Original Article

Differences in Clinical and Laboratory Features of Pregnant and Non-Pregnant Female with Hospitalized COVID-19

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Abstract

Background: The impact of COVID-19 on vulnerable populations, including pregnant female, is critical due to higher risks and potential complications. This study aims to compare the clinical and laboratory features of COVID-19 between pregnant and non-pregnant female. **Materials and Methods:** This retrospective cohort study included 245 COVID-19 patients admitted to Universitas Sabellas Maret (UNS) Hospital, Indonesia, from March 2020 to May 2022. Among them, 72 were pregnant, and 173 were non-pregnant. Data on demographics, clinical presentations, and laboratory findings were collected from medical records. Statistical analysis utilized Chi-square or Fisher exact tests, Mann-Whitney or independent t-tests, and multiple linear regression. **Results:** No significant demographic differences were found, except in hospitalization status. Clinically, pregnant female had a higher prevalence of symptoms such as cough (p = 0.002), fatigue (p = 0.025), and shortness of breath (p = 0.035), with no differences in other symptoms or length of stay. Laboratory findings indicated significant differences in White Cell Count (WCC), Absolute Lymphocyte Count (ALC), High Fluorescence Lymphocyte Count (HFLC), lymphocyte percentage, neutrophil percentage, Neutrophil Lymphocyte Ratio (NLR), Red Cell Count (RCC), Hemoglobin (Hb), Hematocrit (Hct), Platelet Count (PC), Prothrombin Time (PT), International Normalized Ratio (INR), D-Dimer, and Sodium (p values < 0.05). Multivariate analysis identified WCC, lymphocyte percentage, HFLC, neutrophil percentage, PT, INR, D-Dimer, Creatinine, and Potassium as significant predictors of length of stay (R^2adj = 0.874, F = 17.979, p < 0.001). **Conclusions:** Pregnant female with COVID-19 exhibited distinct laboratory profiles compared to non-pregnant female. These findings highlight the need for tailored management strategies for COVID-19 in pregnant patients and provide a foundation for further research.

Keywords: *COVID-19, Indonesia, laboratories, pregnancy, signs and symptoms*

Introduction

The world faces the Coronavirus Disease 2019 (COVID-19) pandemic, a significant health sector problem.[1–4] COVID-19 attacks the human lung as the primary target, but it also attacks multiple organ systems.[5] The COVID-19 pandemic also affects pregnancy. The Indonesian National Population and Family Planning Agency (BKKBN) reported an increase in the birth rate in Indonesia during the COVID-19 pandemic.[6,7] The pregnant female population needs special attention in this pandemic situation. Several studies showed a higher incidence of COVID-19 in pregnant females than in non-pregnant females. Research in Washington shows the reported incidence of COVID-19 was 13.90 per 1000 pregnant females and 7.30 per 1000 non-pregnant females.[8] Several studies have also stated that COVID-19 infection causes more severe clinical signs and symptoms in pregnant females than in non-pregnant females. A report by Zambrano *et al*. (2020) suggests that pregnant females were three times more likely to need treatment in the Intensive Care Unit (ICU), 2.90x more likely to need a ventilator, and 1.70x more likely to die than non-pregnant females.[9] Although there is no reliable data yet, it is estimated that COVID-19 infection may cause vertical transmission to the fetus. Subsequently, vertical transmission of COVID-19 to the fetus could also lead to several complications, such as abortion (2%), Intra Uterine Growth Restriction (IUGR) (10%), and premature birth (39%).[7]

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Considering the danger of COVID-19 infection in the pregnant female population, it is necessary to carry out excellent processes for screening and examination.[2,10] Clinical examination is needed, but there are also various supporting examinations for COVID-19 cases, including chest X-ray, Computed Tomography (CT) scan of the thorax, Real-Time Polymerase Chain Reaction (RT-PCR) from throat swab samples/sputum/lower respiratory aspirate, complete peripheral blood laboratory tests, and blood chemistry laboratory tests. Blood laboratory tests, apart from simple procedures, could be beneficial in managing COVID-19 patient care. Subsequently, biomarkers in COVID-19 laboratory tests can also be useful as screening tools in the early stages, confirmation and classification of severity, reference standards for hospital and ICU admissions, the basis for rational therapy, the basis for assessing therapeutic response, a predictor of outcome, and a baseline for discharge of patients from hospital or ICU.[11]

Research related to COVID-19 infection in pregnancy plays a vital role since the higher severity and complications impact the mother and fetus. This study was conducted to further investigate the differences in clinical and laboratory features between pregnant and non-pregnant females hospitalized with a confirmed COVID-19 diagnosis. Our knowledge is that there is no similar research in Indonesia, so this research can be the basis for the development of subsequent studies and the foundation for decision-making in managing COVID-19 infection in pregnancy.

