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Systematic Review

## Study of inflammatory markers for COVID-19 in control population and in pregnant women: a systematic review

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### ABSTRACT

COVID-19 infection is an inflammatory state and has varied presentation ranging from mild to severe condition. The second wave of COVID-19 resulted in greater mortality and morbidity as compared to first wave both in general as well as in pregnant patient. As the progression of disease is rapid and fatal hence there is a need of reviewing relevant inflammatory markers for predicting the disease course and severity. The inflammatory markers considered are Interleukins, CRP, LDH, serum Ferritin, Neutrophil/ lymphocyte ratio and in some cases serum Procalcitonin. These markers are raised in other inflammatory conditions also and therefore the maximum predictability of various markers differs in different conditions. COVID-19 in pregnancy in itself is challenging as it alters the immunity and hemodynamic and therefore the value of these markers in pregnancy can affect the sensitivity and specificity in predicting the severity of the disease. This review will evaluate the role of inflammatory markers in general population as well as pregnancy with regards to their prognostication in assessing the disease severity.

**Keywords:** Inflammatory markers, COVID-19, Prognostic marker, Reproduction

### INTRODUCTION

The pandemic CORONAVIRUS disease 2019 (COVID-19) emerged in Wuhan, China is caused by single stranded ribonucleic acid (RNA) beta corona virus which shares approximately 79% similarity with (SARS-CoV-1) at nucleotide level hence named (SARS- COV- 2).<sup>1</sup> In India the first case was identified on 30<sup>th</sup> January 2020. Since then, the disease had spread gradually but progressively to reach the peak in mid-September with 90,000 cases reporting each day, which labelled as first wave, dropping to 15,000 per day in January 2021. Nearly six months after the peak of first wave, the country was gripped again in second wave of COVID-19 which began in March 2021. Second wave was more devastating in terms of illness, increasing number of ICU admissions with increasing mortality over four lakh people per day. So, there is a need of early, effective diagnostic tool and timely management to reduce the disease morbidity and mortality. After the

peak of the first wave there was flattening of the curve. The country was gripped again second wave of COVID-19 which began in March 2021 which was rampant with a steep slope affecting over four lakh people per day. As it is well validated that inflammatory response plays the critical role in progression of COVID-19 and several studies have suggested that numerous inflammatory markers are elevated in these patients.<sup>2</sup> There is wide spectrum of potential biomarkers but we need to identify specific and sensitive biomarkers which can be used for diagnosis, assessing severity, prognosis, disease progression and treatment outcome. Pregnancy is considered to be immune modulatory state with suppression of natural immune response. Hence altered immunity and physiological hemodynamic down regulate the maternal immune system and makes pregnancy a vulnerable state to COVID-19 infection.<sup>3</sup> Therefore we need to identify specific and sensitive biomarkers and their

role in COVID-19 infection in general as well as in the pregnancy.

## LITERATURE REVIEW

A comprehensive systematic literature review/search of medical electronic databases including PubMed database was performed for relevant data published from March 2020 to July, 2021. Search words were “inflammatory markers”, “COVID-19”, “predictability”, “prognosis”, “pregnancy.” Around 200 review articles published over one year for the general population were reviewed. As regards to the role of inflammatory markers in pregnancy no review article could be searched. After the pursuit of abstract of different articles. Eligible article was used as per authors discretion. The available data was confined mainly to case control and cohort studies. As per the PRISMA guidelines search was narrowed down to 15 such articles after applying inclusion and exclusion criteria as depicted in Figure 1.

### Inclusion and exclusion criteria

Studies included in this review met the following criteria- The studies being case control or cohort design, the studies reporting on inflammatory marker level and patients categorized into severe/critical or non-severe as well as survivor and non-survivor.

Studies excluded in this review if they met the following criteria- Case reports, not in English language, incomplete data on clinical outcome and no measure of inflammatory markers.

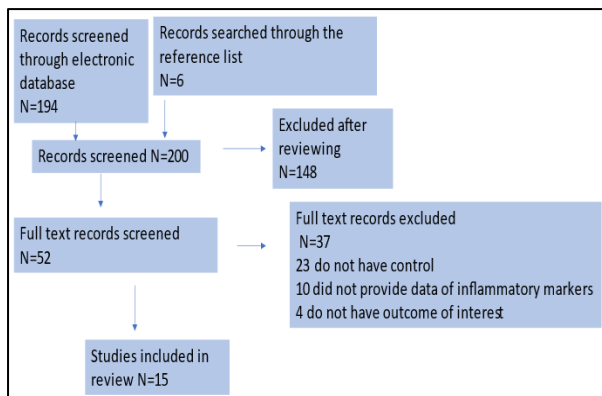


Figure 1: Methods of the study review.

