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ORIGINAL RESEARCH INTENSIVE CARE

Association between inflammatory biomarkers and maternal mortality in parturients with COVID-19 infection requiring ICU admission: a retrospective study from Northern Malaysia

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ABSTRACT

Background: Parturients with COVID-19 infection requiring Intensive Care Unit (ICU) admission are at increased risk of a poorer prognosis. Significance and predictive value of inflammatory biomarkers in these parturient remains unclear due to the ongoing physiological adaptations. This study evaluates the association between biomarkers and maternal mortality in parturients with COVID-19 infection in the ICU.

Methodology: In this retrospective study, 64 pregnant and postpartum patients with COVID-19 admitted to the ICU of Hospital Sultanah Bahiyah, Kedah, Malaysia, from January 2021 to June 2022 were reviewed.

Parturients were categorized into maternal mortality versus survival group, and records were analyzed to include information on maternal outcomes and laboratory variables.

Results: Of the 64 parturients (86% antepartum, mean age 31.7± 5.9 years old), 10 (15.6%) resulted in maternal mortality. The maternal mortality group showed significantly increased mean levels of C-reactive protein (CRP) and ferritin, with decreased mean levels of PaO2/FiO2 (P/F) ratio on ICU admission. For biomarker analysis via ROC curve analysis, CRP, ferritin, and D-dimer showed moderately good diagnostic performances (AUC: 0.7-0.8, $P < 0.05$). Based on univariate logistic regression analysis, CRP and D-dimer showed significant independent interactions with maternal mortality. Notably, COV of CRP (COV: 89.21 mg/L) and D-dimer (COV: 2.19 ug/mL) indicated an increased risk of maternal mortality for 10-fold and 4-fold, respectively. Non-laboratory parameters significantly associated with maternal mortality include invasive and prone ventilation with increased length of stay in the ICU.

Conclusion: Elevated levels of CRP and D-dimer were significantly associated with maternal mortality in pregnant and postpartum women with COVID-19 in ICU.

Keywords: COVID-19 Maternal Mortality; Biomarkers; CRP; D-Dimer; Ferritin

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1. INTRODUCTION

The COVID-19 pandemic, caused by SARS-CoV-2 infection, has affected many pregnant and postpartum women worldwide. The maternal and fetal implications in Malaysia are significant. A total of 18,277 mothers have been infected with COVID-19 between March 2020 and January 2022, i.e., 0.64% of the total number of infected individuals in Malaysia. Among them, 3.0 to 5.5% required intensive care unit (ICU) admissions (updated on 30th December 2021). A total of 191 maternal deaths due to COVID-19 infection in Malaysia as of 24th February 2022. COVID-19 infections caused the largest proportion of cause of maternal deaths (41%) when compared to other causes such as postpartum hemorrhage, preeclampsia, and such in Malaysia for the year 2021.[1]

Although the earliest data from China indicated that pregnant women with SARS-CoV-2 infection did not have poorer outcomes than non-pregnant women of the same age,[2] however, according to the newest multinational cohort study, pregnant women with a COVID-19 diagnosis were associated with consistent and substantial increases in severe maternal morbidity and mortality and neonatal complications when compared with pregnant women without a COVID-19 diagnosis.[3]

Pregnant women are a high-risk population due to pregnancy-related physiological changes; unfortunately, there is limited understanding of the clinical course of COVID-19 in pregnancy.[4] Cardio-respiratory physiological changes in pregnancy also decrease the ability of the respiratory system to compensate for the cardio-respiratory stress caused by COVID-19-related complications, therefore, may predispose pregnant patients to hypoxic respiratory failure.[4] In addition, pregnancy puts women in a state of altered immunity, which enables the coexistence of the mother and fetus with the placenta.[4] There is a shift from Th-1-mediated immunity to Th-2-mediated immunity[5] which increases the risk of maternal susceptibility to various microorganisms, including viruses.[6] COVID-19 disease severity in pregnancy could be related to an increased release of pro-inflammatory cytokines and impaired adaptive immune response, causing systemic inflammation, organ dysfunction, and death.[7] However, to date, there is no report on the characterization of the immune response in pregnant women with COVID-19 infection.