Materials and Methods

This clinical observational study, using a retrospective cohort design, included 245 hospitalized, confirmed COVID-19 patients admitted to Universitas Sabellas Maret Hospital (RS UNS), a secondary care center in Central Java, Indonesia, between March 2020 and May 2022.

The inclusion criteria were as follows: (1) Female patients, (2) individuals aged 18 years or older, and (3) Patients with a diagnosis of COVID-19 confirmed through RT-PCR. Samples who refused to participate in the study and samples with incomplete data were excluded. Samples with Hepatitis B Surface Antigen (HBsAg) and Human Immunodeficiency Virus (HIV) reactive were also excluded from the study. This study used a quota sampling technique to select participants. The total sample size of 245 was calculated using a formula proposed by Lemeshow, Hosmer, Klar, and Lwanga (1990), which stipulates that $n = Z^2 (p) (1\text{-}p)/d^2$ and interpreted as follows: n = sample size, Z = value of normally distributed variate, which for a 95% confidence interval takes the value of 1.96 (5%), and p = estimated proportion of female to the number of patients with COVID-19 within the catchment area, which is 0.2 (20%) based on data. The d = desired precision or standard error was set at alpha 0.05 (sig. 5%).

Confirmation of the COVID-19 diagnosis was carried out using the RT-PCR test. Samples were obtained from nasopharyngeal and oropharyngeal swabs. RNA was extracted using the Liferiver Novel Coronavirus (2019-nCoV) RNA Isolation Kit (for Automatic Extraction) (Liferiver ME-0012, Shanghai ZJ Bio-Tech) according to the instructions provided by the manufacturer. RT-PCR assays utilizing the Novel Coronavirus (2019-nCoV) Real-Time Multiplex RT-PCR Kit were done to detect 3 Genes. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) open reading frame lab (Orfa), N, and E gene fragments were amplified at 45°C for 10 minutes and 95°C for three min, followed by 45 cycles of 95°C for 15 sec and 58°C for 30 sec. When both targets (ORF1ab, gene N, and gene E) showed positive results, the case was deemed laboratory-confirmed. A Cycle Threshold Value (CT value) less than 37 was considered positive, whereas a value larger than 41 was considered negative. A CT number between 37 and 40, representing a medium load, necessitated retesting.

RS UNS uses a Medical Record (MR) file system to collect all clinical and laboratory data. Collected data included (1) demographic: age, patient status: pregnancy or non-pregnancy, (2) comorbidities; Diabetes Mellitus (DM), Hypertension (HT), Cardiovascular Disease (CVD), thyroid dysfunction, chronic lung disease, Chronic Kidney Disease (CKD), stroke or Transient Ischemic Attack (TIA), cancer, and epilepsy, (3) Hospitalized status: natural airflow, negative pressure, or ICU, (4) length of stay, (5) COVID-19 symptoms: (A) upper respiratory tract infection symptoms, including headache, fever, fatigue, myalgia, rhinorrhea, and sore throat (B) lower respiratory tract infection symptoms, including cough, Shortness Of Breath (SOB), sputum production, and hemoptysis, (C) other symptoms, including ageusia, anosmia, anorexia, nausea, vomiting, diarrhea, and confusion. Subsequently, additional data collected from the pregnant group included (1) obstetric history: Gravidity, Parity, Abortus (GPA system), and (2) gestational age (and classification by trimester).

