ORIGINAL ARTICLE

Assessment of Inflammatory Biomarkers as Predictor of Mortality in COVID-19 Patients

MUHAMMAD MANSOOR HAFEEZ[1], MUHAMMAD TAHIR KHAN[1], TANIA AHMED SHAKOORI[2], WAQAS MAHMOOD[3], MUHAMMAD SOHAIL KHALID[4], MUHAMMAD ASIM RANA[5], SITARA RAZA[6]

[1]Institute of Molecular Biology and Biotechnology (IMBB), The University of Lahore, Pakistan
[2]Professor, Department of physiology, University of Health Sciences, Lahore, Pakistan
[3]Consultant Intensivist, King Saud Medical City, Riyadh, Kingdom of Saudi Arabia
[4]Assistant Professor of Gastroenterology, Continental Medical College, Lahore, Pakistan
[5]Assistant Professor Critical Care Medicine, Amna Inayat Medical College/Visiting Consultant Bahria International Hospital, Lahore, Pakistan
[6]Physician Assistant, Critical Care Medicine, Bahria International Hospital, Lahore
Correspondence to: Muhammad Asim Rana, Email: drasimrana@yahoo.com, Cell: 0343-5807006

ABSTRACT

Background: In individuals with coronavirus, a cytokine storm is an important cause of illness and demise. The purpose of the study was to assess whether pro-inflammatory cytokines had an impact on progression and risk of mortality in patients with COVID-19.

Study Design: Retrospective study

Place and Duration of Study: Intensive Care Unit (ICU) and Medical Wards, Bahria Town International Hospital from 21st August 2020 to 17th September 2021.

Methodology: One hundred and thirty-six patients of confirmed cases of COVID-19 disease were enrolled. Their demographic, blood and biochemical parameters were collected within 48 hours after admission from the medical record of patients. Patients were divided into two groups according to the final outcome, the survivors and non survivors. The data were investigated to assess the prognostic importance of the blood marker and inflammatory variables for the prognostic importance.

Results: The mean age and body mass index (BMI) were statistically higher in the non-survivors than in the survivors (p=0.017 and 0.03 respectively). For those with asthma and chronic obstructive pulmonary disease, the number was statistically higher in non-survivors (p = 0.002 and 0.04, respectively). The inflammatory markers concentrations of CPR, D. Dimer, serum ferritin, procalcitonin, and interleukin-6 were significantly higher within 48 hours of admission for non-survivors (p = 0.003, 0.007, <0.001, 0.015, and <0.001 respectively). Except ferritin levels, multi-variate logistic regression analysis exhibited that the CRP, D. Dimer, Procalcitonin and IL-6 were associated statistically significant higher risk of mortality (OR 1.235, p=0.007, 95% CI 5.621-42.652, OR 1.906, p=0.003, 95% CI 1.481-1.982, OR 3.967, p=<0.001, 95% CI 4.256-23.981, and OR 7.589, p=0.009, 95% CI 4.561-113.852 respectively).

Conclusion: The inflammatory markers have the prognostic importance in patients suffering from covid-19 infection as we found higher levels of these markers were related with the poor prognosis.

Keywords: Inflammatory markers, Corona virus, Prognostic markers, Interleukin -6, Mortality

INTRODUCTION

Coronavirus disease 2019 (COVID-19) has impacted millions of inhabitants of this world and has caused a large number of causalities globally. While the majority of cases are asymptomatic or moderate, a small percentage of individuals develop severe illness, which is frequently linked to a hyperinflammatory condition known as a cytokine storm.[1] Due to poor management of inflammatory cytokines generated in the process of immunological dysregulation, cytokine release syndrome causes widespread tissue damage and end-organ malfunction.[2] This triggers a cytokine storm, resulting in an increase in intensity of pro-inflammatory cytokines. It is believed that the efficient reduction of pro-inflammatory cytokines is very much necessary to regulate the hyperinflammatory state in severe conditions of COVID-19 and may be linked to better objective results.[3]

Cytokine storm is an abrupt hyperinflammatory response that occurs in these people, resulting in a malfunction of the organic system and a catastrophic disease. Sweating is a common symptom for patients with COVID-19, just like fever. However, some COVID-19 patients exhibit abundant continuous perspiration, even when they are afebrile. Clinically, cytokine storms cause rapid clinical degradation with coagulopathy, hypotension and various terminal organ failures.[4] A number of clinical severity measures have been proposed to detect individuals who develop a cytokine storm early, and then monitor and predict them.[5] Anti-inflammatory drugs designed to lower the levels of these cytokines were linked to better clinical outcomes. It is though that the early increase in the inflammatory markers associated with the bad outcome. So, the current research was design to evaluate the prognostic importance of inflammatory markers in COVID-19 disease. For this we select the C-reactive protein, Procalcitonin, serum ferritin levels, D. Dimer and the interleukin-6 (IL-6).

MATERIALS AND METHODS

This was a retrospective analysis included 136 confirmed cases of COVID-19 infection on RT-PCR and conducted from 21st August 2020, to 17th September 2021 at Bahria town International Hospital Lahore after the approval of institutional review board and ethical committee (IRBEC) of the hospital. The participants were divided into two groups. First group contained the survivors (discharged from the hospital) and second group consisted of non-survivors. The patients with age group 18 to 70 years, both male and female were recruited in the study.

The medical records were analyzed, and data was collected for further analysis. As this was a retrospective analysis, the need for consent was waived off. The data, included demographic variables like Age, gender, body mass index (BMI), laboratory parameters such as haemoglobin (Hb), total leukocyte count (TLC), serum creatinine, bilirubin, absolute lymphocyte and neutrophil count, serum sodium (Na^{+2}), Potassium (K^-) and chloride (Cl^-) levels were noted within the 48 hours of the admission. Similarly, the inflammatory markers of prognostic importance C-reactive protein, D, Dimer, serum ferritin, procalcitonin and IL-6 levels were recorded for the further analyses. Individual values were compared between the groups by using Fisher's exact test and Chi-square test for categorical variables. The independent sample t-test for continuous variables (continuous variables) having normal distribution, and the Wilcoxon-rank test for non-normal distributed parameters, as applicable. The odds of death related with the markers were investigated using a multi-regression analysis. SPSS software version 25 was used to analyze the data, and a p value of less than 0.05 was considered statistically significant.

RESULTS

The percentage of males in non-survivors' group was 59.1% and 55.4% in survivors' group. The mean age measured for non survivors (52.54 years) was significantly higher (p= 0.017) than the survivors (44.41 years). Similarly, the body mass index (BMI) was statistically greater in Non-Survivors (P=0.04). the most common comorbid condition in both groups was hypertension followed by the diabetes. The asthmatic and chronic obstructive pulmonary disease (COPD) patients were greater in non survivors as compared to survivors (p value 0.002 and 0.04 respectively). The laboratory parameters are also shown in the Table 1. The independent t test showed that the total leukocytes count (TLC) and serum potassium levels were statistically significant higher in non survivors. The other variables were not differed between the groups.

The comparison of inflammatory markers in both groups showed that the CPR, D. Dimer, serum ferritin, procalcitonin and interleukin-6 levels were significantly greater within 48 hours of admission in non survivors (p= 0.003, 0.007, < 0.001, 0.015 and < 0.001 respectively). This comparison revealed that the elevated levels of inflammatory markers are predictor of bad outcome (Table 2).

Multi-variate logistic regression analysis showed that CRP, D. Dimer, procalcitonin and IL-6 were associated statistically significant higher risk of mortality. (OR 1.235, p=0.007, 95% CI 5.621-42.652, OR 1.906, p=0.003, 95% CI 1.481-1.982, OR 3.967, p=<0.001, 95% CI 4.256-23.981, and OR 7.589, p=0.009, 95% CI 4.561-113.852 respectively). Serum ferritin in our study did not show any statistically significant relationship with the mortality in COVID-19 patients (Table-3).

DISCUSSION

In our study, advanced age and a high BMI score were linked to a poor result. The same findings were found in research by Hendren et al.[6] Obese persons were much more prone to be hospitalized with COVID-19, and they have the more risk to die in the hospital or require mechanical breathing, especially if they were young, according to their findings. Obese individuals are also more prone to suffer from thromboembolism phenomenon especially the venous, which necessitates dialysis. The need of a strong healthcare message and thorough commitment to COVID-19 preventative measures in all obese persons, regardless of age, is highlighted by these findings. Several studies have been conducted to examine if there is a connection between inflammatory indicators and overall COVID-19 patient outcomes. In coronavirus disease, markers responsible for inflammatory process have been demonstrated to be predictive of mortality.[7] A primary cause of death in patients with severe COVID-19 illness has been related to a cytokine storm caused by the production of pro-inflammatory factors, similar finding were reported in other infection.[8] Within 10 days of hospitalization, the level of inflammatory variables in effected patients having moderate and

Table 1: Descriptive statistics of co morbid and blood parameters in both groups

Variable	Non-survivors (n=44)	Survivors (n=92)	P-value
Age (years)	52.54±4.21	44.41±13.65	0.017
Gender			
Male	26 (59.1%)	51 (55.4%)	0.32
Female	18 (49.9%)	41 (44.6%)	0.09
BMI (Kg/m^2)	29.5±6.4	27.8±11.8	0.03
Co-morbid conditions			
Diabetes mellitus	18 (40.91%)	30 (32.60%)	0.71
Hypertension	19 (43.18%)	34 (36.95%)	0.06
Asthmatic	14 (31.81%)	11 (11.965)	0.002
COPD	16 (36.36%)	19 (20.65%)	0.04
Coronary artery disease	4 (9.10%)	10 (10.87%)	0.81
Chronic kidney disease	6 (13.63%)	9 (9.78%)	0.08
Laboratory tests			
Hb (g/dl)	10.9±1.9	11.5±2.1	0.23
TLC (x10^9)	12.6±3.9	10.2±1.6	0.02
Abs. Lymphocytes (x10^9)	1.05±0.6	1.8±0.4	0.52
Abs Neutrophils (x10^9)	7.7±2.5	6.3±2.3	0.74
Creatinine (mg/dl)	0.9±0.5	0.8±0.3	0.55
Bilirubin (mg/dl)	1.3±0.7	1.1±0.6	0.69
Na^{+2} (mEq/L)	132.3±6.1.9	134.1±3.5	0.09
K$^+$ (mEq/L)	4.7±0.6	4.3±0.4	0.04
Cl$^-$(mEq/L)	94.4±1.2	101.2±1.9	0.057

Table 2: Comparison of inflammatory parameters of prognostic importance in both groups

Variable	Non-survivors (n=44)	Survivors (n=92)	P-value
CRP (mg/dl)	132.65 (3.6 – 468.5)	33.64 (1.6 – 394.56)	0.003
D. Dimer µg/ml	1.7 (0.8-4.2)	0.4 (0.2-1.0)	0.007
S. Ferritin (ng/ml)	898 (72.5 – 6584)	497 (21.56 -4567)	< 0.001
Procalcitonin (ng/ml)	0.58 (0.02- 38.02)	0.11(0.02- 18.6)	0.015
IL-6 (pg/ml)	65.21 (10.2-883.74)	34.34 (12.5- 1008)	< 0.001

Table 3: Multi-variate logistic regression analysis model among both groups

Variables	Odds Ratio	95% CI	P-Value
CRP (mg/dl)	1.235	5.621-42.652	0.007
D. Dimer µg/ml	1.906	1.481-1.982	0.003
S. Ferritin (ng/ml)	1.002	1.652-8.965	0.097
Procalcitonin (ng/ml)	3.967	4.256-23.981	<0.001
IL-6 (pg/ml)	7.589	4.561-113.852	0.009

severe coronavirus illness decreased significantly, however no significant drop was noted in the group of patients who did not survive later in the study cohort.[9] Higher CRP levels within the 48 hours of admission were shown to be more strongly linked with a negative end result in our study. CRP levels at the time of admission, as well as prior to discharge or death, have previously been reported to be predictors of poor prognosis in COVID-19 patients.[10] During the early stages of the illness, higher CRP levels were linked to higher CT severity scores and more extensive lung involvement.[11] In comparable study cohorts, higher CRP concentrations were strongly linked with greater mortality in COVID-19 patients.[12]

In this study, we discovered that non-survivors had much higher blood ferritin levels. According to one research, high serum ferritin levels before to the terminal event were more significantly related with death.[13] Another study reported that at the time of admission the elevated serum levels of ferritin are significantly

associated with the severity of disease.[14] It is noted in other research that the increased levels of serum ferritin are although linked with severity but not always related to the bad prognosis.[15] Research disputed our findings, which found that serum ferritin levels were not linked to worse outcomes. As a result, more research is encouraged before making a final decision. Furthermore, greater D. Dimer levels were connected to a worse overall patient prognosis. This has also been suggested by other studies published in the literature.[16] D. dimer has been linked to an increased risk of death in individuals with severe COVID-19.[17] This study showed that increased procalcitonin levels were linked to a poorer outcome in our research. These findings are in line with those of previous research published in the literature.[18] According to subgroup studies done in a meta-analysis, elevated procalcitonin levels were related with higher mortality.[19] We reported that group of non-survivors had much greater levels of IL-6 than survivors in our research. These findings support previous research demonstrating coronavirus disease is a hyperinflammatory condition that is associated with an increase in pro-inflammatory cytokines. These studies concluded that this that higher the inflammatory markers the greater will be the chances of poor prognosis.[20,21]

In our study we also checked some other blood parameters such as haemoglobin and TLC levels in both groups but there was no different noted. The previous study also reports the similar results. The Absolute lymphocyte counts were also not significantly associated with the disease progression. In previous studies lymphocytes counts were decreased in severe cases and found to be associated with mortality. Serum electrolyte studied in our study only lower potassium levels were seen statistically significant with mortality. In literature we found mixed result related to the electrolytes disturbance in COVID-19 patients.[22] The Cox regression model was used to examine all the variables that had a significant p-value on analysis. Only serum ferritin levels, however, was found to be related with insignificant overall prognosis. This can be explained by the fact that the sample size for multi-variate analysis is so small. Our research has some limitations as well. The sample size was small, and the study design was not experimental. Moreover, we did not take into account the anti-inflammatory drugs influence on the variables because it was a retrospective study.

CONCLUSION

The inflammatory biomarkers such as serum ferritin, CRP, IL-6, procalcitonin, and D. Dimer have proven significant predictor of prognosis in coronavirus infection. Inflammatory markers with higher levels have been correlated with a higher risk of mortality. A surge in these inflammatory markers is an early predictor of cytokine storm in these patients, which is an indication of a poor prognosis. This will allow physicians to quickly identify those at high risk. As a consequence, early monitoring of these inflammatory indicators can help predict patient outcomes. Patients' therapy may be adjusted to be more timely, appropriate, efficient, and effective, resulting in improved outcomes.

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