Original Article

Inflammatory Markers in Expectant COVID-19 Positive Patients: A Relationship with Clinical Severity in a Tertiary Care Referral Facility

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Abstract

Background: SARS-Co-V2 infection which was declared as a pandemic by the WHO has caused significant impact on morbidity and mortality to the mother and the fetus, especially the delta variant of the COVID-19. Hence it is important to identify the subgroup of women who are prone to adverse complications and prevent maternal and perinatal mortality. Inflammatory biomarker is one such tool to identify the high-risk expectant mothers.

Methods and Results: A total of 158 patients were identified in this retrospective study and they were classified based on the clinical signs and symptoms as per the society of maternal fetal medicine. 96.2% belonged to the non-severe group and 3.8% belonged to the severe infection group. Cough and fever were the most common symptoms. Inflammatory markers which were done on admission were correlated with the clinical disease severity. The difference in mean values of CRP, LDH and ferritin between the severe and non-severe group was significant statistically. The markers IL-6 and d-dimer were raised but did not correlate with disease severity. Neutrophil lymphocyte ratio (NLR) calculated from the blood counts was abnormal in all the patients in the severe group and statistically significant. Overall, the maternal outcome was good and maternal mortality rate was 1.89% (3/158). Neonatal outcome was good with stillbirth rate of 3.16% which was higher when compared to non-covid stillbirth rates (0.5%).

Conclusion: inflammatory biomarkers like CRP and LDH are sensitive in predicting the adverse maternal fetal outcome. NLR is a simple ratio that has a good positive predictive value in identifying the need for more vigilant monitoring in expectant COVID-19 positive patients.

Keywords: COVID-19 in pregnancy, inflammatory markers, C-reactive protein, Neutrophil Lymphocyte ratio(NLR), Stillbirth.

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Introduction

SARS-CoV2 which causes coronavirus disease (covid-19), a respiratory infectious disease is a novel coronavirus discovered in 2019. It was first reported in December 2019 in Wuhan: China[1]. The disease soon spread globally and was declared as a pandemic by the WHO.[2] Pregnancy is regarded as a high-risk state in the context of infectious diseases, as the immunological changes in pregnancy may increase the susceptibility to infection. The novel coronavirus did not cause much impact on pregnancy during the first wave , whereas the second wave with a predominant delta variant has caused a significant impact on pregnant women leading to increased mortality and morbidity to both mother and the fetus. Hence identifying the disease severity and its correlation with the blood markers will help us deal with COVID-19 patients and improve our treatment methods in the future.

Aims and objectives:

1. Identification and classification of pregnant COVID-19-positive patients according to the disease severity based on the symptoms and signs.
2. Correlation of the clinical severity of the disease with relation to the rise in inflammatory markers.

Materials and Methodology

The study was a retrospective observational study and included all pregnant women who were tested COVID-19 positive by RT-PCR and admitted to our hospital which is a tertiary care center and a district referral center for COVID-19 patients. The study included the patients admitted between the period of March 2021 and August 2021. Ethical committee approval to carry out the study was obtained from the institutional ethics committee. (21/253).

The patients were listed from the hospital information system and the patient details such as name, age, parity, gestational age, symptoms if present on admission, and examination findings at admission were collected from the patient information system in the hospital database. The patients were classified according to disease severity based on admission findings into asymptomatic, mild, moderate, severe, and critical as per Society of maternal-fetal Medicine (SMFM)guidelines.[3]

- Asymptomatic disease or presumptive infection is defined as a positive COVID-19 test result with no symptoms.
- Mild disease is defined as flu-like symptoms, such as fever, cough, myalgias, and anosmia without dyspnea, shortness of breath, or abnormal chest imaging.
- Moderate disease is defined by evidence of lower respiratory tract disease with clinical assessment (dyspnea, pneumonia on imaging, abnormal blood gas results, refractory fever of 39.0 C /102.2 F or greater not alleviated with acetaminophen while maintaining an oxygen saturation of greater than or equal to 94% on room air at sea level.
- Severe disease is defined by a respiratory rate greater than 30 breaths per minute (bpm), hypoxia with oxygen saturation less than 94%, a ratio of arterial partial pressure of oxygen to a fraction of inspired oxygen of less than 300, or greater than 50% lung involvement on imaging.
- Critical disease is defined as multi-organ failure or dysfunction, shock, or respiratory failure requiring mechanical ventilation or high-flow nasal cannula.

