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Association of Maternal Outcome with Inflammatory Markers in 2nd Wave of Covid Pandemic

Dr. Berkha Garg*, [1]Dr. Yasmeen Farooq, [2]Dr. Astha Lalwani, [3]Dr. Rehana Najam
[1]Resident, [1]Assistant Professor, [2]Professor, [3]Head of Department,
Department of Obstetrics and Gynecology, Teerthanker Mahaveer Medical College, Moradabad, Uttar Pradesh

***Corresponding Author:**
Dr. Berkha Garg
Resident, Department of Obstetrics and Gynecology, Teerthanker Mahaveer Medical College, Moradabad, Uttar Pradesh

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Abstract

Background: Pandemic has affected pregnant patients directly through COVID-19 infection and indirectly through disrupting maternal wellbeing services. Pathophysiology of disease in the pregnant women still needs to be explored as feto maternal outcome remains unpredictable. In the present retrospective study, we assessed the adverse maternal outcome in COVID 19 positive pregnant patients in 2nd wave of covid and their correlation with inflammatory markers.

Method: A total 50 pregnant women infected with COVID-19 virus (asymptomatic, mild, moderate or severe) were included in my study.Affected women who were admitted in hospital were enrolled from March 11 to Dec 11, 2021; this period corresponds to the first 9 months of the SARS-CoV-2 pandemic. COVID-19 testing to detect SARS-CoV-2 infection was performed by nasopharyngeal swab and quantitative polymerase-chain-reaction test.

Results: The majority of the studied patients were having BMI below 25.0 (48.0%). 70.0% of the total studied women were multi gravid and 76.0% were having parity greater than one. The significant elevated levels of TLC, D-dimer, C-Reactive-Protein, LDH, S. ferritin, CK-MB, interleukin-6, urea, and sodium were related with severe, and fatal cases of COVID-19. By using the Pearson correlation, we observed the laboratory markers did not show any significant correlation with ICU admission, Cesarean delivery and duration of hospital stay ($p>0.05$). Negative sign indicates the inversely association.

Conclusion: Significant elevated levels of TLC, D-dimer, C-Reactive-Protein, LDH, S. ferritin, CK-MB, interleukin-6, urea, and sodium were related with severe, and fatal cases of COVID-19.

Keywords: COVID-19; SARS-CoV-2, Asymptomatic, Maternal Outcome

Introduction

SARS-CoV-2 infection has rapidly become a public health emergency of international concern culminating in the WHO declaration of the pandemic. Scientists from all over the world are investigating the pathogenetic mechanisms of SARS-CoV-2 action, but little is known about particular groups of patients. Clinical manifestation of COVID-19 can be characterized by mild or asymptomatic infection of the upper respiratory tract, infection of the lower-respiratory tract with or without life-threatening pneumonia and eventually acute respiratory distress syndrome.

The pandemic directly affected the pregnant patients through infection COVID-19 and indirectly via unsettling maternal health services. Pathophysiology of disease in the pregnant women still requires to explored as feto maternal outcome remains serious.

The problem has been further added by merciless second wave in our country, India.During first wave, most studies reported mild or asymptomatic infection

in the pregnant women with very low mortality-rate, contrary to this, the second wave has huge death-toll in Indian population and other developing countries owing probably to high rate of transmission, and quick emergence of new viral strains. In South Africa, 22.70% increase in the maternal mortality, 4.80% increase in the neonatal mortality, and 3.40% increase in the perinatal mortality has been reported. India also experienced 23.0% increase instead of 5.50% annual decline in the ratio of maternal mortality during pandemic, which must draw urgent consideration of policymakers.The uneven impact of COVID 19 on maternal, and the perinatal outcome has raised in two waves world-wide and between the high-income nations, and lower-middle income countries.

