SYSTEMIC REVIEW

Inflammatory and other biochemical markers in Monitoring COVID-19 Disease: A Systemic Review

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ABSTRACT
The COVID-19 spread and outburst since December, 2019 lead to many serious complications. Old age people and the patients with co-morbid conditions like hypertension, Diabetes and COPD, are more susceptible to severe Covid-19 disease. We searched the related articles via Medline/PubMed, Scopus, PMC, google scholar and Web of Sciences. In this review we included, original research articles, Case reports and Meta-Analysis. We observed that the biochemical biomarkers like interleukin-6, Ferritin, C-reactive protein, lactate dehydrogenase were elevated in COVID -19 patients. Many studies showed the association of inflammatory biomarkers and severity of COVID -19 Disease. The levels of these biomarkers are highly elevated in critically ill or non-survivor COVID -19 patients. Hence these inflammatory parameters can be useful as laboratory biomarkers and could help to the clinician/physician to rapidly identify the severity of COVID -19 disease.
Keywords: COVID -19, CRP, LDH, Ferritin, IL-6, NLR

INTRODUCTION

In December 2019, the first case of COVID-19 was detected in Wuhan city of China. The spread and outburst of coronavirus disease 2019 (COVID- 19) since December, 2019, has led serious challenges to global public health (1). On January 30th 2020, the World Health Organization (WHO) declared the outbreak of COVID-19 to be a "public health emergency of international concern". Acute respiratory syndrome coronavirus 2 (SARS-CoV-2) may be transmitted from person to person through close contact, respiratory droplets and aerosol (2).

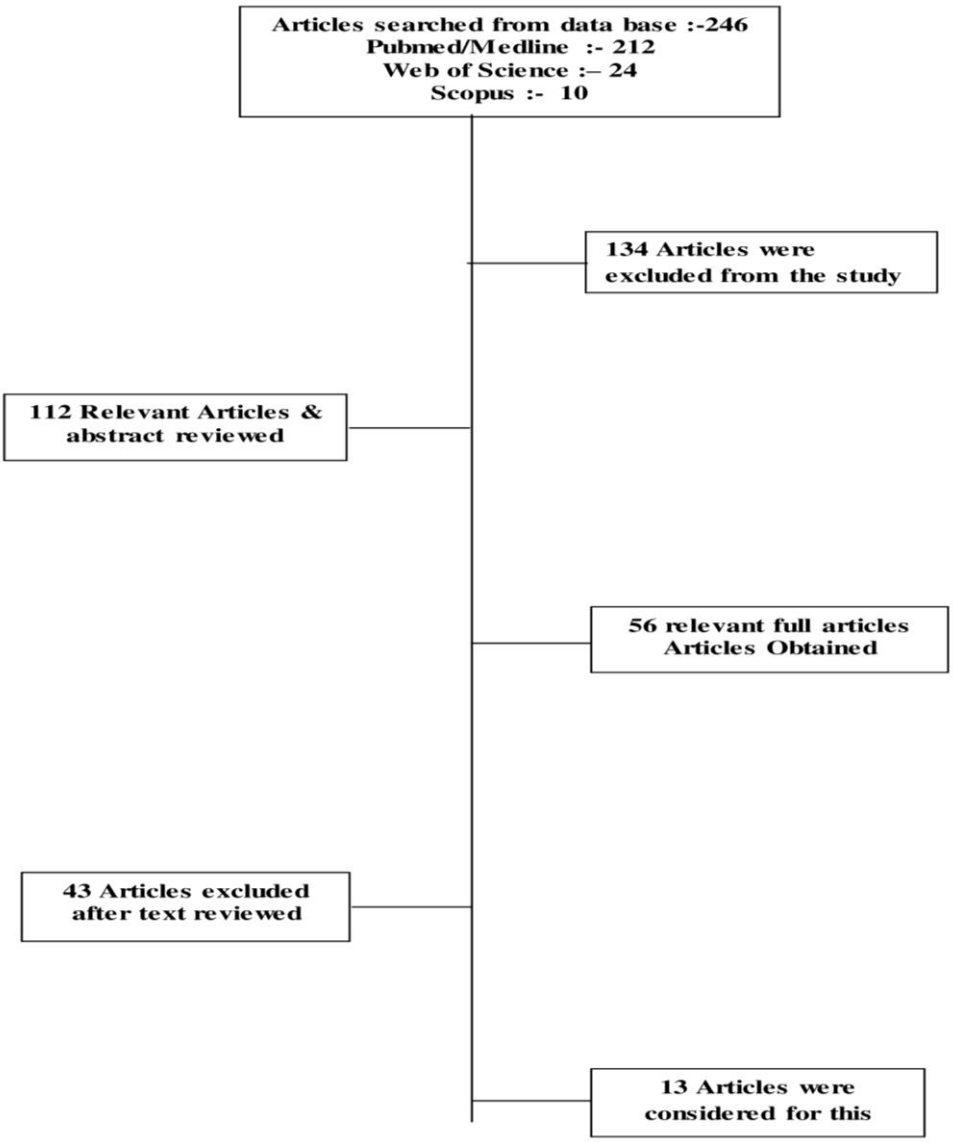
The incubation period of COVID-19 may vary from 1 to 14 days and causes respiratory tract infection characterized by a broad spectrum of clinical presentation with a different degree of severity, from asymptomatic patients to pneumonia which may lead to acute respiratory distress syndrome and multiple organ failure, leading to death (3). Elderly individuals (>65 years) and the patients with comorbidities like, diabetes, hypertension, and chronic obstructive pulmonary disease, are more susceptible to severe disease. The clinical laboratory may provide critical support for the appropriate clinical management of COVID-19 patients, from screening to diagnosis, prognosis, and monitoring (4).