The objective of this study was to evaluate the association between inflammatory biomarkers at presentation and maternal mortality in patients with COVID-19 infection in the ICU.

2. METHODOLOGY

In this retrospective cohort study, maternal (pregnant and postpartum) patients with COVID-19 admitted to the ICU of Hospital Sultanah Bahiyah from January 2021 to June 2022, i.e. 18-month period, were identified by reviewing of the ICU and obstetric COVID-19 admission registry. The study was conducted after receiving approval from the Ethics Committee of Universiti Sains Malaysia (USM/JEPeM/22040250) and the Medical Research and Ethics Committee of the Ministry of Health Malaysia, NMRR ID-22-01246-PLR (IIR).

All pregnant and postpartum patients with laboratory-confirmed COVID-19 infection admitted to the ICU of Hospital Sultanah Bahiyah within the study period who fulfilled the inclusion criteria and without any exclusion criteria were recruited in the study.

Inclusion criteria were pregnant women at any gestational age up to postpartum women, i.e., within 42 days post-delivery, aged 18 years or more, with COVID-19 infection confirmed by both symptoms and reverse transcription polymerase chain reaction (rt-PCR), and/or antigen rapid test kit (RTK-Ag) of SARS-CoV-2 virus (COVID-19 virus), and admitted to the ICU.

Exclusion criteria were patients with immunocompromised or immunosuppressed conditions/state, e.g., malignancy, on chemotherapy, radiotherapy, or long-term steroid therapy, autoimmune diseases, e.g., systemic lupus erythematosus (SLE), acquired immunodeficiency syndrome (AIDS), or organ transplant patients; as we considered these groups of patients may have confounding biomarker levels.

Table 1: Demographic characteristics of study subjects

Variable	Overall (n = 64)	Maternal mortality (n = 10)	P value
Mean maternal age, year (SD)	31.7 ± 5.9	33.2 ± 4.4	0.374
Ethnicity			
• Malay	57 (89.1)	9 (90.0)	0.918
• Others	7 (10.9)	1 (10.0)	
• Chinese	1 (1.6)	0 (0.0)	
• Indian	4 (6.3)	1 (10.0)	
• Indonesian	1 (1.6)	0 (0.0)	
• Siamese	1 (1.6)	0 (0.0)	
BMI (kg/m2)			
• Overall	31.6 ± 7.3	31.6 ± 6	0.987
• Normal (<24.9)	10 (15.9)	1 (10.0)	0.087
• Overweight (25.0-29.9)	15 (23.8)	4 (40.0)	
• Obesity Class I (30.0-34.9)	20 (31.7)	1 (10.0)	
• Obesity Class II (35.0-39.9)	11 (17.5)	4 (40.0)	
• Obesity Class III (≥40.0)	7 (11.1)	0 (0.0)	
Comorbidities			
• No/NKMI	24 (37.5)	3 (30.0)	0.594
• Gestational DM	22 (34.4)	5 (50.0)	
• Bronchial asthma	5 (7.8)	2 (20.0)	
• Essential HPT	2 (3.1)	0 (0.0)	
• Drug abuse	2 (3.1)	0 (0.0)	
• Smoker	1 (1.6)	0 (0.0)	
• Arrhythmia	1 (1.6)	0 (0.0)	
• Valvular heart disease	1 (1.6)	0 (0.0)	
• Primary pulmonary HPT	1 (1.6)	0 (0.0)	
• Hypothyroidism	1 (1.6)	0 (0.0)	
• Hyperthyroidism	1 (1.6)	0 (0.0)	
• Syphilis	1 (1.6)	0 (0.0)	
• Hepatitis B	1 (1.6)	0 (0.0)	
• Epilepsy	1 (1.6)	0 (0.0)	