Inflammatory markers like ferritin, CRP, LDH, and IL-6 which were sent on the day of admission were noted. NLR (neutrophil-lymphocyte ratio) which is easily available from the complete hemogram by dividing the absolute neutrophil count and the absolute lymphocyte count was also included as a biomarker in the study. Blood collection was performed by peripheral venipuncture, in which 10 mL of blood was collected for analysis. D-dimer was measured using the Enzyme-Linked Fluorescent Assay (ELFA) technique, while CRP was measured by turbidimetry. Ferritin was measured using the electro-chemiluminescence technique. The normal values for these biomarkers were taken as per the reference range given by our NABL-accredited laboratory. The patients were followed up till discharge and the maternal outcomes were tabulated in the Excel sheet. If the pregnancy was terminated, then the mode of delivery and fetal outcomes were included in the study.

The correlation between the rise in inflammatory markers and the disease severity was analyzed. Statistical analysis was done using the chi-square test and t-test and a P value of < 0.05 was considered significant.

Results

A total of 158 patients were included in the study who were tested positive for COVID-19 and admitted to the obstetrics and gynecology department between March 2021 and August 2021. The patients were in the age group ranging from 20 and 38 years with a mean age of 27.7 (SD 4.26). Primigravida constituted 56.3% whereas multigravida was 43.6% of the total. The gestational age of these women ranged between 6 weeks to 40 weeks with a mean gestational age of 30 weeks (SD - 8.61). Of them, 65.8% of women were in the third trimester 25.3% were in the second trimester of pregnancy. 8 patients were in the first trimester and two were ectopic pregnancies (Table 1) On analysis of the symptoms present at admission, the most common symptoms present were cough (48.7%) followed by fever (41.8%) and others as shown in Fig 1

Patients were classified according to SMFM guidelines according to the symptoms and signs present at admission. The classification and number of patients in each group are shown in Table 2. Asymptomatic, mild, and moderate were regrouped into the non-severe infection group (96.2%), and severe and critical were grouped into the severe infection group (3.8%). High-resolution Computerized tomography (HRCT) was done in 21(13.3%) of the patients. It was done only in patients who had saturation falls or required ICU admission as per hospital protocol. A total of 10 (6.32%) patients were admitted to ICU and intubation was needed for 4 of them. 17(10.7%) patients required oxygen support via mask or NIV, 35(22.2%) received steroids and remdesivir was given to 18 (11.4%) of the patients as per hospital protocol.

Inflammatory markers which were sent on the day of admission were collected and analyzed. The mean value of C Reactive protein which is one of the important acute phase inflammatory markers was compared between the severe infection group and non-severe infection group. The mean CRP in the severe group was 11.2 with an SD of 8.77 and the mean value in the non-severe group was 1.65 with an SD of 2.75 and the difference was statistically significant. (P < 0.001). table 3

Ferritin level which is also an acute phase reactant was analyzed and the mean value among the non-severe group was 86.3 and among the severe group was 208.6 and the difference in mean values is statistically significant. (P = 0.006). The values of LDH among the severe group were raised significantly, the mean being 483.2 and the mean LDH among the non-severe group was 244.3 and the difference is statistically significant (<0.01).

The difference in mean values of Interleukin-6 and d-dimer was not statistically significant between the two groups. The mean values of all the inflammatory markers in severe and non-severe groups along with standard deviation and P values are shown in Table 3.

The neutrophil-lymphocyte ratio, which was calculated from the complete hemogram, was abnormal in all the patients in the severe group. The mean neutrophil-lymphocyte ratio (NLR) in the non-severe group was 4.35 and in the severe group, it was 10.41. Considering the normal NLR in pregnancy as </=3, normal and abnormal NLR was tabulated in a 2x2 table between the severe and non-severe group, and it was found that all the patients in the severe group had abnormal NLR as shown in Table 4.and the difference was statistically significant (P - 0.014)

Regarding the pregnancy outcome 76 patients out of the 158 delivered during the admission period. 64 patients had cesarean section and 12 patients delivered vaginally. Intrauterine fetal demise was seen in 5 cases (3.16%). There were no associated comorbidities in all these cases. Neonatal outcome was good in the rest of the cases.