During pregnancy, the immune system undergoes relevant changes, and the immunological shifts that occur in pregnancy that are partially related to changes in hormonal levels. The immune system of pregnant woman is characterized by an anti-inflammatory immunological tolerance, and for this reason, many auto-immune diseases go into diminution, only to flicker again in early postpartum period. Clearly, this could leave the mother more susceptible to viral infections, as a Th1 response better helps to contrast viruses, even if little is known about the response to SARS-CoV-2.

Different laboratory markers are implicated as an indicator of disease severity, progression and outcome. The deranged cell counts, such as polycythemia, leukopenia, anemia, and leukocytosis with the neutrophil predominance, and reduced platelet count were found related with severe disease, and worse outcome in the hospitalized patients. Similarly raised liver enzymes, and bilirubin levels were recognized in severe, and critical patients.11

Raised inflammatory response as manifested by the raised laboratory values of different interleukins, and C-reactive proteins were also reported. In addition, the raised coagulation markers such as fibrinogen, and prothrombin time were identified in severe, and critical patients.12

Imbalance in electrolyte in both the directions, hypo and hyper levels were reported for potassium, sodium, and calcium levels in patients with severe disease, and worse outcome; hypothesized to the result from effect of disease on body system, or medication side effects.

Since laboratory medicine has always supported clinical decision making in various infectious diseases, it is very important to evaluate the ability of laboratory-derived biomarkers to facilitate risk stratification of COVID-19 disease in pregnant women. Therefore, in the present retrospective study, we evaluated the adverse maternal outcome in COVID 19 positive pregnant patients in 2nd wave of covid and their correlation with inflammatory markers.

Material & Methods:

This retrospective study was performed at the TMU, Moradabad after receiving the ethical approval from Institutional Review Board. A total 50 COVID-19 positive pregnant women (asymptomatic/ mild, moderate or severe) were included in my study. Consecutive pregnant women having COVID-19 admitted in hospital were enrolled from March 11 to Dec 11, 2021; this period corresponds to the first 9 months of the SARS-CoV-2 pandemic. COVID-19 testing to detect SARS-CoV-2 infection was performed by nasopharyngeal swab and quantitative polymerase-chain-reaction test.

Asymptomatic: An asymptomatic laboratory-confirmed case is a person infected with COVID-19 who does not develop clinical symptoms and chest imaging findings.

Mild or moderate disease: Mild or moderate clinical features. Chest imaging showed mild pneumonia manifestation.

Severe/ Critical disease: defined as respiratory rate of ≥30minute, dyspnea, blood oxygen saturation of ≤93%, partial pressure of the arterial oxygen to fraction of an inspired oxygen ratio of <300, and lung infiltrates on chest X-ray; and critical disease was described as septic shock, respiratory failure, and multiple organ failure.

Treatment given was recorded – anti-inflammatory or immunomodulators, anticoagulants (ENOXAPARIN, LMWH, antivirals and plasma therapy).

Maternal outcomes in terms of ARDS, pneumonia, pulmonary edema, pulmonary thromboembolism, venous thromboembolism, disseminated intravascular coagulation, myocardial infarction, maternal intensive care unit admission, need for mechanical ventilation, septic shock, MODS, Supplemental oxygen, intrauterine fetal death, maternal death were seen.

Volume 5, Issue 6; November-December 2022; Page No 476-483

Statistical Analysis:

Data was recorded on a predesigned Performa and managed in a Microsoft Excel spreadsheet. The data obtained were analyzed using SPSS software version 20.0 for Windows (SPSS, Chicago, IL). Categorical data are presented as the percent frequency occurrence. To test the association / difference in proportions between the variables, Chi-square test / Fisher exact test was used. The means of quantitative variables were compared using among One Way ANOVA test. P value <0.05 was considered as statistically significant.

Results:

The severity of COVID-19 was assessed as per Ministry of Health, and Family Welfare (MOHFW) guidelines, Government of India. It was observed that 20 (40.0%) studied patients were in mild group, moderate group 16 (32.0%) and rest 14 (28.0%) pregnant women were showing the Severe/Critical group COVID-19.