Data presented as mean (standard deviation) or frequency (percentage; P < 0.05 is statistically significant; HPT - Hypertension. DM - Diabetes mellitus

The patients were categorized into the maternal mortality during hospital admission and the survival until hospital discharge group. Their electronic medical records (using e-Hospital Information System, eHis), clinical records (antenatal record book) and laboratory examinations were comprehensively reviewed to extract the study variables, which included demographics (age, sex, and race), clinical variables (comorbidities, BMI and gestational age), maternal outcomes (survived until discharge or maternal death during admission) and laboratory variables on admission, e.g. arterial blood gas (ABG) with PaO2/FiO2 ratio (P/F ratio), white cell count (WBC), neutrophil count, lymphocyte count, platelet count, neutrophil-to-lymphocyte ratio (NLR), C-reactive protein (CRP), ferritin, D-dimer, procalcitonin (PCT) and interleukin-6 (IL-6). There was no potential bias in our study methodology as all the data were collected from the electronic medical record retrospectively.

The sample size of this study was based on the difference between two independent means (2 groups). The desired power of 0.8 and two-tailed α of 0.05. The dropout rate of 10% and a total of 57 patients are required.

All data were transferred to IBM SPSS software version 27. For descriptive statistics, data were presented as mean (standard deviation) or frequency (percentage). Numerical variables were compared using an independent T-test, while categorical variables were compared using a chi-square test. Comparative analyses were employed to determine the difference and distribution of data between the presence and absence of maternal mortality as a supplementary analysis. For biomarker analysis, laboratory parameters were analyzed by a receiver operating characteristic (ROC) curve to check the diagnostic performance. The optimal cut-off value (COV) for the respective parameters was determined by the Youden index. The laboratory parameters with potentially moderately good diagnostic performances (AUC 0.7-0.8) were further analyzed by univariate and multivariate analysis. A P-value less than 0.05 indicates a statistically significant difference.

3. RESULTS

Demographic details and clinical characteristics of parturients with COVID-19 requiring ICU admission are detailed in Table 1. A total of 65 parturients were identified to be admitted to the ICU with COVID-19 during the study period. 64 parturients were included in the analysis as 1 was excluded due to her

Table 2: Obstetric history data

Parameter	N (%)	P-value
Gestational age – COVID-19		
Diagnosis (PCR) (weeks)	28.6 (11.4)	0.829 [a]
Symptoms onset (weeks)	28.3 (11.6)	0.783 [a]
Ward admission (weeks)	28.9 (11.4)	0.860 [a]
ICU admission (weeks)	26.6 (11.8)	0.754 [a]
Postpartum admission (days)	7.3 ± 10.5	0.594 [a]
Delivery of the fetus gestational age of delivery (weeks)	35.0 (3.0)	0.885 [a]
Indication for delivery		
Spontaneous vaginal delivery (SVD)	1 (14.3)	0.202 [b]
LSCS for fetal indication	0 (0.0)	
LSCS for maternal indication	2 (28.6)	
LSCS for COVID-19 (local protocol)	4 (57.1)	
Ectopic pregnancy	0 (0.0)	
Difference of P/F ratio between pre and post-delivery	-1.46 (152.33)	0.306 [a]
Maternal mortality		
Antepartum mortality	3 (30.0)	0.981 [b]
Postpartum mortality	7 (70.0)	

Data presented as mean ± SD or n (%);
a Numerical variables were compared using independent T-test.
b Categorical variables were compared using chi-square test.
P < 0.05 is statistically significant

underlying autoimmune disease, i.e., systemic lupus erythematosus (SLE). 10 out of the 64 patients (15.6%) had mortality, where 7 of them suffered postpartum mortality (death within 42 days post-delivery of the fetus). In general, there was no significant difference in the demographic
variables between the survival and maternal mortality groups.