It has been suggested that notable increase in proinflammatory cytokines and cytokine storm are significant contributors to the progression of disease because these are significantly correlate to the severity and COVID-19 mortality (5). Apart from this, the infiltration of immune cells, and progressive lymphopenia, mainly neutrophil-to-lymphocyte ratio (NLR) is recognized as a prognostic marker (6). rRT-PCR is the standard method for the diagnosis of COVID-19, CT-scan may assist in diagnosis with high risk factor (7).

COVID-19 may transmit infection to the endothelial cells, causing vasoconstriction in many organs; this may be associated with hypercoagulability and edema. COVID-19 infection may worsen the management of chronic illnesses, like liver disease, renal disease and diabetes mellitus. (8) As there are so many studies have been published on dynamics in biochemical parameters in Covid-19, the treating clinician needs to be effectively updated to offer the best care at the bed side. The assessment of laboratory markers can provide additional objective information which can significantly impact many components of patients care. Hence the aim of this systemic review was to find the association biochemical and immunological parameters with severity and mortality of COVID-19 patients.

MATERIAL AND METHOD

The results of the initial search strategy were first screened by title and abstract. The relevant articles were screened as per inclusion and exclusion criteria. In this study, we have included all the published study which shows biochemical indices and COVID-19. In this review, we use Medline/PubMed, Scopus, PMC, google scholar and Web of Sciences search engines. The keywords used for the searching are: "Novel coronavirus", "SARS-Co-V-2", "Novel coronavirus 2019", "2019 nCoV", "COVID-19", "coronavirus, "pneumonia", "C-reactive protein" OR "ferritin" OR "procalcitonin" OR "interleukin-6" OR "interleukin-10" OR "interleukin-2R" OR "tumor necrosis factor-α" OR "neutrophil-to-lymphocyte ratio" OR "inflammatory markers" OR "inflammatory parameters"), "Renal Dysfunction" OR "Cardiac biomarker" OR "Hepatic biomarkers".



ROLE OF BIOMARKERS

The characteristic that can be objectively measured and evaluated as an indicator of normal biological and pathological processes, or pharmacological responses to a therapeutic intervention is termed as Biomarkers-" (9). Hospital laboratories play an important role in

the detection of the viruses along with follow-up of patients (10). Laboratory parameters validated for SARS-CoV-2 are important for the management of COVID-19 as they support the clinical decision-making process for controlling infections through speedy isolation, adequate treatment and consequently reduced contagion rates (11). The following parameters-, the absolute neutrophilia, thrombocytopenia, hypoalbuminemia, elevation in liver enzymes, creatinine and non-specific inflammatory markers such as C-reactive protein (CRP) and Interleukin 6 (IL-6) were observed as an unfavorable parameters in the course of disease progression (13). Besides this the outer important biomarkers are lymphopenia, elevated D-dimer and elevated ferritin. We can also consider lactate dehydrogenase (LDH), Creatine phosphokinase (CPK) and troponin as biomarker. (14)