The laboratory tests were collected and include: (1) complete blood count: total White Cell Count (WCC) (normal reference range; NR: 4.50–11 × 10 (3)/ul), Absolute Lymphocyte Count (ALC) (NR: >1500/ul), High Fluorescence Lymphocyte Count (HFLC) (NR 0%–1.40%), lymphocyte percentage (NR: 22%–44%), neutrophil percentage (NR: 50%–70%), Neutrophil Lymphocyte Ratio (NLR), total Red Cell Count (RCC) (NR: 4.10–5.10 × 10 (6)/ul), Hemoglobin (Hb) (NR: 12 g/dl–15.60 g/dl), Hematocrit (Hct) (NR: 35%–45%), and platelet count (NR: 150–450 × 10 (3)/ul), (2) coagulation profile: Prothrombin Time (PT) (NR: 11–18 sec), International Normalized Ratio (INR) (NR: 0.85–1.15), Activated Partial Thromboplastin Time (aPTT) (NR: 27–42 sec), and D-Dimer (NR: <500 ng/ml), and (3) electrolyte and renal profile; creatinine (NR: 0.50 mg/dl–1.10 mg/dl), Sodium (Na) level (NR: 135 mmol/liter–145 mmol/liter), Potassium (K)

level (NR: 3.50 mmol/liter–5.50 mmol/liter), and Calcium (Ca) level (NR: 1.10 mmol/liter–1.35 mmol/liter).

Descriptive statistics were employed to describe the demographics and characteristics of the entire sample and additional data from the pregnancy group. Data were presented as mean and standard deviation for continuous or quantitative variables and frequency (number and percentage; %) for categorical variables. To assess the differences between characteristic, clinical, and laboratory features between the pregnancy vs. non-pregnancy group, a Chi-square or Fisher exact test was used for the categorical variables, and an independent *t*-test or Mann-Whitney test was used for the continuous variables. Multiple linear regression was used to investigate multiple predictors of laboratory features for length of stay. Data were analyzed using the Statistical Package for the Social Sciences (version 27.00) for statistical analysis software (IBM Corp, Armonk, New York, USA). p <0.05 (with a confidence limit of 95%) was considered statistically significant.

Ethical considerations

Research ethical issues, including anonymity and confidentiality, were addressed carefully during the study. The research ethical clearance approval letter was obtained from the Research Ethics Committee at Dr. Moewardi Hospital, Central Java, Indonesia, with an Ethical Clearance number of 1263/IX/HREC/2022 (Issued on 31 October, 2022).

Results

Among 245 patients screened, 72 (29.40%) patients were classified into the pregnancy group and 173 (70.60%) patients into the non-pregnancy group. The demographic characteristics of the entire sample (both groups) are summarized in Table 1. Most of the sample was aged 20-39 (95.50%). Meanwhile, based on comorbidities, 32.70% of the samples had comorbidities, with the majority of comorbidities being diabetes mellitus (11.8%) and hypertension (11.40%). According to hospitalization status, the majority of the sample was admitted to negative pressure (77.20%), natural airflow (15.00%), and the rest (7.30%) were admitted to the Intensive care unit. Regarding demographic factors, the comparison of the two groups was not statistically significant. However, the difference between the two groups was statistically significant regarding hospitalization status (natural airflow and negative pressure).

Demographic characteristics of the pregnancy group (n = 72) are described in Table 2. Based on the obstetric history (GPA system), most of the samples in this study were multigravida (63.90%) and primiparous (44.00%). The mean gestational age (in weeks) was 34.85 (8.60).

The differences in clinical features are presented in Table 3. According to clinical features, the average length of stay of all patients in this study is 8.70 (3.37) days. Based on symptoms, most of the samples were symptomatic (91.4%), with the most common symptoms being cough (57.60%), shortness of breath (48.60%), fever (49.80%), and nausea (31.80%). The pregnancy group had a lower length of stay than the non-pregnant group, although not statistically significant (8.96 [0.48] vs. 9.29 [0.40], p = 0.630). Subsequently, significant differences were found between the pregnant and

Table 1: Demography of entire sample (*n*=245)