Overall Maternal outcome was good with a mortality rate of 1.89%. There was no mortality in the non-severe group and three out of six patients had mortality in the severe group as shown in table 5. The other three patients in the severe group had a good outcome (recovered) after a prolonged stay in the ICU and all required steroids, remdesivir, oxygen, and ventilator support.

Table1: Characteristic distribution of pregnancy with COVID-19

		N	Percentage %
Maternal age	< or = 20	6	3.79%
	21 to 25	42	26.58%
	26 to 30	72	45.56%
	31 to 35	26	16.45%
	36 to 38	12	7.59%
Mean age	27.7	4.263(SD)	
Parity	Primigravida	89	56..35
	Multigravida	69	43.65
Gestational age	First trimester	8	5.06%
	Second trimester	40	25.3%
	Third trimester	110	69.6%
Maternal co-morbidities	Preeclampsia &hypertension	7	
	Anemia	12	
	Diabetes	24	
	APLA	2	
	Heart disease	2	
	Hypothyroid	13	
	Bronchial asthma	2	
	Obesity	2	
	Twins	3	
	Ectopic	2	

Table 2: Classification of COVID-19 patients as per society of maternal fetal medicine guidelines

Classification	SMFM classification	N	Percent%
Non severe	Asymptomatic	47	29.7
	Mild	87	55.1
	Moderate	18	11.4
		152	96.2
severe	Severe	4	2.5
	Critical	2	1.3
		6	3.8
	Total	158	100.0

Table 3: Inflammatory markers in severe and non-severe group

Inflammatory marker	Mean value in non-severe group(152)	Standard deviation	Mean value in Severe group(6)	St.andard deviation	P Value
CRP	1.656	2.75	11.23	8.77	<0.001 *
Ferritin	86.27	100.53	208.6	197.26	0.006 *
LDH	244.32	122.27	483.17	178.97	<0.001*
IL-6	43.48	243.58	83.71	91.71	0.688
D DIMER	1.93	1.77	2.50	1.20	0.439

Table 4: Neutrophil lymphocyte ratio (NLR) in severe and non-severe covid-19 pregnant women

Classification	Normal NLR (</= 3)	Abnormal NLR(>3)
Severe group (N=6)	0	6(100%)
Non-severe group (N=152)	78(51.3%)	74 (48.6%)

P = 0.014*

Table 5: Maternal and fetal outcome

Classification	No complication	Complication requiring ICU	Maternal death	Intrauterine fetal death	Neonatal death
Non-severe	147	5	0	4	nil
Severe	0	6	3	1	nil

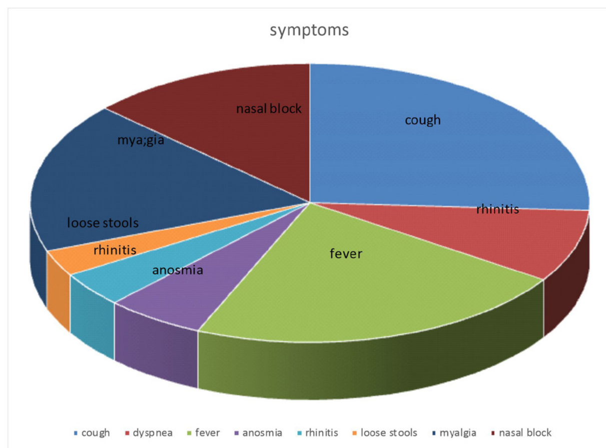

Figure 1: symptoms present on admission.

Discussion

Pregnant patients are more vulnerable to all kinds of infection just like elderly, immunocompromised, and cancer patients. Immunological changes in pregnancy may increase the susceptibility to infections and their associated complications.[4] The management of COVID-19-infected pregnant women has been a challenge for the treating obstetricians. Pregnant women infected with COVID-19 are more prone to develop respiratory failure and obstetric complications like miscarriage, preterm delivery, fetal growth restriction, and intrauterine death.