PATHOGENESIS OF COVID -19

Corona viruses are spheroidal in shape with single-stranded RNA and a diameter of 80–220 nm. Corona viruses consists of four structural protein namely spike(S), membrane (M), envelop (E) and nucleocapsids (N).(15) It's evident that COVID-19 is not a localized respiratory infection but a multisystem disease. Transmission of SARS-CoV-2 may occur either through exposure to micro-droplets from infected individuals or by contact transmission through contaminated fomites. The virus reaches the smaller airways and alveoli, and targets the bronchial and alveolar epithelial cells. ACE2 is main host for the viral entry and has been observed to be highly expressed in nasal epithelial cells. (16) The spike surface glycoprotein S on the virus binds to ACE-2, along with alveolar macrophages and dendritic cells. ACE-2 is a membrane carboxypeptidase present in distal airways and alveoli.

ACE-2 is also expressed on the vascular endothelium, nasopharyngeal, nasal, oral, oropharyngeal epithelia, renal proximal tubular cells, skin, reticulo-endothelial, gut epithelia, cardiac pericytes and the central nervous system (17). Expression of ACE-2 depends on genetic factors, gender, age and presence of comorbid conditions like chronic cardiopulmonary disease, obesity and cancer. Renin acts on angiotensinogen and produce angiotensin I and it is further changed to angiotensin II by ACE. Angiotensin II function as fibrotic remodeling, inflammation (angiotensin II type 1 receptor) and leads to vasodilation and growth inhibition (angiotensin II type 2 receptor). (17a)

ACE-2 acts on Angiotensin II and synthesized angiotensin 1–7. It counteracts the harmful effects of the ACE/Ang II/AT1 axis. After viral infection ACE-2 may leads to downregulation and upregulation of angiotensin II. Activation of downstream inflammation by angiotensin type 1 receptor may lead to the cytokine storm, which affect multiple organs. (18)

Table: Reported biomarkers in COVID-19 Patients.

HEMATOLOGICAL	
Lymphocyte count	Decrease
Neutrophil count	Increase
NLR (Neutrophil to Lymphocyte Ratio)	Increase
Platelet count	Decrease
INFLAMMATORY PARAMETERS	
C-Reactive Protein	Increase
Prolactin	Increase
Ferritin	Increase
IL-6	Increase
Lactate Dehydrogenase	Increase
HEPATIC MARKERS	
Alanine Transaminase	Increase
Aspartate Transaminase	Increase
Bilirubin	Increase
Albumin	Decrease
CO-AGULATIVE MARKERS	
D-Dimer	Increase
Fibrinogen	Increase
Fibrin Degradation Products (FDP)	Increase
Prothrombin Time	Increase
aPTT (Activated Partial Thromboplastin)	Increase
CARDIAC MARKERS	
Cardiac Troponin	Increase
Peptide (BNP)/NT-proBNP	Increase
RENAL MARKERS	
Creatinine	Increase

MUSCLES	
Creatine Kinase	Increase
Myoglobin	Increase
ELECTROLYTES	
Sodium	Decrease
Potassium	Decrease
Calcium	Decrease

STUDY OF BIOMARKERS IN COVID-19

INFLAMMATORY MARKERS

CRP AND PROCALCITONIN

Mahat *et al.* in their meta-analysis revealed that the concentrations of serum CRP, erythrocyte sedimentation rate (ESR), procalcitonin (PCT), IL-6, IL-10, IL-2R, ferritin, and NLR were elevated in severe COVID-19 patients compared to non-severe COVID-19 patients and the increase in CRP, PCT, IL-6, ferritin, and NLR indices were higher in non-survivors as compared to survivors. They concluded that these inflammatory parameters can help the clinicians to rapidly diagnose the severity of COVID-19 patients.(19)

In a study by Iqbal *et al*. found an increase in serum CRP, LDH, IL-6, and ferritin levels in COVID-19 patients and they also conclude that these parameters can be used as laboratory biomarkers for a poor outcome in COVID-19. In addition to this, CRP may not only be used as a prognostic marker, but also to monitor disease improvement in COVID-19. (20)