In present study majority of patients were of age above 30 years (68.0%) while 32.0% of them were below 30 years of age. The majority of patients were having BMI below 25.0 (48.0%). 70.0% of the total studied women were multi gravid and 76.0% were having parity greater than one. [Table 1]

In this research it was found that the significant elevated levels of TLC, D-dimer, C-Reactive-Protein, LDH, S. ferritin, CK-MB, interleukin-6, urea, and sodium were associated with severe, and very fatal COVID-19 cases. [Table 2]

ICU admission, need for oxygen and ventilatory support, rate of cesarean delivery, and length of hospital stay were comparatively higher in severe/critical cases followed by moderately affected covid-19 positive pregnant women. There was no maternal mortality reported in present study. [Table 3]

By using the Pearson correlation we observed the laboratory markers did not show any significant correlation with ICU admission, Cesarean delivery and period of hospitalization ($p>0.05$). Negative sign indicates the inversely association. [Table 4]

Apgar Score 5min<7 and Covid status in baby were comparatively higher in severe/critical cases of covid-19 positive pregnant women but no effect on the birth weight of the neonates were noted. There was no neonatal mortality in this study. [Table 3] By using the Pearson correlation we observed that only CPK was significantly associated with birth weight; while other laboratory markers did not show any correlation with APGAR score, birth weight and NICU admission ($p>0.05$). Negative sign indicates inverse association. [Table 4].

Table 1: Demographic characteristics of studied cases:

		Frequency (n=50)	Percentage
Maternal age (Years)	**≤30**	16	32.0%
	>30	34	68.0%
Pre-pregnancy BMI (kg/m^2)	**Normal BMI (<25.0)**	23	46.0%
	Overweight (25.0-30.0)	24	48.0%
	Obese (>30)	3	6.0%
Gravidity	**Prim-gravida**	15	30.0%
	Multi-gravida	35	70.0%
Parity	**One**	12	24.0%
	Greater than one	38	76.0%

Table 2: Distribution of Laboratory findings

Volume 5, Issue 6; November-December 2022; Page No 476-483

	Group			P value*
	Mild	Moderate (n=105)	Severe/Critical (n=105)	
Haemoglobin (gm%)	12.54±1.69	12.17±1.53	11.77±2.02	0.488
TLC (10^9/L)	7.15±2.35	12.61±4.52	22.30±12.70	**<0.001**
D-DIMER (ng/mL)	430.95±136.33	474.50±208.02	788.06±364.08	**<0.001**
CRP (mg/L)	40.95±52.27	53.32±39.22	101.62±56.41	**0.003**
LDH (U/L)	217.30±85.60	307.25±58.78	336.79±97.85	**<0.001**
S. Ferritin (ng/ml)	286.30±155.94	806.93±543.41	1099±831.30	**<0.001**
IL6 (pg/mL)	7.323±3.61	11.90±7.78	18.96±14.00	**0.002**
Urea (mg/dl)	18.95±8.80	30.00±11.72	31.1417.72	**0.011**
Creatinine (mg/dl)	1.01±0.39	1.10±0.13	1.24±0.43	0.169
Sodium (mEq/L)	138.19±4.56	136.80±3.65	132.36±4.96	**0.002**
Potassium (mmol/L)	4.00±0.30	4.13±0.48	4.23±1.06	0.585

***One Way ANOVA test**

Table 3: Maternal outcomes stratified by disease severity

		Group		
		Mild (n=20)	Moderate (n=16)	Severe/Critical (n=14)
Maternal outcomes	**ICU admission**	0 (0.0%)	2 (12.5%)	4 (28.57)
	Oxygen support	0 (0.0%)	1 (6.25%)	3 (21.43)
	Ventilator	0 (0.0%)	0 (0.0%)	2 (14.29%)
	Length of stay (days) (Range)	10-14	15-20	>20
	Normal delivery	14 (71.4%)	9 (56.25%)	6 (42.76%)
	Maternal mortality	0 (0.0%)	0 (0.0%)	0 (0.0%)
Neonatal outcomes	**Apgar Score 5min <7**	0 (0.0%)	1 (6.25%)	3 (21.43%)
	LBW <2.5Kg	4 (20.0%)	5 (31.25%)	4 (28.57)
	NICU admission	2 (28.6%)	3 (33.3%)	3 (60.0%)
	Covid status in baby	0 (0.0%)	0 (0.0%)	1 (20.0%)
	Neonatal Mortality	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table 4: Pearson correlation between maternal outcome with laboratory parameters