It is important to identify the women who are likely to develop such complications. During the pandemic, certain inflammatory biomarkers in addition to clinical assessment helped for risk stratification.

C Reactive protein is an acute phase serum reactant and its concentration rapidly increases in response to tissue trauma and inflammation.[8].In the present study, among the inflammatory biomarkers CRP, LDH showed a statistically highly significant P value ($p<0.001$) in correlating the severity of the disease which was similar to the study done by Andrea et al,[9] which concluded that C Reactive protein is the inflammatory biomarker that better mirrors the course of the disease whereas d-dimer and ferritin are not reliable predictors of the poor outcome. Similarly in the study done by Lili et al,[10] various biomarkers were compared between asymptomatic, mild, and severe groups. The only variable that had significant differences between the groups was C-reactive protein. In the study done by Kim et al,[6] among the tests performed immediately after hospitalization, the maternal serum ferritin and CRP levels showed statistically significant differences between the two groups with higher levels in the group with adverse outcomes. They concluded that an increase in CRP or ferritin levels indicates a high possibility of adverse outcomes and therefore an active treatment plan should be established in such cases.[6,10]

Ferritin is an intracellular protein, that has a pivotal role in immune dysregulation. Hyperferritinemia has been associated with higher disease severity and adverse clinical outcomes in COVID-19, including mortality. In a cross-sectional study done in northern Brazil, the concentrations of D-dimer ($p = 0.0122$) and ferritin ($p \leq 0.0001$) were significantly higher among pregnant women with COVID-19, especially among those hospitalized in the ICU.11 Similar to this finding we had a mean ferritin level of 86.2 in the non-severe group whereas the mean ferritin in the severe group was 208.6 p value - 0.006. This was supported by the research done by Lili et al and

Kim et al 6,10 which concluded that ferritin and CRP levels are associated with poor prognosis and can predict adverse outcomes in women with COVID-19.

D dimer acts as a global indicator of coagulation and activation of the fibrinolytic process. As the activity of plasmin increases in the blood, an increase in d-dimer levels is observed.[12,13]In a systematic review done by Mehrdad Rostami et al, they concluded that D-dimer concentration in the early stages of COVID-19 disease in the general population, a 3 to 4-fold increase is linked to poor prognosis.[14] Another meta-analysis and systematic review done by Muhammad et al showed pooled results of all studies revealed that D-dimer concentrations were significantly higher in patients with more severe COVID-19 disease.[15] Although few studies found a positive correlation between increased d dimer with poor prognosis for the patients, most of the studies show that d dimer is not reliable, as the specificity of D dimer is significantly reduced during pregnancy.[13,16], which is evidenced by the study done by Merve et al [12] where there was no significant difference in D-dimer levels when it was compared with pregnant patients with covid-19 and those without the disease. Similarly, a study done by Andrea et al [9] concluded that d-dimer and ferritin are not reliable predictors of poor outcomes. Hence D-dimer cannot be used as a poor prognostic criterion in pregnant women with COVID-19 infection. Similarly, in our study, the mean D-dimer values between the severe and non-severe groups were almost similar and the P value was not statistically significant.

COVID-19 infection seems to have an impact on the cytokine profile of pregnant women varying according to pregnancy trimesters and cytokine levels seem to be correlated with disease severity. Atakanel al[17] in a prospective study found Statistically significant positive correlations for IFN γ and IL-6 with disease severity ($r = 0.41$ and $p < 0.001$ for IFN γ and $r = 0.58$ and $p < 0.001$ for IL-6). In our study, though there is a significant rise in the levels of IL-6 in COVID-19 pregnant women, there is no statistically significant difference between the increase in severe and non-severe groups. (p-value - 0.688)

The neutrophil-to-lymphocyte ratio, calculated as a simple ratio between the neutrophil and the lymphocyte counts measured in the peripheral blood, is a biomarker that conjugated two faces of the immune system. It is a marker of inflammation that predicts the severity and mortality due to disease at hospital admission. It has also been suggested that it can predict endothelial damage associated with inflammation.[18] NLR is the most significant factor in the incidence of disease severity and has a significant predictive value. In a study done by Dorina Supak et al,[19] statistical analysis showed that NLR values were significantly higher in patients with fatal COVID-19 compared to those who survived the disease. The advantage of the usage of the NLR as a marker of COVID-19 severity is that it can be easily applied in low-resource settings.