Arora *et al*. studied on 169 COVID 19 patients and concluded that serum CRP, alanine transaminase (ALT), aspartate transaminase (AST), urea, creatinine, troponin and PCT have very good accuracy in predicting the severity of COVID-19 infection. (21) In addition to this they also concluded that the severity of COVID-19 mostly occurred in older people with co-morbid conditions like hypertension, diabetes and cancer. A meta-analysis showed that elevated PCT values were associated with a nearly 5-fold higher risk of severe infection. (22)

FERRITIN

Serum ferritin is well known as an acte phase reactant, and marker of acute and chronic inflammation. For the dysregulation of immune response ferritin is a key element, mainly under supreme hyperferritinemia, via direct immune-suppressive and pro-inflammatory effects, contributing to the cytokine storm**.** (23) In a study of 99 COVID patients, the 63 patients have serum ferritin level above normal range.(24) Many study and meta-analysis showed that the serum ferritin levels were elevated in COVID-19 patients (25**)** and the increase was more in the more severe patients therefore it was concluded that ferritin were closely related to the severity of the COVID- 19 (26). Elevated ferritin levels were found also in autopsies of 12 patients whose cause of death was SARS-CoV-2 infection.(27)

LACTATE DEHYDROGENASE (LDH)

LDH has two major subunits and five isozymes. Since 1960s, LDH has been used as a marker of cardiac damage. Altered measurement may result in multiple organ injury and decreased oxygenation with upregulation of the glycolytic pathway. Increased lactate from infection and tissue injury triggers the activation of metalloproteases and enhances macrophage mediated angiogenesis. Severe infections may cause cytokine-mediated tissue damage and LDH release [28].

Isoenzyme 3 of LDH is present in lung tissue. Severe COVID-19 infections can be expected to release greater amounts of LDH in the circulation leading to severe form of interstitial pneumonia. However, the contribution of the different LDH isoenzymes to the LDH elevation observed in COVID-19 has not been determined. LDH levels may also elevated in thrombotic microangiopathy, which is associated with renal failure and myocardial injury. (29)

Henry *et al* in their pooled study observed, elevated LDH values were associated with 6- fold increased odds of severe COVID-19 disease. They concluded that, elevated LDH was associated with >16-fold increase in odds of mortality.(30)

HEMATOLOGICAL MARKERS

HEMOGLOBIN

Bellmann *et al.* in their study observed that, anemia and altered iron homeostasis were common in hospitalized COVID-19 patients. The magnitude of anemia was 24.7% in COVID- 19 subjects. (28) Wang *et al.* in their study found that the magnitude of anemia was 24.9%, in COVID- 19 subjects (65) while another study found the magnitude of anemia was 35.5%. (31)

LYMPHOCYTES

Normal WBC count or leucopenia, lymphopenia were noted in COVID- 19 patients. Lymphopenia may be due defective immune response to the virus. SARS-CoV-2 may also inhibit bone marrow haematopoiesis through certain receptors resulting in lymphopenia (32). Steroid treatment in COVID- 19 patients may cause lymphopenia. Many researchers in their study showed, lymphopenia, a reliable marker for severity and progression of disease with magnitude higher in dead and/or ICU patients than non-severe or "survivor" patients. (33).

Lymphocytopenia is directly correlated with severity of disease and death. A study showed that lymphocyte counts were lower in patients with acute respiratory

distress syndrome (ARDS), severe patients admitted in ICU, and in non-survivors (34). A temporal model based on lymphocyte counts at two time points showed that patients with < 20% and < 5% lymphocytes at days 10–12 and 17–19 from the onset of symptoms respectively had the worst prognosis. (35)

NEUTROPHILS

Patients requiring admission to the ICU had higher percentage and absolute number of neutrophils (18). Many studies showed, neutrophilia was a common finding in severe patients. (33, 36)

EOSINOPHILS

Nair *et al.* in their study reported high prevalence of eosinophilia in symptomatic COVID-19 patients. In their study they found that the eosinophil count was negatively correlated with oxygen supplementation, mechanical ventilation and duration of ICU admission and positively correlated with lymphocyte count. Their findings indicated the protective role of eosinophils in reducing the severity of inflammatory diseases through an inhibitory mechanism, as evidenced by lower CRP. (37)