## RESULTS

The electronic data was analysed and the results of these studies elicited that inflammatory marker (interleukin, D Dimer, serum Ferritin, Neutrophil/lymphocyte ratio and Procalcitonin) do correlate with the disease. Higher levels of these markers are associated with the need of oxygen requirement, prolonged hospital stay, ICU admission, intubation and increase mortality in general population. In pregnancy IL6, CRP and Neutrophil/Lymphocyte ratio are

better correlated with the severity of disease than other markers due to altered physiological changes of pregnancy as the studies related to the inflammatory marker are limited to case control and cohort studies, more research is needed in the pregnant patients to draw conclusive results.

## DISCUSSION

The inflammatory response plays a major role in the pathogenesis of COVID-19. Accumulating evidence supports that the unbalanced pro-inflammatory immune response might be involved in the progression towards severe and critical forms of the disease.<sup>4</sup> The various inflammatory markers are as follows-

### Interleukins

Interleukins studied were IL-1 $\beta$ , IL-6, IL-10, IL-17, TNF $\alpha$ . Among various interleukins IL-6 is most extensively studied. IL-6 is produced by immune cells more appropriately by T-helper 17 (TH17) cells during acute phase of inflammation and infection and is also involved in COVID-19 interstitial pneumonia and ARDS. Calculated cut-off level of IL-6 levels (42) pg/ml could pick >90% of patients regarding their risk of severity (AUROC= 0.972). In addition, the proposed threshold value of IL-6 (83 pg/ml) was highly predictive of progression to death (AUROC= 0.94, OR=184) after a median of 3 days. The cut-off for IL-6 in relation to severity of disease reported in different studies are ranging between 24 and 32 pg/ml.<sup>5-7</sup> A meta-analysis based on a total of nine studies included 1426 patients a cut-off value of 55 pg/ml is suggested to identify severe disease while one study has defined IL-6 value and range of 80 pg/ml is associated with need for mechanical ventilation with a median time of 1.5 days.<sup>8</sup> Indeed, the IL-6 values in severe COVID-19 are 10- to 200-fold lower compared to those observed in patients with the hyper-inflammatory phenotype of acute respiratory distress syndrome (ARDS) and septic shock. It has been hypothesized that the hyper-inflammatory response is primarily induced in lung tissues with a high local concentration of IL-6 compared with their circulating plasma levels.<sup>9-14</sup> During pregnancy the levels of IL-6 levels do not vary with each trimester and hence correlate with disease severity in pregnant COVID-19. In contrast IL-2, IL-4 and IL-10 are generally raised in pregnancy to provide immune tolerant microenvironment for conception and hence cannot be relied upon.<sup>15</sup> IL-10 levels are generally increased in pregnancy as it is produced by the placental villous trophoblasts, decidual monocytes and uterine natural killer cells as an adaptive response to prevent early pregnancy loss.<sup>16</sup>

To conclude due to altered milieu in pregnancy, IL-6 is the only cytokine which has some prognostication for severe form of the disease. Inhibition of IL6 may be a novel target for therapeutics for the management of abnormally regulated host responses in COVID-19 patient and high-quality studies of intervention in this field are urgently required.

## CRP

CRP is an acute-phase protein of inflammation produced by the liver and is a marker of bacterial, viral infection and inflammation. Its role as predictive marker of severe forms of the COVID-19 has been proven by several studies. The normal levels of CRP in blood are less than 10 mg/l and rises rapidly within 6 to 8 hrs with highest peak in 48 hours with onset of disease. Half-life of CRP is about 19 hours and its concentration decreases when the inflammation subsides.<sup>17</sup> It binds to phosphocholine expressed on damaged surfaces and activates complement system to modulate phagocytic activity to clear the virus and once the damaged cells are phagocytized the CRP levels fall down. Many studies have found high serum concentration of CRP in patients with SARS-COV-2 positive patients and levels above 26 mg/l are a predictor of severe form of the disease.<sup>18</sup> It has also been observed that patients with low oxygen saturation ( $SpO_2 \leq 90\%$ ) had significantly higher levels of CRP (median 76.5 mg/l) compared with patients with high oxygen saturation ( $SpO_2 > 90\%$ ) (median 12.7 mg/l), indicating that patients with severe lung damage have elevated levels of CRP.<sup>19</sup> The patients who died of COVID-19 had CRP levels which were 100 times higher than the control group, with each unit increase of CRP the rate of mortality increased by 5%.<sup>20</sup> In context of pregnancy; statistically significant levels have been found in severe form of the disease and the elevated CRP concentration were associated with an increased risk of preterm delivery.<sup>21</sup> Its value correlates with the severity of disease in pregnancy and is not altered by the physiological changes of pregnancy.<sup>22</sup> Hence such patients need to be under close scrutiny and need early triaging so as to prevent mortality and morbidity.

## Neutrophil/ lymphocyte ratio

Neutrophil/Lymphocyte ratio is the ratio of absolute neutrophil to absolute lymphocyte count. Neutrophils are increased in inflammation and suggest super added bacterial infection and hyper inflammatory state and decreased lymphocyte count is due to sequestration and apoptosis.<sup>23</sup> The human response to viral infection depends upon T lymphocyte and Natural killer cells. Lymphocytes express ACE2 receptor on their surface and SARS-COV-2 directly causes lysis of the receptors and lymphopenia occurs. The associated cytokine storm cause release of other inflammatory markers (IL-6, 2 and 7, TNF alpha, granulocyte stimulating factor) which further promotes apoptosis. The decrease in T cells results in decreased immunity which could ultimately result in disease progression.<sup>24</sup> It has been demonstrated in studies that N/L ratio had better accuracy compared to total leukocyte count, neutrophil or lymphocyte count and it is less influenced by physiological interference such as that seen with dehydration or physical activity.<sup>25</sup> The cut off range is between 5.9-14 and this range also varies from study to study.<sup>26</sup> The increased N/L has been found associated with severe disease, oxygen requirement, ICU care and development of ARDS. N/L ratio of  $>4$  served a predictor

of severe form of the disease and increased rates of admission to the ICU. Study suggests low lymphocytes in COVID-19 pregnant patients are found to be associated with increased likelihood of receiving oxygen during hospitalization and a better predictor of severe form of the disease.<sup>27</sup> A study suggested that lymphocytes are lower in COVID-19 pregnant patients with associated comorbidities like diabetes and hypertension which makes them more vulnerable to severe form of the disease. Similarly, the neutrophils count has also been found to be raised in COVID-19 pregnant patients with associated comorbidities suggesting probability of severe course of disease in them.<sup>28</sup> Some studies suggest that N/L ratio and leucocytosis are better correlated with disease severity but no significance of lymphopenia.<sup>29</sup> N/L ratio may be a rapid, widely available, useful prognostic factor in the early screening of critical illness in patients with confirmed COVID-19 but in comparison during pregnancy as hemodynamic of pregnancy produce changes in blood counts hence their reliability is uncertain and more studies are needed in deciding cut off in pregnancy.

## Serum Ferritin

Ferritin is a cytosolic protein that stores iron in the body and releases it in a controlled fashion as per our body's demand. Low levels are indicators of iron deficiency anaemia and elevated levels could be related to iron overload. Serum Ferritin also represents as an acute phase reactant and a marker of acute and chronic inflammation. Endotoxins released during infection, upregulate Ferritin production and therefore increased levels are found in acute and chronic inflammatory conditions like chronic kidney disease, rheumatoid arthritis and other autoimmune disorders, acute infection and malignancy.<sup>30</sup> The normal serum Ferritin levels range from 12-300 nanograms/ml for males and 12-200 nanograms for females and levels may vary slightly amongst different laboratories. Its application as a biomarker of inflammation has far presented high importance in the disease progression demonstrated by previous studies in the field.<sup>31</sup> A number of recent studies indicate that patients with COVID-19 have elevated levels of serum Ferritin and increased levels may be a predictor of an acute inflammatory reaction. A study on preliminary predictive criteria for COVID-19 evaluated that the high levels of serum Ferritin observed in the first seven days of hospitalization is a predictor for the cytokine storm syndrome.<sup>32</sup> S. Ferritin levels as a predictor of adverse outcome has shown conflicting results in other studies. A retrospective study reported minimal role of serum Ferritin in predicting ICU admissions, need for ventilatory support and even mortality in COVID-19 patients.<sup>33</sup> Even a systematic review and meta-analysis on data analysis observed that plasma Ferritin had no significant association with the combined outcome or death.<sup>34</sup> On other hand, meta-analysis of 6320 patients by Elshazli et al revealed significantly increased levels of serum Ferritin among non-survived patients compared with survived patients.<sup>35,36</sup> These findings are similar to another meta-analysis, indicating that Ferritin levels could indicate

severe disease and mortality. It has been observed in studies that a mean of 337 among pregnant women was associated with moderate COVID-19 and concluded that SARS-COV-2 leads to increased serum Ferritin levels in pregnancy.<sup>37</sup> COVID-19 pregnant patients are also being speculated but this increase can be partially concealed by the low levels of this compound in pregnancy due to physiological changes of pregnancy.<sup>38</sup> Hence, we need more studies to validate the role of Ferritin in the pregnancy.