Laboratory Features	Total samples (*n*=245) Mean (SD)/*n* (%)	Pregnancy (*n*=72) Mean (SD)/*n* (%)	Non-Pregnancy (*n*=173) Mean (SD)/*n* (%)	*p*
Age (years)	29.25 (5.34)*	29.25 (5.34)*	29.10 (5.87)*	0.844***
<20 years	2 (0.80%)**	0 (0.00%)**	2 (1.20%)**	1.000****
20-39 years	235 (95.50%)**	68 (94.40%)**	167 (96.50%)**	0.486****
40-60 years	8 (3.30%)**	4 (5.60%)**	4 (2.30%)**	0.239****
Comorbidities				
Present of any Comorbidities	80 (32.70%)**	20 (27.80%)**	60 (34.70%)**	0.368*****
Diabetes Mellitus	29 (11.80%)**	8 (11.10%)**	21 (12.10%)**	0.992*****
Hypertension	28 (11.40%)**	6 (8.30%)**	22 (12.70%)**	0.446*****
Cardiovascular Disease	18 (7.30%)**	6 (8.30%)**	12 (6.90%)**	0.910*****
Thyroid Dysfunction	7 (2.80%)**	1 (1.40%)**	6 (3.50%)**	0.677****
Chronic Lung Disease	23 (9.30%)**	4 (5.60%)**	19 (11.00%)**	0.277*****
Chronic Kidney Disease	3 (1.20%)**	0 (0.00%)**	3 (1.70%)**	0.558****
Stroke/Transient Ischemic Attack (TIA)	0 (0.00%)**	0 (0.00%)**	0 (0.00%)**	
Cancer	0 (0.00%)**	0 (0.00%)**	0 (0.00%)**	
Epilepsy	3 (1.20%)**	1 (1.40%)**	2 (1.20%)**	1.000****
Hospitalized Status				
Natural Air Flow	37 (15.00%)**	4 (5.30%)**	33 (19.10%)**	0.013*****
Negative Pressure	190 (77.20%)**	63 (87.50%)**	127 (73.40%)**	0.025*****
Intensive Care Unit	18 (7.30%)**	5 (6.90%)**	13 (7.50%)**	1.000*****

*Mean (SD), **n (%). ***Independent t-Test, ****Fisher Exact Test, *****Chi-square test

non-pregnant groups in symptoms: cough (41.70% vs. 64.20%, p = 0.002), fatigue (36.10% vs. 21.40%, p = 0.025), and shortness of breath (59.70% vs. 43.90%, p = 0.035). However, there were no significant differences in other clinical features.

The differences in laboratory features are described in Table 4. This study showed significant differences between the pregnancy and non-pregnancy groups in all parameters of complete blood count: WCC (10.02 [3.09] vs. 7.95 [3.17] [× 10 (3)/ul], $p \leq 0.001$), ALC (1462.21 [661.12] vs. 1946.79 [946.35] [/ul], $p < 0.001$), HFLC (0.53 [0.68] vs. 0.93 [1.06] [%], $p \leq 0.001$), Lymphocyte percentage (15.68 [7.29] vs. 26.56 [10.74] [%], $p \leq 0.001$), Neutrophil percentage (75.60 [11.71] vs. 64.09 [11.81] [%], $p \leq 0.001$), NLR (6.55 [4.06] vs. 3.30 [2.45] [%], $p \leq 0.001$), RCC (4.07 [0.46] vs. 4.69 [0.56] [× 10 (6)/ul], $p \leq 0.001$), Hb (11.45 [1.46] vs. 12.75 [1.74] [g/dl], $p \leq 0.001$), Hct (33.51 [3.74] vs. 37.603 [4.54] [%], $p \leq 0.001$), and PC (251.35 [80.81] vs. 281.31 [100.25] [× 10 (3)/ul], p = 0.025). Differences were also found in the coagulation profile, including PT (10.35 [1.55] vs. 14.44 [9.56] [seconds], p = 0.004), INR (0.69 [0.13] vs. 1.07 [0.89], p = 0.005), and D-Dimer (2396.75 [2524.67] vs. 869.65 [1446.86], $p \leq 0.001$), as well as the electrolytes and renal profile: Na (139.16 [2.80] vs. 140.84 [3.35] [mmol/liter], p = 0.043). Meanwhile, other parameters, including aPTT, creatinine, K, and Ca, showed no statistically significant differences.

Last, we also examined the groups of laboratory feature variables in multiple linear regression analysis to predict the length of stay. The result indicated that the length of stay was significantly predicted by the following variables: WCC, lymphocyte percentage, HFLC, neutrophil percentage, PT, INR, D-Dimer, Creatinine, and K: (R^2=0.0.962, R^2adj = 0.874, F = 17.979, $p \leq 0.001$). Regression models are shown in Table 5.