Lymphopenia has also been a common finding in patients with COVID-19 and blood eosinophil counts correlated positively with lymphocyte counts in both severe and non-severe cases. Generally, eosinophils are present in fewer numbers in peripheral blood and present in mucosal surfaces where viruses can overcome the host defense. Eosinophils have various granules and inflammatory mediators that have antiviral activity. (38)

MONOCYTES AND BASOPHILS

Dawood *et al* (39) in their study showed that the severity of COVID19 was associated with lymphopenia, monocytosis, and elevated NLR and platelet to lymphocyte ratio (PLR) values. On the other hand, both values (NLR and PLR) could be used as hematological predictors for disease severity and the outcome of in COVID-19 patients.

PLATELETS

Thrombocytopenia and thrombocytosis have been observed in COVID-19, while severe thrombocytopenia and bleeding are uncommon (40). Thrombocytopenia associated with other coagulation parameters and may increase the risk of mortality. (41)

CARDIAC MARKERS

Many serum biochemical parameters, LDH, creatine kinase (CK), creatine kinase MB (CK-MB), myoglobin (Mb), cardiac troponin (cTnI), AST and brain natriuretic peptide (BNP), have been studied in diagnosis, treatment, and prognosis. Elevated levels of these parameters have been observed in patients with COVID-19. (42) Some literatures indicated that increased in troponin I (43), CK-MB, and NTproBNP (44) were indicators of possible cardiac damage during SARS-CoV-2 infection.

On the other hand, CK-MB, cTnI, Mb, and NT-proBNP are more myocardial injury specific and increased to varying degrees, especially in severe and critical illness. Furthermore, higher levels were associated with higher mortality. (45) Cardiac biomarkers have been seen to be in tandem with other biomarkers; patients with myocardial injury had higher leukocyte, lower lymphocyte and lower platelet counts. (46) However, cardiac biomarkers need to be used judiciously as routine tests in all patients may be misleading. A meta-analysis included 4189 confirmed case of COVID- 19 indicated that the levels of cardiac biomarkers increased above normal by the midpoint of hospitalization and reached maximum immediately before death. The increase in levels was more in severe cases. (45)

A study by Li *et al* (47) observed significantly higher levels of CRP, D-dimer, IL-6, PCT, and higher percentages of neutrophils, lymphocytes, and monocytes within the first week of admission. Cardiac markers like, BNP, hs-TNI, α- hydroxybutyrate dehydrogenase (α-HBDH), CK-MB, and LDH, were also found to be elevated in severe/critically ill patients during the first week of admission. In their study they found that the patients with an elevated cardiac marker during hospitalization/ICU admitted patient showed a significantly higher mortality than the patient having normal serum levels. (47)

LIVER MARKERS

Liver function tests are the measures of live injury, bile duct injury/chlolestasis and measures of synthetic capacity. Due to that we can measure the levels of AST, ALT, ALP, and Gamma-glutamyl transpeptidase (GGT), bilirubin, albumin and prothrombin time. A study by Saini *et al* observed that 41.5% patients were with normal liver enzyme and 58.5% were with elevated liver enzyme, out of 58.5%, 43.31% patients were more sever having liver injury and admitted in ICU. The patient having elevated serum liver enzyme, increased levels of bilirubin, decreased levels of albumin and total serum protein. They found the positive association between inflammatory markers and liver parameters. (48)

Many patients showed decreased levels of albumin, prior to the COVID- 19, suggesting decreased liver synthesis.(49) In the context of inflammation, hypoalbuminemia may also reflect albumin extravasation as a consequence of increased capillary permeability.(50) Additional factors that could explain the observed hypoalbuminemia in severe COVID-19 are increased catabolism and malnutrition. Decreased albumin level in serious patients is multifactorial and is responsible to increased capillary permeability, increased turnover, decreased protein synthesis, decreased serum albumin, increased volume

of distribution, and increased expression of vascular endothelial growth factor. (14).

Many cohort studies from China showed the prevalence of elevated ALT among COVID-19 patients ranged between 4% and 33%, and in a cohort study from New York it was as high as 39% (49, 51-52). The prevalence of increased AST ranged between 4% and 53% in Chinese cohorts, and was 58% in the US cohort (49, 53-57). Many case reports have described severe liver function test (LFT) abnormalities (58-59) or acute-on-chronic (60-61) liver failure in patients with COVID-19.