### **D-dimer**

D-dimer represents ongoing activation of the haemostatic system. It is normally undetectable in the blood but it is produced when the body is trying to break down a blood clot.<sup>39</sup> The body releases plasmin to break down the clot or thrombus and in this process fibrin degradation products (FDP) are produced, of which one of the fragments is the D-dimer, consisting of pieces of crosslinked fibrin. Therefore, presence of D-dimer indicates increased fibrinolytic activity. The reference concentration of D-Dimer is <0.4 mcg/mL. Importantly, various studies suggest its relation with the novel coronavirus infection and is therefore used to prognosticate the severity of the disease. The basic pathophysiology in relation to COVID-19 pulmonary infection is that the virus causes alveolar damage and results in activation of inflammatory cascade, fibrinolytic activity and elevations of D dimers in COVID 19.<sup>40-42</sup> In review of multiple biomarkers significant coagulation abnormalities were observed in patients with SARS-CoV-2 compared with healthy controls and D-Dimer sensitively correlated with disease severity.<sup>43</sup> In a study it is observed that D-dimer levels greater than one is an independent risk factor for coagulation complications, critical illness and death during hospitalization.<sup>44</sup> As pregnancy is a hypercoagulable state and D Dimers are normally increased in pregnancy specially in the third trimester, levels above 1000U/L have been associated with proper prognosis. The increased D Dimer serves as a guide to start antithrombotic therapy. The published data on the prognostic value of D Dimer in pregnancy are very conflicting due to altered hemodynamic and more studies are needed to come to any conclusion.

### **Lactate dehydrogenase (LDH) levels**

LDH is an intracellular enzyme found in cells of many tissues in the body, especially in the kidneys, skeletal muscle, heart, liver, RBCs, brain, and lungs.<sup>7</sup> LDH was traditionally used as a marker of cardiac damage since the 1960 but abnormal values can result from multiple organ injury, decreased oxygenation, neoplastic conditions, pancreatitis, muscle injury, cell membrane damage, liver and lung diseases.<sup>45,46</sup> Since LDH is present in lung tissue patients with severe COVID-19 infections can be expected to release greater amounts of LDH in the circulation. Various studies have shown that LDH levels are higher in severe COVID-19 patients compared with non-severe.<sup>47</sup> LDH cut off ranged from 240 to 253U/l. The best LDH cut

off for death prediction was 731. In a study elevated LDH levels are found in 95% of non-surviving compared to 60% survivors and value more than 6-fold is related to severity and more than 16-fold to mortality.<sup>48</sup> Various authors found elevated levels of LDH in COVID-19 pregnant women in their study and prognostic significance.<sup>49</sup> Pregnancy itself does not affect the LDH level but its value is observed to be high in preeclampsia and eclampsia patients. In regard to pregnancy more studies are needed to establish the prognostic value of LDH in assessing severity of the disease.

### **Procalcitonin**

Procalcitonin is produced by parathyroid gland and it is produced by other tissues in bacterial sepsis. There are sequence homologies between Procalcitonin and other cytokines and this supports the hypothesis that it could be a marker of inflammation. Generally, the viral infection does not cause any increase in their values. Its value is increased by IL6, TNF alpha and inhibited by IFN gamma. The reference value below 0.1 in adults is considered normal and levels more than 0.25 can indicate infection. Raised Procalcitonin in patients of COVID-19 patients signifies superadded bacterial infection and is an indicator to start antibacterial therapy to prevent serious superadded complications.<sup>50</sup> The Procalcitonin levels are not altered by physiological alteration of pregnancy as well as can be utilized as a marker of sepsis in this subset of the population also.<sup>51</sup>

### **Evolving markers**

Liver function test are also found deranged and signifying liver injury resulting from COVID-19. Most specifically Alanine Aminotransferase (ALT) is specific for liver injury and levels above 40 U/L were found in more than 30% of COVID-19 at the time of admission.<sup>52</sup> But in contrast authors have observed normal levels in COVID-19 pregnant women. COVID-19 patients with associated hypertension have been found to have higher level of liver function derangement than the control group.<sup>53</sup>

Kidney function test (creatinine measurement) is raised in 11 to 15% of COVID-19 patients and signify acute kidney injury but no such correlation was found in pregnant COVID-19 patients.<sup>54</sup>

Troponin levels are also found to be raised in 15 to 44% of COVID-19 patients.<sup>55</sup> Hypoalbuminemia (albumin level <35 g/l) has been found independent marker of severe injury in COVID-19 patients.<sup>56</sup> Studies with regard to COVID-19 pregnant women and hypoalbuminemia and troponin T levels are under evaluation.

## **CONCLUSION**

Inflammatory markers have established their importance in the management of COVID-19 patients. IL-6, CRP, Neutrophil/Lymphocyte ratio, LDH, and serum Ferritin



are thoroughly studied in general population. In regards to pregnancy IL-6, CRP, N/L ratio are less altered by the physiological changes of pregnancy hence can be used in forecasting severity of the disease progression. The data regarding the role of inflammatory markers in general population has been derived from various reviews and meta-analysis and their role is well established in general population but with regard to pregnancy more studies are needed to arrive to any conclusive recommendations.

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