Table 2: Demography of Pregnancy Group (n=72)

Laboratory Features	Mean (SD)/*n* (%)
Obstetric History [Gravidity, Parity, Abortus (GPA) System]	
Gravidity	1.94 (0.85)*
Primigravida	26 (36.10%)**
Multigravida	46 (63.90%)**
Parity	0.83 (0.73)*
Nullipara	26 (36.10%)**
Primipara	32 (44.00%)**
Multipara	14 (19.40%)**
Abortus	0.15 (0.43)*
Gestational Age (weeks)	34.85 (8.60)*
1st Trimester	5 (6.90%)**
2nd Trimester	5 (6.90%)**
3rd Trimester	62 (86.10%)**
Pre-Term	9 (12.50%)**
Early-Term	15 (20.8%)**
Full-Term	32 (44.40%)**
Late-Term	5 (6.90%)**
Post-Term	1 (1.40%)**

*Mean (SD). **n (%)

Table 3: Clinical feature differences

Clinical Features	Total samples (n=245) n (%)	Differences		
		Pregnancy (n=72) n (%)	Non-Pregnancy (n=173) n (%)	p
Length of Stay (days)	8.70 (3.38)	8.96 (0.48)	9.29 (0.40)	0.630*
Symptoms				
Present of any Symptoms	224 (91.40%)	70 (97.20%)	154 (89.00%)	0.066***
Fever	122 (49.80%)	30 (41.70%)	92 (53.20%)	0.133***
Cough	141 (57.60%)	30 (41.70%)	111 (64.20%)	0.002***
Fatigue	63 (25.70%)	26 (36.10%)	37 (21.40%)	0.025***
Anorexia	10 (4.10%)	1 (1.40%)	9 (5.20%)	0.289**
Shortness of Breath	119 (48.60%)	43 (59.70%)	76 (43.90%)	0.035***
Sputum Production	17 (6.90%)	5 (6.90%)	12 (6.09%)	1.000**
Myalgia	16 (6.50%)	6 (8.30%)	10 (5.80%)	0.570**
Headache	49 (20.00%)	12 (16.70%)	37 (21.40%)	0.505***
Confusion	3 (1.20%)	0 (0.00%)	3 (1.70%)	0.558**
Rhinorrhea	60 (24.50%)	23 (31.90%)	37 (21.40%)	0.112***
Sore Throat	43 (17.60%)	10 (13.90%)	33 (19.10%)	0.431***
Hemoptysis	0 (0.00%)	0 (0.00%)	0 (0.00%)	
Vomiting	46 (18.80%)	13 (18.10%)	33 (19.10%)	0.995***
Diarrhea	24 (9.80%)	3 (4.20%)	21 (12.10%)	0.094***
Nausea	78 (31.80%)	18 (25.00%)	60 (34.70%)	0.183***
Anosmia	22 (9.00%)	5 (6.90%)	17 (9.80%)	0.636***
Ageusia	8 (3.30%)	1 (1.40%)	7 (4.00%)	0.443**

*Independent T-Test, **Fisher Exact Test, ***Chi-square test

Discussion

This study reports the presentation of COVID-19 in hospitalized pregnant and non-pregnant females. Data from demographics, clinical manifestations, and laboratory examinations were analyzed. This study was conducted for a longer period (3 years) than other studies (less than one year).[12,13] This study also uses a sample with a younger mean age (29.25 [5.34] years old) compared to other studies.[14–17] According to this study, the clinical presentation of SARS-CoV-2 infection during pregnancy mostly seems similar to that of non-pregnant females, as previously reported.[14–17] However, we found cough to be the most common presenting symptom in the entire sample, as opposed to fever, which was previously described as the most common presenting symptom. Nevertheless, fever was the second most common clinical symptom in the whole sample of this study.

Based on clinical features, the results showed significant differences in clinical symptoms (cough, fatigue, and shortness of breath). Regarding cough symptoms, pregnant females experience significantly fewer cough symptoms, inversely proportional to non-pregnant females who mostly show cough. Studies showed that cough is the second most common symptom (58%) of COVID-19.[18]