Elevated ALP was reported in 2%-5% of patients, and elevated GGT was reported in 13%-54% of patients. (49, 62-63) Many studies showed, during admission, the prevalence of increased total bilirubin was between 1% and 18% in COVID- 19 patients. (49, 53, 64)

PANCREATIC MARKERS

Mild pancreatic injury has been seen in some COVID-19 patients, this can be due to the direct cytopathic effects of SARS-CoV-2 and by indirect and immune-mediated systemic inflammatory cell responses. In-addition, the SARS-CoV-2 receptor of ACE-2 is highly expressed in cells of the pancreatic islets and exocrine glands, which can cause the infection to damage the islets and result in acute diabetes (65).

The severity of the COVID-19 is related to the concentration of glycosylated ACE-2 receptors in pulmonary epithelium; thus, increased receptors in lung of patients with uncontrolled Diabetes Mellitus can extend binding of the virus and increase severity (66) Again, COVID-19 infection can magnify the glycemic control by damaging the pancreatic beta cells either directly by SARS-CoV-2 or via cytokine mediated damage. A study by Schepis *et al* (67) reported the detection of SARS-CoV- 2 RNA in a fluid sample obtained from a pancreatic pseudocyst in a patient with COVID-19 pneumonia and acute pancreatitis. The interaction of COVID-19 with pancreatic endocrine system complicates the scenario for COVID-19 patients with diabetes mellitus. Hyperglycemia in diabetes has been found to have poor prognosis with increased morbidity and mortality. (66, 68)

RENAL MARKERS

Kidney disease in COVID-19 patients may be in the form of acute kidney injury (AKI), hematuria or proteinuria, promoting a greater mortality risk. It is unclear whether AKI is due to hemodynamic changes and cytokine release or the direct toxicity of the virus (69).

Xiang *et al* studied on 154 confirmed cases of COVID -19, out of which 125 were mild cases and 29 were in severe condition. On admission, they found, 16 patients were with renal dysfunction. Cystatin C and creatinine levels were increased and eGFR was decreased in severe patients compared with those in mild patients. Renal dysfunction was more prevalent in severe patients and by using multivariate logistic regression, they found that male gender, older age and hypertension were three importantly independent risk factors for renal dysfunction in COVID-19 patients. In their study, they observed a weekly positive correlation between BUN and CRP and negative correlation between of cystatin C with eGFR and CRP, and they did not found any significant correlation between inflammatory cytokines with creatinine and uric acid among COVID- 19 patients. (70)

A registry conducted in Europe and America, observed a high prevalence of kidney disease in hospitalized COVID-19 patients. About 30% of them had evidence of kidney disease on admission, with elevated serum creatinine, and this was associated with greater in-hospital mortality. High prevalence of kidney disease at hospital admission may be due to past history of CKD in COVID-19 patients. (71) These patients have a pro-inflammatory state with functional defects in innate and adaptive immune cell populations (72) and are known to have higher risk pneumonia. (73)

DISCUSSION

This review discuss the correlation of biochemical and inflammatory parameters with severity and mortality in COVID -19. We reviewed many research articles and observed that, the levels of CRP, D-Dimer, ferritin, PCT, IL-6, LDH, CK-MB and NLR were increased in the severe group as compared to the non-severe group and the increase in CRP, NLR, Ferritin, LDH, Procalcitonin and D-Dimer were more in non-survivors as compared to survivors.

In this review, we mentioned that some studies showed increased levels of AST, ALT, GGT, bilirubin and decreased levels of albumin and this may be due to liver damage. The levels of liver enzyme (AST & ALT) may be increased due to drug toxicity, cytokine storm and/or preumonia associated hypoxia. On pathological examination SARs confirmed shows virus in liver tissue and the ACE-2 is expressed in liver as well as in cells of bile duct. As the expression of this enzyme is higher in bile duct cells, so the liver injury in COVID-19 more related to its damage.(74) Many studies showed changes in hepatic markers not clinically significant and have no impact on COVID -19 outcomes. In most studies, liver dysfunction appears to be mild, transient, not clinically significant and to have no impact on COVID-19 outcomes (75) but these patients had higher risk of progressing to severe disease during hospitalization. (76)

