e-ISSN: 0975-1556, p-ISSN:2820-2643

Available online on www.ijpcr.com

International Journal of Pharmaceutical and Clinical Research 2023; 15(11); 644-650

Original Research Article

Serum Inflammatory Markers in COVID-19 Disease: A Retrospective Analysis

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Received: 16-08-2023 / Revised: 28-09-2023 / Accepted: 05-10-2023
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Conflict of interest: Nil

Abstract:

Background: To combat the spread of coronavirus illness 2019, a rapid clinical diagnosis is required to give symptomatic medication, immediate access to the intensive care unit, and patient isolation (COVID-19). The elevated inflammatory markers might be independent biomarkers for identifying severity of the disease and its poor clinical outcomes.

Aims and Objectives: To study the serum inflammatory markers and their correlation with disease severity and outcome in patients with covid-19 disease.

Materials and Methods: Three hundred laboratory-confirmed COVID-19 patients were studied in a retrospective observational study at the Department of Medicine, Gandhi Medical College, Bhopal, from June 2021-June 2022. Patients were divided based on WHO criteria of clinical severity of Covid 19 into Mild Disease (n=100), Moderate Disease (n=100), and Severe Disease (n=100). Detailed history, vital signs, Hb, WBC, neutrophil, lymphocyte, monocyte, platelet count, NLR, LMR, ESR, CRP, D-dimer, HbA1c, S ferritin, LDH, S PCT, Troponin-I, PRO-BNP, HRCT chest were recorded. NLR and LMR in all patients were calculated. The duration of hospital stay and outcome of each patient, along with the type of respiratory support needed by each patient, was also recorded.

Results: Incidence of COVID-19 infection was more common in patients aged 41-50 years (24%), 51-60 years (18.7%), and 31-40 years (18%). Males outnumbered females (58.3% to 41.7%). The mean NLR in severe Covid-19 instances was considerably greater (6.963.8) compared to moderate cases (4.483.45) and mild cases (3.312.44) (p0.001). There was no significant relationship between LMR and illness severity (p=0.154). According to receptor operating curve analysis, NLR, LMR, and CRP were important predictive markers for disease severity. Among the important parameters, NLR had the highest area under the curve (0.846; p0.001). The area under the curve for LMR was 0.154, indicating that it is a poor instrument for predicting the outcome based on the AUC value.

Conclusion: Inflammatory markers, especially CRP, d-dimer, PCT, ferritin, Pro-BNP, WBC, Neutrophils, NLR and LDH, were positively correlated and lymphocytes, monocytes and platelet counts were negatively correlated with the severity and outcome of COVID-19. Measurement of inflammatory markers might assist clinicians to monitor and evaluate the severity and prognosis of COVID-19.

Keywords: COVID-19, Inflammatory Markers, lymphocyte-to-monocyte ratio, Mortality.

Introduction

COVID-19, also known as the noble coronavirus CoV, has been declared as a global pandemic, and rightfully so since to date, 219 million people have been infected by this disease. The death toll has reached 4.55 million worldwide, making it one of the worst pandemics in the history of mankind. [1] According to the World Health Organization - Western Pacific, Covid19 is more severe amongst patients who are 60 years or older with underlying health conditions such as diabetes, obesity, heart and lung disease. [2]

A prompt clinical diagnosis is essential to provide symptomatic therapy, immediate access to the intensive care unit, and patient isolation to stop the spread of the disease.

One of the most significant risk factors in COVID-positive individuals is higher expression of inflammatory helper T-cell-associated cytokines, as most disease associated with infection is determined to be cytokine storm, resulting in lung tissue damage and other severe consequences. [3]

When compared to non-severe patients, Covid-19 extremely ill patients had higher levels of pro-inflammatory cytokines, the most common of which was interleukin (IL-6). Furthermore, a substantial relationship between higher mortality and a shift in the Th1-Th2 balance has been discovered.