Table 4: Laboratory feature differences

Laboratory Features	Total sample (*n*=245) Mean (SD)	Differences		*p*
		Pregnancy (*n*=72) Mean (SD)	Non-Pregnancy (*n*=173) Mean (SD)	
Complete blood count				
White Cell Count (WCC) [x10 (3)/ul]	7.397 (3.38)	10.021 (3.09)	7.949 (3.17)	<0.001*
Absolute Lymphocyte Count (ALC) [/ul]	1664.04 (860.00)	1462.21 (661.12)	1946.79 (946.35)	<0.001**
High Fluorescence Lymphocyte Count (HFLC) [%]	1.05 (0.93)	0.53 (0.68)	0.93 (1.06)	<0.001*
Lymphocyte [%]	27.69 (14.69)	15.68 (7.29)	26.56 (10.74)	<0.001*
Neutrophil [%]	63.90 (16.69)	75.60 (11.71)	64.09 (11.81)	<0.001*
Neutrophil Lymphocyte Ratio (NLR)	4.13 (4.26)	6.55 (4.06)	3.30 (2.45)	<0.001*
Red Cell Count (RCC) [x10 (6)/ul]	4.55 (0.51)	4.07 (0.46)	4.69 (0.56)	<0.001*
Hemoglobin (Hb) [g/dl]	12.79 (1.28)	11.45 (1.46)	12.75 (1.74)	<0.001*
Hematocrit (Hct) [%]	37.62 (3.77)	33.51 (3.74)	37.60 (4.54)	<0.001*
Platelet Count (PC) [x10 (3)/ul]	253.57 (76.97)	251.35 (80.80)	281.31 (100.25)	0.025*
Coagulation profile				
Prothrombin Time (PT) [seconds]	10.73 (1.49)	10.35 (1.55)	14.44 (9.56)	0.004*
International Normalized Ratio (INR)	0.72 (0.11)	0.69 (0.13)	1.07 (0.89)	0.005*
Activated Partial Thromboplastin Time (aPTT) [seconds]	33.35 (7.49)	35.09 (22.49)	43.93 (32.44)	0.128*
D-Dimer [ng/ml]	903.90 (1102.26)	2396.75 (2524.67)	869.65 (1446.86)	<0.001*
Electrolytes and renal profile				
Creatinine [mg/dl]	0.66 (0.19)	0.52 (0.16)	1.10 (2.62)	0.380*
Sodium (Na) [mmol/liter]	141.25 (2.66)	139.16 (2.80)	140.84 (3.35)	0.043*
Potassium (K) [mmol/liter]	3.52 (0.67)	3.62 (0.73)	3.49 (0.50)	0.794**
Calcium (Ca) [mmol/liter]	0.98 (0.07)	0.99 (0.15)	0.95 (0.12)	0.162*

*Independent *t*-Test, **Mann-Whitney test

Table 5: Multiple linear regression analysis predicting length of stay

Model	Unstandardized Coefficients B	Std. Error	Correlation Coefficients	*t*	*p*
(Constant)	80.62	12.24		6.59	<0.001*
White Cell Count (WCC) [x10 (3)/ul]	−0.60	0.16	−0.41	−3.71	0.003*
Lymphocyte [%]	−0.90	0.12	0.02	−7.37	<0.001*
High Fluorescence Lymphocyte Count (HFLC) [%]	−1.23	0.43	0.33	−2.88	0.013*
Neutrophil [%]	−0.80	0.11	−0.10	−7.28	<0.001*
Prothrombin Time (PT) [seconds]	16.92	4.15	0.12	4.07	0.001*
International Normalized Ratio (INR)	−235.21	55.43	0.09	−4.24	0.001*
D-Dimer [ng/ml]	0.00	0.00	0.15	4.90	<0.001*
Creatinine	4.04	1.88	0.12	2.15	0.051*
Potassium (K) [mmol/liter]	−1.90	0.57	−0.24	-3.35	0.005*

*Multiple linear regression test

However, most pregnant females infected with COVID-19 are asymptomatic. A study in New York found that 29 of 33 (87.90%) pregnant females with confirmed COVID-19 were asymptomatic.[19] Furthermore, a study in Indonesia also showed that only 24.20% of pregnant females who were confirmed positive for COVID-19 had signs and symptoms (cough, fever, dyspnea, odynophagia, myalgia, nausea, and vomiting) at admission.[20]

Fatigue was one of the most commonly reported symptoms in pregnant females with COVID-19 infection after fever and cough.[21] This study shows that the prevalence of fatigue in maternal COVID-19 was significantly higher than in non-pregnant females. This is in line with several studies that showed an increasing risk of fatigue in pregnant females with COVID-19 infection, as well as a 2.4-fold increased risk in more severe infection.[21,22] Fatigue during COVID-19 or other acute infections may be linked to inflammation mechanisms and dysregulation of the hypothalamic-pituitary-adrenal axis and the autonomic nervous system.[4,22] Even though the exact cause remains poorly understood, several immune response factors are suggested to play roles in short-term and long-term fatigue symptoms in pregnant females with COVID-19 infection.[22] In addition, this study also showed a significant difference in the higher presence of shortness of breath in pregnant patients. In cases of pulmonary infections such as COVID-19, shortness of breath occurs due to inflammation that fills the alveoli with exudate; this inhibits the diffusion of oxygen from the alveoli to the capillaries.[23] Subsequently, in a normal pregnancy, there is also an increase in the basal metabolic rate, which makes the body need more oxygen. In addition, there is also edema of the airway mucosa and an increase in the diaphragm due to an enlarged uterus. This causes difficulties in meeting oxygen needs, manifesting as shortness of breath.[24] However, there were no significant differences in other clinical symptoms.