The mean gestation age at admission to the ICU was 27.7 weeks (27.8 for survival group versus 26.6 for mortality group); only 8 admissions (12.5%) occurred during postpartum period (mean = 5.8 days post-partum). There was a total of 45 deliveries of babies during the admission with the mean gestational age of delivery at 34.8 weeks. The majority of the mode of delivery were lower segment caesarean section (LSCS) (82.2%) for maternal indication (35.6%) of respiratory compromise (Table 1).

Laboratory findings and clinical characteristics of a parturient with COVID-19 requiring ICU admission are detailed in Table 2. The maternal mortality group showed significantly higher mean values for CRP (102.17 vs 55.20 mg/L, P = 0.001), ferritin (991.67 vs 368.18 ng/mL, P = 0.003) and D-dimer (3.08 vs 2.99 µg/mL, P = 0.712); and lower mean value for P/F Ratio on ICU admission (120.47 vs 263.42, P = 0.001). Clinical characteristics that are significantly associated with maternal mortality are invasive ventilation (P < 0.001), prone ventilation (P = 0.013) and increased length of stay in the ICU (P = 0.001) (Table 2).

For biomarker analysis, receiver operating characteristic (ROC) curve analysis were done for all biomarkers in this study (Table 3). CRP, ferritin, and D-dimer showed moderately good diagnostic performances (AUC: 0.7-0.8, P < 0.05), but not P/F ratio on ICU admission (AUC < 0.5). However, notably, all CRP, ferritin, and D-dimer had moderate sensitivity (66.67-80.0%) and low specificity (22.2-34.0% only) (Table 3).

The independent effect of these three variables on the likelihood of maternal mortality was interrogated by a univariate logistic regression analysis, and the results are reported in Table 4. We noted that CRP (OR= 10.4, 95% CI 1.978, 54.695, P = 0.006) and D-dimer (OR= 4.667, 95% CI 1.077, 20.217, P = 0.039) showed significant independent interactions (Table 4).

Multivariate logistic regression analysis was also done, but there was no significant interaction (Table 4). A value over the COV of CRP (COV: 89.21 mg/L) and D-dimer (COV: 2.19 ug/mL) indicated an increased risk of maternal mortality for 10-fold and 4-fold, respectively, compared to those below the COV (Table 3).

4. DISCUSSION

This retrospective cohort study was conducted to determine the association of the various biomarkers with maternal mortality among parturients with COVID-19 admitted to the ICU. Most of the previous studies were done on the general non-pregnant population, which may not apply to maternal patients who are expected to have significant immunological and physiological adaptation in pregnancy, whereby biomarker levels could be altered physiologically. Good biomarkers will enable risk stratification and identification of patients who will potentially have a severe outcome. This can enable early, proactive, and more aggressive management and effective allocation of healthcare resources, especially in the context of the increased burden of the pandemic on the healthcare system.

Table 3: Clinical profile and laboratory findings of the study subjects.

Variables	Total (n = 64)	No maternal mortality (n = 54)	Maternal mortality (n = 10)	P value
HFNC	44 (68.8)	38 (70.4)	6 (60.0)	0.516
Invasive ventilation	24 (37.5)	14 (25.9)	10 (100.0)	<0.001*
Prone ventilation	3 (4.7)	1 (1.9)	2 (20.0)	0.013*
Open tracheostomy	4 (6.3)	3 (5.6)	1 (10.0)	0.594
Pulmonary embolism	15 (28.8)	12 (26.7)	3 (42.9)	0.379
LOS hospital	18.16 (9.12)	17.72 (9.06)	20.50 (9.54)	0.380
LOS ICU	8.41 (7.97)	7.06 (6.94)	15.70 (9.55)	0.001*
Laboratory Biomarkers Investigation±				
PF Ratio on hospital admission	330.53 (133.94)	342.84 (138.10)	262.19 (83.94)	0.097
PF Ratio on ICU admission	241.08 (129.31)	263.42 (124.74)	120.47 (79.09)	0.001*
C-reactive protein (mg/L)	62.54 (43.56)	55.20 (40.47)	102.17 (39.63)	0.001*
White blood cell ($x10^9$/L)	10.28 (5.14)	10.72 (5.34)	7.93 (3.10)	0.116
Neutrophil count ($x10^9$/L)	8.15 (4.54)	8.46 (4.72)	6.52 (3.07)	0.218
Lymphocyte count ($x10^9$/L)	1.51 (2.78)	1.59 (3.02)	1.07 (0.54)	0.592
Neutrophil-Lymphocyte ratio	7.76 (4.88)	7.80 (4.73)	7.52 (5.92)	0.870
Platelet count ($x10^9$/L)	248.69 (78.91)	254.13 (78.55)	219.30 (78.24)	0.202
Ferritin (ng/mL)	463.29 (601.71)	368.18 (437.86)	991.67 (1039.21)	0.003*
D-Dimer (µg/mL)(FEU)	3.08 (4.40)	2.99 (4.61)	3.55 (3.19)	0.712*
Procalcitonin (ng/mL)	11.54 (49.58)	1.43 (2.92)	30.49 (84.14)	0.187
Interleukin-6 (pg/mL)	51.84 (74.77)	41.21 (49.41)	70.44 (114.14)	0.561

Data presented as mean ± SD or n (%);

Numerical variables were compared using an independent T-test, while categorical variables were compared using a chi-square test. P < 0.05 is statistically significant

Our study findings showed that increased CRP and D-dimer were associated with maternal mortality. These biomarkers are indeed inflammatory biomarkers, where their levels typically rise in various inflammatory processes or conditions. This is a unique characteristic of COVID-19 where there is an excessive release of large amounts of proinflammatory cytokines in a condition known as "cytokine storm" which correlates with ARDS, multiorgan failure, and poor prognosis of COVID-19.[8,9]

CRP is an acute-phase protein produced by the liver. Its production is stimulated by various inflammatory cytokines, especially interleukin-6 (IL-6).[10] In our study, the mean CRP level was significantly higher at almost double in the mortality group (102.17 vs 55.20 mg/L, P = 0.001). Under receiver operating characteristic (ROC) curve analysis, its area under curve (AUC) showed a good discriminatory ability at 0.791 (95% CI: 0.619, 0.962, P = 0.004). Its optimal cut-off value (COV) by the Youden index was 89.21 mg/L. A unit increase of CRP above 89.21 mg/L is associated with a 10.4-fold (95% CI: 1.978, 54.695; P = 0.006) increase in the risk of maternal mortality, compared to those with CRP < 89.21 mg/L. Being a non-specific inflammatory biomarker, the CRP test had a low specificity (22.9%) for maternal mortality, but also a moderate sensitivity (80.0%) in our study.

In a retrospective study by Lombardi et al (2021), among the biomarkers studied, CRP was the biomarker that varied more significantly during COVID-19 infection in obstetric patients, backing its use as a test to monitor the evolution of the disease.[11] Another retrospective study, with 139 non-obstetric subjects, showed that at CRP levels > 41.8 mg/L, there was an increased likelihood of progressing to severe COVID-19 disease.[12] D-Dimer is a degradation product of cross-linked fibrin clot by plasmin cleavage. Raising levels of D-dimer indicates activation of coagulation and fibrinolysis. It is increasingly recognized that pulmonary vascular endothelialitis, thrombosis, and microangiopathy are an important part of the COVID-19 pathophysiology.[13]

Table 4: ROC curve analysis of biomarkers for differential analysis with maternal mortality outcomes

Variable	AUC (95% CI)	P value	COV	Ss (%)	Sp (%)
PF Ratio on 1st admission	0.290 (0.113, 0.467)	0.046*	281.85	33.3	68.0
PF Ratio on ICU admission	0.131 (0.000, 0.266)	<0.001*	136.00	30.0	77.8
C-reactive protein (CRP)	0.791 (0.619, 0.962)	0.004*	89.21	80.0	22.2
WBC	0.343 (0.172, 0.513)	0.116	8.85	50.0	53.7
Neutrophil counts	0.369 (0.194, 0.543)	0.189	6.51	40.0	59.3
Lymphocytes count	0.365 (0.174, 0.556)	0.177	1.08	40.0	59.3
N-to-L ratio (NLR)	0.452 (0.255, 0.649)	0.631	6.48	50.0	50.0
Platelet count	0.378 (0.177, 0.578)	0.222	231.00	40.0	57.4
Ferritin	0.773 (0.637, 0.910)	0.010*	327.50	66.7	34.0
D-Dimer	0.730 (0.584, 0.876)	0.022*	2.19	70.0	31.4
Procalcitonin	0.575 (0.315, 0.835)	0.561	0.22	62.5	40.0
Interleukin-6 (IL-6)	0.536 (0.132, 0.940)	0.850	15.75	75.0	42.9

AUC = area under curve; 95% CI = 95% confidence interval; COV = cut-off value; Ss = sensitivity; Sp = specificity

Table 5: Univariate logistic regression analysis of selected biomarker parameters

Variable	Univariate Logistics Regression	P value
	OR (95% CI)	
C-reactive protein	10.400 (1.978, 54.695)	0.006*
Ferritin	3.667 (0.852, 15.772)	0.081
D-Dimer	4.667 (1.077, 20.217)	0.039*

OR = odds ratio. Note: The selected variables were analyzed by multivariate analysis, but there is no significant interaction indicated. P < 0.05 is statistically significant

Many researchers, including Huang et al. (2020) found that D-dimer levels on admission could be incorporated as part of the triage of patients into critical care.[14]

In our study, the mean D-dimer level was higher in the maternal mortality group (3.55 vs 2.99 µg/mL), but statistically insignificant, with P = 0.712. However, for the biomarker analysis, the ROC analysis showed good discriminatory ability of AUC 0.730 (P = 0.022). The optimal COV determined by the Youden index was 2.19 µg/mL. Subsequent univariate logistic regression showed an odds ratio of 4.667 (P = 0.039). The results of our study were consistent with those of Zhang et al. (2020). In their 343 non-obstetric patient retrospective study, D-dimer levels of 2.0 µg/mL or more on admission were the optimal COV to predict in-hospital mortality with a sensitivity of 92.3% and a specificity of 83.3%.[15]

Our small sample size study, however, fell short in terms of lower sensitivity of 70.0% and specificity of 31.4%.

It must be acknowledged that there is a physiological increase of D-dimer values, especially in the third trimester.[16] Therefore, published data on D-dimer's role as a prognostic tool in pregnancy is unsurprisingly conflicting and requires further studies.[17]

In normal pregnancy, serum ferritin decreases gradually and reaches a nadir during weeks 35 to 38, and subsequently increases during the month before delivery.[18] In our study, the mean ferritin level was significantly higher (991.67 vs 368.18 ng/mL, P = 0.03) with a good AUC of 0.773 (95% CI 0.637, 0.910, P = 0.010). However, its univariate logistics regression analysis was insignificant (P = 0.081). The potential of ferritin as part of the biomarkers panel in the assessment of maternal COVID-19 is promising; a larger sample size study can hopefully yield significant results in future studies.

In Lombardi et al study, the ferritin levels were well above those observed in normal pregnancy, but well below those observed in several cohorts of non-pregnant COVID-19 patients. This has led to their postulation that the inflammatory state of COVID-19 leads to increased serum ferritin in obstetric patients, but this increase is masked partly by the physiological low level in the pregnant state.[11]

P/F ratio, also known as the oxygenation index, is used to assess the efficiency of oxygenation of the lungs, where higher values signify better oxygenation. It is part of the Berlin Criteria for diagnosis of Acute Respiratory

Distress Syndrome (ARDS)[19] which is also part of the spectrum of severe COVID-19. The P/F ratio reflects the severity of any respiratory impairment, and its reduction signifies already impaired oxygenation. Therefore, its role in COVID-19 is mainly for disease severity assessment and stratification, rather than a biomarker for prognostication purposes. Furthermore, it also functions as a guide for ventilatory support and for monitoring of therapeutic response.

The P/F ratio is slightly lower in pregnant women than in non-pregnant women.[20] This is due to the dynamic interactions between various pregnancy-related physiological changes, such as reduced functional residual capacity (FRC) and increased basal metabolic rate (BMR), etc. In our study, the mean P/F ratio of the maternal mortality group was significantly lower than survival group (120.47 vs 263.42, P = 0.001); however, its AUC was only 0.131 (AUC < 0.5), indicating P/F ratio as poor discriminatory ability in our study.

In our study, the mean P/F ratio improved after delivery of the fetus (mean = 57.32), where the survival group showed an improvement of P/F ratio of 68/21; the mortality group, on the other hand, showed a marginal reduction of 1.46. However, the results were statistically insignificant as the P-value was 0.306. In an earlier study, delivery slowed the deterioration of the P/F ratio in these patients.[20]

Importantly, interventional delivery is not without its risks, e.g., transfer of unstable, critically ill and infectious patients to the operating theatre, complication of prematurity and vertical transmission, interruption of anticoagulation, exposure risk for surgeons, Anesthetists, pediatricians and staff. Therefore, interventional delivery of the fetus via caesarean section for maternal respiratory failure indication should be a multidisciplinary and individualized decision-making.

Other laboratory biomarkers investigated e.g., P/F ratio on hospital admission, white cell count (WBC), neutrophil count, lymphocyte count, neutrophil-lymphocyte ratio (NLR), platelet count, procalcitonin (PCT), and interleukin-6 (IL-6), all had AUC <0.7, indicating poor diagnostic performance. Besides, their means had no statistically significant difference. (P > 0.05). However, this was contrary to a study by Fatima et al. that shows elevated IL-6 (≥ 30 pg/mL), CRP (≥ 100 mg/L), PCT (≥ 0.5 ng/mL), and D-dimer (≥ 1 µg/mL) were significantly associated with higher mortality (P < 0.05).

A combination of all four results served as a prognostic marker for mortality in critically ill COVID-19 patients.[21]

5. LIMITATIONS

Our study had its limitations. It was a retrospective single-centre study involving mainly an almost homogenously Malay ethnicity (89.1%), which caused its inherited caveats. However, considering the correlation of our results with other studies on obstetric patients in Italy and also multicenter studies on the general non-obstetric population, it appears that our results were consistent with the broader population of COVID-19 patients.

Our study findings are also based on univariate analysis, not multivariate analysis, due to the small sample size. Therefore, it needs more studies with a larger sample size to prove the association. Ideally, prospective, multicenter studies are warranted to validate these findings and develop targeted management strategies to improve outcomes in this vulnerable population.

6. CONCLUSION

In this retrospective study, elevated levels of CRP and D-dimer were significantly associated with an increased risk of maternal mortality with COVID-19 in the ICU. These findings suggest that monitoring these biomarkers could serve as a valuable tool in identifying high-risk cases and guiding appropriate interventions for pregnant and postpartum women with severe COVID-19.

7. Data availability

The numerical data generated during this research is available with the authors.

8. Conflict of interest

All authors declare that there was no conflict of interest.

9. Funding

The study utilized the hospital resources only, and no external or industry funding was involved.

10. Authors' contribution

TAK. Conceived and designed the study, collected data, performed the analysis, and wrote the draft.

PS, CSE, LM, NMN, AZ, AAMA, SCO: Facilitated data collection, reviewed and edited manuscript, and supervised of project

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