CRP protein is an acute-phase inflammatory protein produced by the liver and regulated at the transcriptional level by the cytokine IL- 6 and IL-1.(77) It is an important index for diagnosing and evaluating severe pulmonary infectious diseases.(78)

Magnitude of the inflammation associated with CRP levels and the concentration of CRP is not concerned

with the factors like sex, physical condition and age.(79) Patients having severe pneumonia have elevated CRP level, its levels can be used for the early diagnosis of pneumonia (80) and it is the most important parameters for the diagnosis and assessment of pulmonary infectious disease (78)**.** Previous studies showed, CRP may be elevated by viral or bacterial infections but the level of CRP significantly increased in bacterial infection than in viral infection. (81)

This review find the role of biomarkers of inflammation, IL-6, CRP, PCT and D-dimer in the prediction of severe disease and need for oxygen therapy in COVIDd-19 patients. It is also found that IL-6 is a strong predictor of hypoxemia requiring oxygen therapy. There are several studies showing association of IL-6 with severity of disease in COVID -19. Almost all the immune system cells produced IL-6 in the lungs and its secretion is stimulated by proinflammatory cytokines, especially IL-1β and tumor necrosis factor α (TNFα). In Covid -19, elevated levels of IL-6 may enhance the development of acute lung injury. IL-6 increases the permeability of lung capillaries causing the ARDS development and it also trigger the coagulation pathway causing microthrombi in lung circulation and increases the risk of thrombotic event. (82)

Many extrathyroid tissues may synthesized PCT during bacterial infection, and this is enhanced by increased levels of IL-6 and TNFα whereas the increased concentration of interferon-γ during viral infection is negatively impacting the synthesis of PCT**.**(83) This is why the level of PCT remains within the normal range in the majority of the patients with non-severe COVID-19 and increased value in severe COVID-19 may indicate secondary bacterial infection. (22) Many studies reported a positive association between PCT and severity of COVID-19. (22, 38)

In this review, we found that comorbidities, including diabetes, hypertension, heart failure, and coronary artery disease, may play important roles in disease severity. In addition, dyspnea was the most prominent symptom in patients with severe cases. Moreover, ferritin level was significantly higher in the severe group and was found to be the only significant predictor of disease severity in linear regression analysis.

In the present study, our results first proved our hypothesis and indicated that elevated NLR was an independent prognostic biomarker that affected pneumonia progression in COVID-19 patients. Our findings were consistent with those of previous studies on the relationship between NLR and prognosis of many other infectious diseases.(84) Neutrophil, the major component of the white blood cell, can activate and migrates from the venous system to the immune organ or system. It can induce DNA cell damage as it releases reactive oxygen species and makes virus free host cell. Hence, the antibody dependent cell mediated cell (ADCC) may destroy the virus directly, may expose virus antigen, and induce cell-specific and humoral immunities.(85) Moreover, virus related inflammatory markers like IL-6, IL-8, TNF-α, etc, may trigger Neutrophil.(86)

The NLR may help in categorizing the severity and progression of disease in COVID-19 patients. A study showed NLR has good predictive values on disease severity and mortality in patients with COVID-19 infection shown by many researchers.(87-88).

CONCLUSION

In this systemic review, we studied many published article and found significantly increased levels of CRP, D-dimer, LDH, ferritin, PCT, IL-6, and NLR in COVID-19 patients. Many studies showed that the levels of these parameters were more in severe patients as compared to non-severe patients suggesting that the levels of these parameters are associated with the severity of COVID-19 disease. Hence these inflammatory parameters can be used as laboratory biomarkers and could help to the clinician to rapidly identify the severity of COVID-19 disease.

LIMITATION OF THE STUDY

In this review, as the quantity and quality of the including studies are limited, so more high-quality and more number of studies are required.

ETHICAL APPROVAL

No ethical approval was required for this study

CONSENT FOR PUBLICATION

Note Applicable

AVAILABILITY OF DATA AND MATERIALS

Not Applicable

COMPETING INTERESTS

The authors declare that they have no competing interests

FUNDING

Not Applicable

AUTHORS CONTRIBUTION

S. Kumar, M. Arora, M. Mishra, D Kumar performed literature review and framed the initial draft. M. Arora, S. Sharma and S. Kumar reviewed the script and revised the initial draft. S. Kumar and M. Arora finalized the revised draft.

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