	ICU Admission	Caesarean section	Duration of hospital stay

Volume 5, Issue 6; November-December 2022; Page No 476-483

TLC	**Pearson Correlation**	-0.245	0.053	-0.031
	P value	0.086	0.715	0.833
D-DIMER	**Pearson Correlation**	-0.052	0.073	-0.014
	P value	0.722	0.615	0.921
CRP	**Pearson Correlation**	-00.197	-0.213	-0.024
	P value	0.169	0.138	0.870
LDH	**Pearson Correlation**	-0.032	0.101	-0.241
	P value	0.827	0.486	0.092
S. FERRITIN	**Pearson Correlation**	0.043	-0.089	-0.124
	P value	0.764	0.539	0.390
IL-6	**Pearson Correlation**	0.032	-0.087	-0.005
	P value	0.825	0.548	0.972
Urea	**Pearson Correlation**	-0.092	-0.268	0.025
	P value	0.527	0.060	0.865
Creatinine	**Pearson Correlation**	-0.015	0.155	-0.142
	P value	0.918	0.283	0.326
Sodium	**Pearson Correlation**	-0.197	-0.217	0.042
	P value	0.170	0.129	0.771
Potassium	**Pearson Correlation**	0.035	-0.115	0.234
	P value	0.811	0.428	0.101

Pearson correlation between neonatal outcome with laboratory parameters

		APGAR Score	**Birth Weight**	**NICU**
TLC	**Pearson Correlation**	0.060	0.264	-0.142
	Sig. (2-tailed)	0.681	0.064	0.326
D-DIMER	**Pearson Correlation**	0.036	-0.162	-0.034
	Sig. (2-tailed)	0.804	0.262	0.815
CRP	**Pearson Correlation**	0.009	-0.043	-0.096
	Sig. (2-tailed)	0.950	0.769	0.508
LDH	**Pearson Correlation**	0.250	-0.012	-0.128
	Sig. (2-tailed)	0.079	0.933	.374
S. FERRITIN	**Pearson Correlation**	0.202	0.097	-0.060
	Sig. (2-tailed)	0.160	0.502	0.678
IL-6	**Pearson Correlation**	-0.148	-0.110	-.0216

Volume 5, Issue 6; November-December 2022; Page No 476-483

	Sig. (2-tailed)	0.305	0.447	0.132
Urea	**Pearson Correlation**	-0.001	-0.037	-0.105
	Sig. (2-tailed)	0.996	0.796	0.468
Creatinine	**Pearson Correlation**	0.085	0.464**	0.033
	Sig. (2-tailed)	0.559	**<0.001**	0.819
Sodium	**Pearson Correlation**	-0.226	-0.012	-0.053
	Sig. (2-tailed)	0.115	0.934	0.713
Potassium	**Pearson Correlation**	-0.163	-0.233	0.010
	Sig. (2-tailed)	0.258	0.103	0.943
****. significant correlation at the 0.01 level (2-tailed)**				
***. significant correlation at the 0.05 level (2-tailed)**				

Discussion:

During first wave, most studies reported asymptomatic, or very mild infection in the pregnant patients with a low-mortality rate, contrary to first, second wave has a huge death-toll in India, and the other nations probably owing to high transmission-rate, and quick emergence of the new viral strains.3 In South Africa, 22.70% increase in the maternal mortality, 4.80% increase in the neonatal mortality, and 3.40% increase in the perinatal mortality has been reported.4 India has experienced 23.0% increase instead of 5.50% annual decline in the ratio of maternal mortality during pandemic,which must draw urgent consideration of policymakers.5 The uneven impact of COVID 19 on maternal, and the perinatal outcome has raised in two waves world-wide as well as between the high-income nations, and lower-middle income countries.7 The present retrospective study was conducted on 50 Covid-19 positive pregnant women admitted in our tertiary care maternity center in Teerthanker Mahaveer medical college, moradabad, India.

Severity of COVID-19 was evaluated as per Ministry of Health, and Family Welfare (MOHFW) guidelines, Government of India. And observed that 20 (40.0%) studied patients were fallen in mild group, moderate group 16 (32.0%) and rest 14 (28.0%) pregnant women were showing the Severe/Critical group COVID-19. Our study also observed 31 (62.0%) cases of Covid-19 infection at admission and rest 19 (38.0%) pregnant women infected before admission.

In present study majority of studied patients were of age above 30 years (68.0%) while 32.0% of them were below 30 years of age with mean age 31.82±4.30 years. Our findings were comparable with studies, Chen et al, they reported 31.0±4.0 years. Liu et al reported 30 years, Zhang et al 92.0±3.0 years in their study. The majority of studied patients were having BMI below 25.0 kg/m2 (48.0%) ,70.0% of the total studied women were multi gravid and 76.0% were having parity greater than one. These findings were supported by Sharma R et al study.

In this study it was found that the significant elevated levels of TLC, D-dimer, C-Reactive-Protein, LDH, S.ferritin, CK-MB, interleukin-6, urea, and sodium were related with severe and very fatal COVID-19 cases. Khan M et al reported the serum levels of CRP, troponin-I, ALP, ALT, serum creatinine, and ferritin are markedly increased in COVID-19 patients. Melo AKG et al study results supported to present findings.Ponti G et al reported the inflammatory CRP, erythrocyte sedimentation rate (ESR), procalcitonin (PCT)), immunological (interleukin IL 6 and biochemical (D-dimer, troponin, creatine kinase (CK), aspartate aminotransferase (AST)) biomarkers were related with COVID-19 disease progression. Tjendra Y et al reported the elevated CRP, reduced lymphocyte count, procalcitonin, raised liver enzymes, reduced renal function, and the coagulation derangements were common in the critically ill patients. Keddie's et al also reported the CRP, LDH, IL-6, IL-10 were strongly correlated with WHO

Volume 5, Issue 6; November-December 2022; Page No 476-483

ordinal scale severity. Malik P et al reported a significant association between elevated levels of CRP, PCT, LDH, D-dimer and COVID-19 severity. While Saini RK et al reported a positive significant correlation between levels of these inflammatory markers and liver function parameters.

The present study noted that ICU admission, need of oxygen and ventilator support, rate of cesarean and length of stay were comparatively higher in severe/critical cases followed by moderately effected covid-19 positive pregnant women. Our study also reported the Apgar Score 5min<7 and Covid status in baby were comparatively higher in severe/critical cases of covid-19 positive pregnant women. One baby Covid-19 positive in Severe/Critical group; but no affect on the birth weight of the neonates. There was no maternal neonatal mortality reported in this study. These findings were similar to Llorca J et al study.

Limitation:

This study has several limitations; first, this is a hospital based retrospective study and participants were from single center rather than multiple centers. It provides no information regarding cause or effect relationship. Although we found significant associations, further studies are warranted to investigate clinical significance of these indicators on patients with COVID-19.

Conclusion:

The study demonstrates the maternal and neonatal adverse outcomes were higher in severe COVID-19 disease with no maternal, or neonatal mortality. Significant elevated levels of TLC, D-dimer, C-Reactive-Protein, LDH, S. ferritin, CK-MB, interleukin-6, urea, and sodium were related with severe, and fatal cases of COVID-19. So, assessing, and checking the above markers at earliest stage of disease could have the considerable input in reducing the disease progression and death-toll.

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Volume 5, Issue 6; November-December 2022; Page No 476-483

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Volume 5, Issue 6; November-December 2022; Page No 476-483