In our study, we found that NLR levels of all the patients in the severe group who were critically ill were abnormal and the values were significantly higher than the patients in the non-severe group. These findings were similar to the study done by Xu et al[20] who concluded that NLR and procalcitonin levels in severe and critically ill patients were significantly higher in patients with moderate symptoms. A study conducted by Eke et al[21] found that an increase in NLR was an independent risk factor for the need for ICU care. The study obtained a cut-off value of >5.3 in predicting the need for ICU care (with 72.7% sensitivity and 91.1% specificity). They concluded that NLR in COVID-19 patients is a cheap, fast, easy, and very reliable test in determining the severity of SARS-CoV and predicting the need for ICU care.[21,22]

In our study though the rate of ICU admission was higher (6.35%) when compared to the literature, the maternal mortality rate was almost similar (1.89%) In a large comprehensive literature review by Ernesto Antonio et al(8 studies including 10966 cases) maternal ICU admission was 3.7%, respiratory support was required in 5.25%, and 1.13% maternal mortality rate overall.[23] Overall covid 19 infections during pregnancy does not seem to be worse than in the general population but the rate of ICU admission was slightly higher (1.5% vs 0.9%) The need for mechanical ventilation was not higher as compared to non-pregnant women.

Stillbirth is a recognized complication of COVID-19 in pregnant women that has recently been demonstrated to be caused by SARS-CoV-2 infection of the placenta. Multiple global studies have

found that massive perivillous fibrin deposition, chronic histiocytic intervillositis, and trophoblast necrosis,collectively termed SARS-CoV-2 placentitis, can cause severe and diffuse placental parenchymal destruction that can affect >75% of the placenta, effectively rendering it incapable of performing its function of oxygenating the fetus and leading to stillbirth and neonatal death via malperfusion and placental insufficiency.

In the study done by Carla L. DeSisto et al,[24] in the United States, women with COVID-19 were at increased risk for stillbirth compared with women without COVID-19 (adjusted relative risk [aRR] = 1.90; 95% CI = 1.69–2.15). The magnitude of association was higher during the period of SARS-CoV-2 B.1.617.2 (Delta) variant predominance than during the pre-Delta period. The rates of stillbirth in women without COVID-19 at delivery in this analysis (0.64% overall) were similar to the known pre-pandemic stillbirth rate of 0.59%.[25] However, 0.98% of COVID–19 affected deliveries pre-Delta and 2.70% during the Delta period resulted in stillbirth. The rate of stillbirth or intrauterine demise in the present study is 3.18%. Analysis of the placenta of these fetuses shows extensive maternal vascular malperfusion in all cases and acute deciduitis and intervillous thrombus in two of the five cases. It shows the thromboembolic enhancing effect of covid 19 as the cause of intrauterine demise in such cases. In a large study done in Belgium the stillbirth rate was 9.5%. among them, 17.4%(4/23) were certainly attributable to SARS-CoV infection.[26]There is now mounting evidence that SARS-CoV-2 infection and adverse fetal events are associated.[24,26]

Conclusion

To conclude, in our study significant elevation of CRP, LDH, and ferritin was seen in both groups with high significance in the severe group. The results imply that even in the non-severe group elevation of these markers indicates a high probability of adverse outcomes irrespective of the symptoms. Hence it is prudent to be more vigilant in monitoring and treatment of these patients. Also, there is enough evidence that SARS-CoV causes perinatal mortality, hence it is prudent to monitor and treat the pregnant patients with this infection more closely.

Conflict of interest: none

Source of funding: self

Ethical clearance: obtained from the institutional ethics committee PSG Institute of medical sciences and research, (ethical approval number 21/253)

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