Other research has demonstrated that cytokines can cause myocardial infarction. Myocardial damage, for example, have been linked to ACE2, owing to the increased expression of ACE2 in the cardiovascular system in Covid-positive patients. [4]

The mechanism associated with SARS-CoV-2 is associated with host cell pyroptosis, that causes the release of damage-associated molecular patterns (DAMPs), which trigger the generation of proinflammatory cytokines and chemokines like type I interferons (IFN-a and IFN-b) that protect from any viral infection. [5]

Previous research found greater levels of proinflammatory markers such IL-2, IL-7, IL-10, IL-6, macrophage inflammatory protein 1a (MIP1), and TNF in COVID-19 patients receiving intensive care. [6] Serum IL-6 levels were shown to be elevated in patients with severe COVID-19 symptoms, and this can be used to predict patients' outcomes early on. [7]

Materials and Methods

A retrospective observational study was performed at the Department of Medicine, Gandhi Medical College, Bhopal, from June 2021-June 2022 on 200 laboratory-confirmed COVID -19 patients over 18 years.

Patients of less than 18 years, patients testing negative for RTPCR, active rheumatological diseases, active tuberculosis were excluded from the present study.

All the patients were divided based on WHO criteria of clinical severity of Covid 19 as Mild Disease [n=100; symptomatic patients meeting the case definition for COVID-19 without evidence of Viral Pneumonia or Hypoxia], Moderate Disease [n=100; clinical signs of pneumonia (fever, cough, dyspnoea, fast breathing) but no signs of severe pneumonia, including SPO2 >/= 90% on room air] and Severe Disease [n=100; clinical signs of pneumonia (fever, cough, dyspnoea, fast breathing) plus one of the following RR >30 per min, Severe respiratory distress or, SPO2 <90% on room air]. [8]

Detailed history and examination of each patient were noted from case records along with vital signs, investigations including Hb, WBC, neutrophil, lymphocyte, monocyte, platelet count, NLR, LMR, ESR, CRP, D-dimer, HbA1c, S ferritin, LDH, S PCT, Troponin-I, PRO-BNP, HRCT chest. The duration of hospital stay and outcome of each patient, along with the type of respiratory support needed by each patient, was recorded.

Statistical Analysis

Data was recorded in Microsoft Excel programme and statistical analysis was performed by the SPSS program for Windows, version 25 (SPSS, Chicago, Illinois). Continuous variables were presented as mean ± SD, and categorical variables were presented as absolute numbers and percentage. Data was checked for normality before statistical analysis. Descriptive analysis was performed to obtain general characteristic of the study population.

Categorical variables was analysed using either the chi square test or Fisher's exact test. Continuous variables was assessed using ANOVA or independent sample t-test. Pearson correlation (r) was performed to establish the correlation between different parameters. Roc curve was prepared to obtain the effectiveness of different instrument. $P<0.05$ was considered statistically significant.

Results

The majority of the Covid-19 patients had an age between 41-50 years (24%), followed by 51-60 years (18.7%0 and 31-40 years (18%). The majority of the mild Covid-19 patients had an age between 21-30 (29%), whereas moderate severity was more prevalent in the age groups of 41-50 years (24%0 and severe Covid-19 cases had an age between 41-50 years (29%) (p=0.078).

The majority were males (58.3%) than females (41.7%). However, no significant difference was obtained between sex distribution and severity of the Covid-19 patients (p=0.149).

Out of 46 deaths in the present study, 45 were among the severe cases. One moderate case progressed to severe disease despite the standard of care and eventually died. This highlights that mortality is more common in patients with severe Covid 19 infection at admission.

Table 1: Baseline Characteristics of the patients.

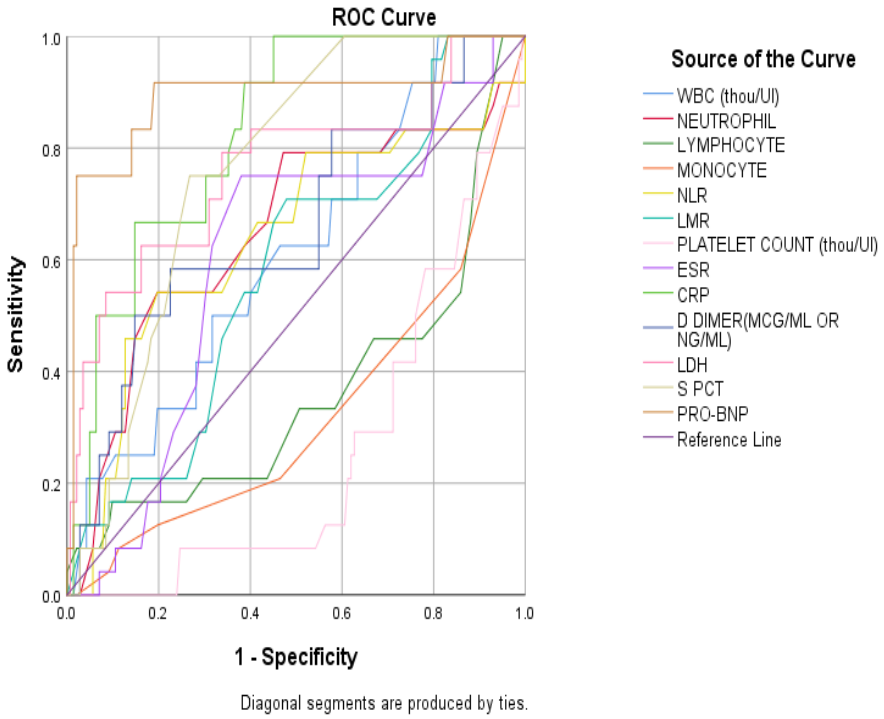
Characteristics	Mild COVID 19 Disease (n=100)	Moderate COVID 19 diseases (n=100)	Severe COVID 19 disease(n=100)	P value
Age; years	41.90±17.89	46.92±15.81	49.86±14.48	0.002
Duration of stay; days	7.88±3.919	9.65±4.65	11.23±7.194	0.002
HB; g/dl	12.246±2.12	12.466±2.08	11.450±2.24	0.002
WBC; thou/Ul	6347.00±2747.76	8112.00±4102.13	10774.40±6757.75	<0.001
Neutrophil;%	67.32±12.80	74.73±10.93	80.16±11.54	<0.001
Lymphocyte; %	27.40±11.55	21.10±9.49	16.12±10.04	<0.001
Monocyte; %	3.52±1.62	2.570±1.41	2.170±1.27	<0.001
NLR	3.31±2.44	4.84±3.45	6.96±3.82	<0.001
LMR	8.38±3.94	9.15±4.44	8.061±3.86	0.154
Platelet count; lac/mm3	2.41±1.8	2.43±0.74	2.24±1.1	0.526
ESR; mm/hr	20.65±9.114	25.93±10.38	30.09±11.174	<0.001
CRP; mg/l	14.80±40.36	52.65±62.40	78.92±67.49	<0.001
D Dimer; mcg/mL	272.03±288.48	448.88±315.32	612.49±429.51	<0.001
HBA1c; %	11.91±52.22	6.05±2.50	6.955±1.83	0.396
Serum Ferritin; mcg/L	188.22±208.03	443.46±388.18	607.74±471.37	<0.001
LDH; iu/L	338.73±155.75	509.85±209.16	673.19±613.80	<0.001
S PCT; mcg/L	0.083±0.046	0.147±0.179	0.360±1.08	0.015
Troponin -I; ng/ml	0.042±0.026	0.28±1.28	0.282±0.783	0.159
PRO-BNP; pg/ml	80.43±151.63	364.26±1223.43	1882.07±4392.47	<0.001
HRCT CHEST; % of lung involvement	15.13±4.84	36.89±13.01	51.56±17.63	<0.001

:Data is represented as mean ±SD

Table 2: ROC analysis for predicting outcomes in patients

Area Under the Curve					
Test Result Variable(s)	Area	Std. Error	P value	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
NLR	0.846	0.071	<0.001	0.707	0.985
LMR	0.154	0.071	0.021	0.015	0.293
CRP	0.462	0.098	0.001	0.270	0.653
D Dimer	0.962	0.038	0.123	0.888	1.000
S Ferritin	0.923	0.052	0.158	0.821	1.000
S PCT	0.808	0.077	0.304	0.656	0.959
Troponin -I	0.769	0.120	0.369	0.534	1.000
PRO-BNP	0.885	0.063	0.199	0.762	1.000
HRCT CHEST	1.000	0.000	0.095	1.000	1.000
Neutrophil	0.846	0.071	0.248	0.707	0.985
Lymphocyte	0.135	0.068	0.223	0.002	0.268
The test result variable(s): TROPONIN -I, LYMPHOCYTE has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.					
a. Under the nonparametric assumption					
b. Null hypothesis: true area = 0.5					

Receptor operating curve analysis found that NLR, LMR, and CRP were significant prognostic markers for the severity of the disease. The area under the curve was highest for NLR (0.846; p<0.001) among the significant parameters. The area under the curve for LMR was 0.154, which is considered a poor instrument in predicting the outcome as per the AUC value, suggesting no value as per the AUC.



Discussion

In clinical practise, the CBC provides a quick, straightforward, and low-cost assessment. It contains detailed information about hematologic contents. When using alternative cut-offs, a few indicators, such as NLR and LMR, offer strong predictive power. [9] A retrospective observational research on 300 Covid-19 patients at Hamidia Hospital in Bhopal looked into NLR and LMR as potential prognostic markers.

In the present research, older age groups are more susceptible to COVID-19 than younger age groups. [10,11] While the majority of people recover from the infection, some do not, and being older is a risk factor for a worse outcome.

In addition, the mechanisms through which advancing age might predispose a person to a poor prognosis have not yet been fully explained. Several hypotheses have been proposed about why older people might be more susceptible to severe COVID-19 infection. One of the hypotheses suggest that there is an age-related deterioration in the clearance of inhaled particles in the small airway region. This notion is supported by the data showing that cilia and ciliated cells in the airway gradually decline with ageing. [12]

According to our research findings, the mean length of hospital stay was significantly longer for those with severe clinical profiles compared to the other two categories ($p = 0.002$). Researchers noted that the patients' age gave the largest risk of death in a study on the prediction of in-hospital mortality for COVID-19. Additionally, a multivariate analysis reveals that immunosuppression, age, the CXR severity index, and age were all significantly linked with in-hospital death. [13]

In the current study, we could not find any statistically significant differences between males and females concerning the severity of the Covid-19 disease (p-value 0.149). Despite this, it has been evident throughout the pandemic's first two years that males, regardless of age, are not only more susceptible to but also have a higher chance of death and more severe illness. According to the clinical classification of severity, men had a greater tendency to acquire more severe cases than women did. As males age, their upper airways shrink and become more easily collapsible than women's. [14] This could be another crucial component in explaining why COVID infection rates differ by gender. However, variables such as an age-dependent decrease in nasal resistance and a steady and relatively linear increase in nasal cavity capacity with advancing age may lead to a higher prevalence of COVID in the elderly population. [15]

In this study, we examined a variety of hematological parameters in patients with COVID-19 with a range of severity levels. We connected those levels with the level of severity as well as the outcome.

According to our findings, severe cases of covid-19 had significantly higher WBC ($p<0.001$) and neutrophil counts ($p<0.001$) than less severe instances. Except for individuals with bacterial infections or superinfections, neutropenia correlates with a hyperinflammatory state and cytokine storm,

which are essential components of the pathogenic mechanism that COVID-19 employs. Neutrophils play an important role in a wide variety of respiratory viruses that are connected with ARDS. This finding tends to correlate with a more severe course and affects a minority of individuals who present with leucocytosis and is accompanied by neutrophilia. [16] Individuals with severe COVID-19 infections had considerably higher levels of leukocytes and neutrophils than patients with less severe COVID-19 infections. In addition, as the COVID-19 disease progressed, severe groups exhibited an increase in both their leukocyte and neutrophil numbers. [17]

We observed considerable lymphopenia in those with severe disease compared to patients with mild to moderate cases of covid-19 illness. ($p<0.001$) Lymphopenia is the most widely recognized hematological aberration in individuals afflicted by COVID-19 infection. This condition manifests itself in up to 85% of severe cases, and the degree to which lymphopenia exists is correlated to the patient's prognosis. [18] This increase in leucocytes is caused by an increase in neutrophils. This rise is the result of a heightened inflammatory state and cytokine storm, which resulted in greater levels of inflammatory mediators such interleukins (IL) and tumour necrosis factor (TNF-), which caused lymphopenia by promoting lymphocyte death. [19]

According to the findings of our research, severe cases had considerably elevated levels of CRP ($p<0.001$), D-dimer ($p<0.001$), serum ferritin ($p<0.001$), LDH ($p<0.001$), and serum PCT ($p = 0.015$). Pro-BNP had a significantly higher abnormality level ($p<0.001$), as did HRCT chest imaging, in severely Covid-19 positive individuals, compared to moderate and mild instances. There is a significant elevation of inflammatory cytokines and biomarkers in the systemic hyperinflammation phase of COVID-19, proposed by Siddiqi and Mehra. [20] These include interleukin (IL)-2, IL-6, IL-7, granulocyte-colony stimulating factor, macrophage inflammatory protein 1-, tumor necrosis factor- (TNF-), CRP, and ferritin. This stage is characterized by the most severe expression of the cytokine storm, characterized by extreme hyperinflammation that may lead to cardiac collapse and failure of many organs. [20] Also, an elevated serum level of CRP, PCT, D-dimer, and ferritin were linked to a worse outcome in COVID-19, according to a meta-analysis. [21]

In the current investigation, we found that the severe patients had elevated levels of CRP, D Dimer, serum ferritin, LDH, and serum PCT ($p=0.015$), among other markers. The mean NLR was substantially greater in severe Covid-19 cases than in moderate Covid-19 or mild Covid-19 cases. In critically ill COVID-19 patients, recent evidence of lung pathology dissection indicated pulmonary small artery obstruction and microthrombosis development. [22] According to a meta-analysis, increased serum levels of CRP, PCT, D-dimer, and ferritin were associated with a worse prognosis in COVID-19. [21]

The study showed that because they have a higher death rate, the majority of the very ill Covid 19 patients in our study were included. The fact that there is no proven cure and that the virus can develop only adds to the confusion. As a result, the initial step in treating Covid-19 without a specific medicine is to separate the patients to prevent disease spread. The primary goal of treatment is to avoid respiratory failure and other potentially deadly outcomes. It has been demonstrated that some Covid-19 patients rapidly progress from a moderate to a severe or critical state, which is associated with a poor prognosis. [23]

In our study, it was found that WBC, Neutrophils, NLR, CRP, LDH, and PRO-BNP all revealed a highly significant positive relationship with outcome, showing that higher levels of these indicators imply a higher risk of death in Covid-19 patients. However, a negative relationship was discovered between Lymphocyte, Monocyte, and Platelet Count and the outcome, implying that abnormally low levels of these parameters in covid-19 positive patients have a higher risk of mortality. Studies showed that increased neutrophil count and NLR, among other test data, are markers of serious sickness. [17] Furthermore, the trajectory of the neutrophil count and NLR early in the course of hospitalisation predicts severity and mortality. [24]

Researchers demonstrated that high -dimer levels increase the risk of severe COVID-19, VTE, and mortality. [25] A D-dimer levels of 1570 ng/ml exhibited a negative predictive value of 97.5% for VTE in a prospective ultrasonography investigation of consecutive non-ICU patients. [26]

There are a few limitations to this study. This investigation was a retrospective study at a single tertiary care hospital. Second, even though all of the investigations were carried out at the time of admission, subsequent studies could not be carried out because of the budgetary and logistical constraints associated with the patients. Third, the sample size was small, so there is a need for additional research with larger samples. Fourth, because the data were obtained retrospectively, patients could not be followed up after discharge to check for ongoing symptoms or post-COVID sequelae. Additionally, HRCT Chest was not performed in all patients.

Conclusion

Collectively, the SARS-Cov-2 infection may result in hyper-reaction of the immune systems accompanied by elevated serum levels of

inflammatory parameters, which may be associated with disease severity and outcomes. Inflammatory markers, especially CRP, d-dimer, PCT, ferritin, Pro-BNP, WBC, Neutrophils, NLR and LDH, were positively correlated and lymphocytes, monocytes and platelet counts were negatively correlated with the severity and outcome of COVID-19. Measurement of inflammatory markers might assist clinicians to monitor and evaluate the severity and prognosis of COVID-19. Furthermore, because our study is retroactive and requires further data, future research will be required to assess these biomarkers and determine their significance.

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