Based on laboratory features, this study found significant differences in almost all laboratory features. Our result study shows a significantly higher percentage of neutrophils and leukocyte values in pregnant females than in non-pregnant females. These results are in line with other studies.[25-28] In cases of infections such as COVID-19, hyperactivity of the immune response may trigger a cytokine storm that continuously stimulates neutrophil production and activation.[29] Subsequently, in normal pregnancy, the leukocyte value physiologically increases to 5,600–13,800/mm^3 in the first trimester, and it tends to increase further with increasing gestational age in response to physiological stress due to the pregnancy process.[30] It should also be remembered that neutrophils are the largest component of leukocytes; disruption of neutrophil apoptosis as a consequence of normal pregnancy causes neutrophilia, which automatically supports the occurrence of leukocytosis.[31] Furthermore, immunosuppression conditions in normal pregnancy also make pregnant COVID-19 patients more susceptible to bacterial coinfection. This condition underlies the increase in neutrophils, considering that neutrophils act as the first line of elimination of extracellular pathogens such as bacteria.[29,32]

However, we found a significantly lower percentage of lymphocytes and ALC in pregnant females. These results are in line with other studies.[26,28] Viral infections generally cause lymphocytosis, with only a few viruses, such as SARS-CoV-2 and Ebola, causing lymphopenia. In cases of COVID-19 infection, lymphopenia may mark the disease's severity.[33] Several mechanisms could cause lymphopenia, including cytokine storm, which produces excessive secretion of pro-inflammatory cytokines, such as Tumor Necrosis Factor α (TNF-α). It may also induce lymphocyte apoptosis, lymphocyte sequestration in target organs such as the lungs and gastrointestinal tract; suppression of the formation of hematopoietic progenitor cells in the bone marrow, suppression of thymus activity; and Activation-Induced Cell Death (AICD) in lymphocytes.[32,34] Subsequently, in normal pregnancy itself, the lymphocyte value also decreases due to several mechanisms, including prostaglandins that are produced by the placenta, which have an immunosuppressive effect of preventing fetal allograft rejection during implantation,[35] increased estrogen in pregnancy that suppresses the activity of the thymus as a site for maturation of T lymphocytes.[36]

Furthermore, HFLC are lymphocytes with high fluorescence activity (B lymphocytes that produce antibodies). An increase in HFLC indicates infection. In the case of COVID-19, there was an increase in HFLC and the worsening of the patient's clinical condition. In this study, the mean percentage of HFLC in both groups was still within normal limits. No mechanism can explain this, but it can be predicted related to the hospital admission time of the sample in this study. It should be noted that the increase in HFLC only occurred in the 2nd week after clinical symptoms appeared.[37] This study also reported a significant difference, where the percentage of HFLC in pregnant COVID-19 patients was lower. This can be attributed to the lower initial number of lymphocytes, even in normal pregnant people, so there are fewer plasma cell-forming precursors during infection.[35] In addition, the NLR was also significantly higher in pregnant COVID-19 females. An increase in neutrophils and a decrease in lymphocytes may automatically increase the NLR value. A previous study shows that NLR could be a mortality indicator in COVID-19 cases.[38]

Afterward, pregnant females' RBC, Hb, and Hct levels were significantly lower. Physiologically, pregnant females experience anemia as indicated by a low RBC count, Hct, or Hb concentration.[39] Another study shows that Hb was significantly lower (27), while the others

show no significant difference.[27,28] The decrease in the number of RBCs was exacerbated by infections in pregnant females, giving a significant difference. This is clarified by the results of a study, which showed that the RBC levels of pregnant females infected with COVID-19 were lower than those of pregnant females who were not infected (3.40 [1.60] vs. 3.80 [1.20] million/µl).[40] On the other hand, increased blood flow to the uterus and several organs during pregnancy also expands circulating blood volume. Plasma volume expansion outweighs the increase of RBCs, explaining the decrease in Hb concentration as one of the maternal anemias pathophysiology's that could complicated by other causes, such as iron deficiency and infection.[41]

Altered inflammatory responses in COVID-19, provoked by harmful effects on the respiratory system, also put the host in inflammatory and hyper-metabolic states. Inflammation, primarily the innate immune system, decreases iron bioavailability in circulation.[42,43] This may complicate the underlying maternal susceptibility to anemia in the first place.[4,42] In addition, there was a disproportionate increase in the volume of RBC and plasma in pregnancy, so that the Hct level may have decreased.[44] Subsequently, COVID-19 infection may also cause significant changes in the size and stiffness of RBC, decreased Hct level, and increased red blood cell amplitude or Red Cell Distribution Width (RDW).[45] The low physiological condition plus the COVID-19 infection suffered by pregnant females in the subjects of this study caused a significant difference in Hct levels in pregnant and non-pregnant females. Hereafter, several studies also reported a drop in platelet count during pregnancy, with lower median and ranges of platelet counts in various trimesters compared to non-pregnant females.[4,41] A similar volume expansion mechanism, as seen in maternal anemia, was found to be related, as well, to the pooling of almost one-third of circulating platelets in the spleen sinusoid due to the lower low flow-rate condition.[46,47] In addition, the inflammatory and hypercoagulability state in COVID-19 may also result in a decrease in circulating platelets that may be due to direct infection in marrow cells, platelet aggregation, platelet destruction, and increased platelet needs due to the formation of microthrombi.[46,48] This may worsen the underlying thrombocytopenia state seen in normal females, as shown in the result of this study, which showed significantly lower mean platelet count in pregnant females infected with COVID-19.[48]

Previous studies stated that PT and aPTT are shortened, especially towards term, in all pregnant females.[41,47] Hypercoagulability during pregnancy may increase clotting factors (factors VII, VIII, and X; von Willebrand factor; D-dimer; C-reactive protein; and fibrinogen).[46] COVID-19 infection may also affect several components of Virchow's triad: stasis and turbulence of blood flow, endothelial injury, and dysfunction that worsen the hypercoagulability state in pregnant females with COVID-19 infection.[4,49,50] This study found shortened PT and international standard calculation of PT, INR. INR is derived from PT calculation-related variations, the type of reagents used, and the sensitivity differences in the tissue factor (TF) activator.[51] This is single-center research; thus, only a slight difference between PT and INR significance was observed due to the same control used in all patients. Significant shortened PT and INR were found but not in aPTT. PT/INR was significantly reduced with slight differences due to INR derived from PT calculation. Shortened PT and aPTT were found in pregnancy, especially towards term, but several studies showed significant shortening of PT but not APTT in pregnancy complicated with COVID-19.[47,50] PT is a marker of the extrinsic coagulation pathway, and aPTT is a marker of the intrinsic coagulation pathway.[51] While the pregnancy hypercoagulability state results in higher activity of both intrinsic and extrinsic pathways, COVID-19 coagulopathy is primarily due to increased complement activation.[50,52] Cytokine storm in COVID-19 immunopathogenesis contributed to endothelial cell damage that resulted in the release of TF and activation of extrinsic coagulation pathways.[52] Although this correlation was confirmed by the interaction between the levels of IL-6, a marker of cytokine storm, and fibrinogen in ICU-admitted COVID-19 patients, more study needs to confirm these findings due to different opinions and results from several studies about this complex interaction, especially in the pregnant patients.[52–54]

This study also shows that D-dimer in pregnant females infected with COVID-19 was significantly higher. These results are in line with other studies.[25-28] An increase in d-dimer is indeed one of the markers of a critical state in COVID-19 infection.[55] Pregnancy typically causes a state of physiological hypercoagulability, increasing fibrin turnover as indicated by the rise in D-Dimer. The D-Dimer reference value range in pregnant females can reach 483-2256 ng/mL in the 3rd trimester.[56] The increase in D-Dimer in COVID-19 occurs because pro-inflammatory conditions during infection cause endothelial dysfunction, resulting in increased thrombotic activity.[57] This may explain the reason why the d-dimer value of pregnant females infected with COVID-19 is much higher. A previous study shows that patients with D-dimer >1000 ng/ml have a 20-fold higher risk of death compared to those with lower D-dimer values, so more intensive monitoring can be carried out on pregnant females infected with COVID-19.[55]

Sodium levels in pregnant females were significantly lower in this study. However, sodium levels in both groups were still within normal limits. