated cutaneous manifestations:

(i) urticarial rash, (ii) confluent erythematous/maculopapular/morbilliform rash, (iii) papulovesicular exanthem, (iv) chilblain-like acral pattern, (v) livedo reticularis/racemosa-like pattern, and (vi) purpuric vasculitic pattern [12,13].

According to our study, the most common skin lesions were pityriasis rosea (66.7%), followed by livedo or necrosis (53.3%) maculopapules, erythema, and pruritus in about half of the patients (51.7%). Others were varicella-like exanthema (51.7%), urticarial lesions (48.3%), vesicular lesions (36.7%), petechiae (33.3%) and pseudo-chilblain (28.3%).

Activation of mast cells and basophils, by direct and/or indirect viral effect, is a possible event, and it is important to be alert to skin manifestations such as the onset of urticaria, atopic dermatitis, or the exacerbation of these conditions, rashes, neutrophilic

<table>
<thead>
<tr>
<th>Demographic data</th>
<th>Group I (N = 60) [n (%)]</th>
<th>Group II (N = 60) [n (%)]</th>
<th>Group III (N = 60) [n (%)]</th>
<th>Test of significance</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>34 (56.7)</td>
<td>33 (55.0)</td>
<td>35 (58.3)</td>
<td>( \chi^2 )</td>
<td>0.934</td>
</tr>
<tr>
<td>Female</td>
<td>26 (43.3)</td>
<td>27 (45.0)</td>
<td>25 (41.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>35.0–82.0</td>
<td>25.0–80.0</td>
<td>25.0–80.0</td>
<td></td>
<td>0.115</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>59.57 ± 13.24</td>
<td>54.58 ± 16.02</td>
<td>58.98 ± 13.37</td>
<td>( F = 2.187 )</td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>62.0 (46.5–69.5)</td>
<td>60.50 (38–65)</td>
<td>60 (51.5–67.5)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\( \chi^2 \), \( \chi^2 \) test.
\( F \): for analysis of variance test.
IQR, interquartile range.
\( P \): \( P \) value for comparing the studied groups.
Group I: patients with skin lesions.
Group II: patients without skin lesions.
Group III: control.
Table 2. Comparison between the three studied groups according to vital signs and laboratory investigations.

<table>
<thead>
<tr>
<th></th>
<th>Group I ($N=60$)</th>
<th>Group II ($N=60$)</th>
<th>Group III ($N=60$)</th>
<th>$F$</th>
<th>$P$</th>
<th>Significance between groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>I vs. II</td>
</tr>
<tr>
<td><strong>Systolic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>120.32 ± 14.73</td>
<td>116.45 ± 6.55</td>
<td>117.83 ± 5.55</td>
<td>2.377</td>
<td>0.096</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td><strong>Diastolic</strong></td>
<td>75.50 ± 9.44</td>
<td>75.32 ± 7.21</td>
<td>76.17 ± 5.85</td>
<td>0.205</td>
<td>0.814</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td><strong>Respiratory rate</strong></td>
<td>26.70 ± 6.68</td>
<td>27.47 ± 7.06</td>
<td>13.93 ± 1.34</td>
<td>14.709*</td>
<td>&lt;0.001*</td>
<td>0.621</td>
</tr>
<tr>
<td><strong>Temperature</strong></td>
<td>38.52 ± 0.60</td>
<td>38.62 ± 0.55</td>
<td>36.95 ± 0.31</td>
<td>204.543*</td>
<td>&lt;0.001*</td>
<td>0.527</td>
</tr>
<tr>
<td><strong>Heart rate</strong></td>
<td>99.05 ± 16.08</td>
<td>96.82 ± 15.27</td>
<td>86.85 ± 4.95</td>
<td>14.709*</td>
<td>&lt;0.001*</td>
<td>0.621</td>
</tr>
<tr>
<td><strong>Os</strong></td>
<td>70.95 ± 7.76</td>
<td>78.80 ± 10.62</td>
<td>97.77 ± 1.63</td>
<td>194.792*</td>
<td>&lt;0.001*</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td><strong>Hemoglobin (g/dl)</strong></td>
<td>11.88 ± 1.55</td>
<td>12.34 ± 1.51</td>
<td>12.32 ± 1.41</td>
<td>1.783</td>
<td>0.171</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>WBCs ($\times 10^9$/μl)</td>
<td>2.73 ± 0.28</td>
<td>2.73 ± 0.36</td>
<td>7.11 ± 1.47</td>
<td>488.873*</td>
<td>&lt;0.001*</td>
<td>1.000</td>
</tr>
<tr>
<td>Platelets ($\times 10^9$/μl)</td>
<td>129.15 ± 5.26</td>
<td>128.15 ± 9.74</td>
<td>280.18 ± 53.22</td>
<td>466.322*</td>
<td>&lt;0.001*</td>
<td>0.983</td>
</tr>
<tr>
<td>TSH (μIU/ml)</td>
<td>1.50 (1.50–1.6)</td>
<td>1.60 (1.5–1.7)</td>
<td>1.60 (1.5–1.7)</td>
<td>4.171</td>
<td>0.124</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>D-dimer (mg/ml)</td>
<td>1.35 (1.2–1.5)</td>
<td>1.40 (1.3–1.5)</td>
<td>0.18 (0.1–0.2)</td>
<td>122.682*</td>
<td>&lt;0.001*</td>
<td>0.173</td>
</tr>
<tr>
<td>CRP (mg/l)</td>
<td>96.0 (96–192)</td>
<td>72.0 (24–96)</td>
<td>1.90 (1.5–2.7)</td>
<td>145.989*</td>
<td>&lt;0.001*</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>

CRP: C-reactive protein; HB: hemoglobin; IQR: interquartile range; OS: oxygen saturation; TSH: thyroid-stimulating hormone; WBCs, white blood cells.

$F$: F for analysis of variance test, pairwise comparison between each of the two groups was done using post-hoc test (Tukey).

$H$: $H$ for Kruskal–Wallis test, pairwise comparison between each of the two groups was done using post-hoc test (Dunn’s for multiple comparisons test).

$P$: $P$ value for comparing between the studied groups.

Group I: coronavirus disease 2019 patients with dermatological manifestations.

Group II: coronavirus disease 2019 patients without dermatological manifestations.

Group III: control.

Fig. 1. Percent distribution of skin lesions in COVID-19 patients with skin manifestations. COVID-19, coronavirus disease 2019.
dermatoses and skin manifestations of hypercoagulable states, such as acral ischemia. Considering the cutaneous manifestations described, some aspects of SARS-CoV-2 infection may be caused by cytopathic effects on the endothelium dermal vessels or even stimulated by cytokines in arterioles and capillaries. The direct cytopathic effect of SARS-CoV-2 can occur in the described vesicular or papular—vesicular lesions, which are very similar to those caused by the Herpesviridae family.

Angiotensin-converting enzyme 2 (ACE2) is known as a ligand for the spike protein of SARS-CoV-2 for entering human cells [14]. There is a high expression of ACE2 on keratinocytes [15]. Thus, SARS-CoV-2 can directly infect keratinocytes resulting in necrosis. As YKL-40 is a potent stimulator of the SARS-CoV-2 receptor ACE2 [16] it has an important role in the pathogenesis of skin manifestations in COVID-19 patients.

Rashes may be para-viral due to cytokines or due to drug exposure during treatment of the disease [17].

The pathogenesis has been linked to a disproportionate response of the immune system. An uncontrolled systemic inflammatory response, known as cytokine release syndrome, was observed in severe COVID-19 patients. It results from the release by immune and nonimmune effector cells of substantial amounts of proinflammatory cytokines and seems to contribute to SARS-CoV-2 pulmonary inflammation and extensive lung damage. In addition, hypercoagulation and thrombosis resulting from the important release of proinflammatory cytokines contribute to the lethality of patients severely infected with SARS-CoV-2 [18,19]. One of those markers is YKL-40, also known as CHI3L1 [20].

CHI3L1 and IL-6 exhibited a significant positive correlation with CRP, ESR, D-dimer, ferritin, LDH, and lymphocytopenia levels. A strong correlation among laboratory tests was observed between serum IL-6 and CHI3L1. This also supports the idea that CHI3L1 and IL-6 are potentially useful inflammatory markers in diagnosing COVID-19 [21].

To the best of our knowledge, this study may be the first one that investigates YKL-40 and its correlation with skin manifestations of COVID-19 patients in a sample of Egyptian patients. So, this case—control study was conducted on 180 participants, including 60 COVID-19 patients with skin manifestations and 60 COVID-19 patients without skin manifestations besides 60 age-matched and sex-matched healthy individuals as a control group. COVID-19 positive cases were selected from those attending El-Bagour isolation hospital during the period from March 2020 to March 2021.

In our study, we examined the circulating YKL-40 serum levels in COVID-19 cases and their relation to cutaneous manifestations. We reported a significant increase in serum YKL-40 level mean values in COVID-19 patients than the control group. Also, the mean levels of YKL-40 were significantly higher in severe COVID-19 patients than in moderate cases.

Table 3. Comparison between the three studied groups according to YKL-40.

<table>
<thead>
<tr>
<th>YKL-40</th>
<th>Group I (N = 60)</th>
<th>Group II (N = 60)</th>
<th>Group III (N = 60)</th>
<th>H</th>
<th>P</th>
<th>Significance between groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Minimum–maximum</td>
<td>12.11–350.0</td>
<td>9.29–67.10</td>
<td>12.0–23.35</td>
<td>115.520*</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>94.85 ± 84.50</td>
<td>38.09 ± 12.12</td>
<td>17.25 ± 3.16</td>
<td>350.0</td>
<td>0.290</td>
</tr>
<tr>
<td></td>
<td>Median (IQR)</td>
<td>58.70 (41.8–138)</td>
<td>38 (30.1–44.93)</td>
<td>17.41 (14.5–20)</td>
<td>0.054</td>
<td>0.021</td>
</tr>
</tbody>
</table>

Table 4. YKL-40 serum levels regarding severity of the disease in the studied coronavirus disease 2019 patients.

<table>
<thead>
<tr>
<th>YKL-40 (ng/ml)</th>
<th>COVID-19 severity</th>
<th>U</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Moderate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group I (N = 60)</td>
<td>(n = 29)</td>
<td>378.0</td>
<td>0.290</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>73.62 ± 50.31</td>
<td>114.72 ± 104.10</td>
<td>0.054</td>
</tr>
<tr>
<td>Median (minimum–maximum)</td>
<td>54.87 (12.11–204)</td>
<td>60.14 (14.1–350)</td>
<td>0.021</td>
</tr>
<tr>
<td>Group II (N = 60)</td>
<td>N = 32</td>
<td>1433.0</td>
<td>0.054</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>34.44 ± 11.67</td>
<td>42.26 ± 11.45</td>
<td>0.021</td>
</tr>
<tr>
<td>Median (minimum–maximum)</td>
<td>35.84 (9.29–54.0)</td>
<td>40.0 (27.0–67.10)</td>
<td>0.021</td>
</tr>
<tr>
<td>Total patients (N = 120)</td>
<td>N = 61</td>
<td>1756.50</td>
<td>0.054</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>56.27 ± 39.27</td>
<td>77.01 ± 85.22</td>
<td>0.054</td>
</tr>
<tr>
<td>Median (minimum–maximum)</td>
<td>44.64 (9.29–203.9)</td>
<td>42.69 (12.6–350)</td>
<td>0.054</td>
</tr>
</tbody>
</table>

As for clinical data of our patients, there was no significant relationship between YKL-40 serum levels and any type of skin lesions in COVID-19 patients with skin manifestations. According to the study, YKL-40 serum level was an excellent marker for the prediction of COVID-19 patients from the control group. YKL-40 serum level was a good marker for the prediction of COVID-19 patients with skin lesions from COVID-19 patients without skin lesions. Serum levels of YKL-40 were an excellent marker for the prediction of COVID-19 patients with skin lesions from the control group.

In line with our study, Schoneveld et al. [20] concluded that COVID-19 patients had higher levels of YKL-40 compared with a control population (HS, COPD, and ILD), and De Lorenzo et al. [22] concluded that within the COVID-19 population YKL-40 was an indicator of the seriousness of infection as it is linked to complications such as admission to the ICU, ARF, or MOF. This marker could also be a predictive marker to anticipate management at the ICU and is useful for the prognosis of the onset of an ILD later.

4.1. Conclusion

YKL-40 serum level was an excellent marker to predict COVID-19 patients from the control group and to predict COVID-19 patients with skin lesions from COVID-19 patients without skin lesions.

Conflict of interest

There are no conflicts of interest.

References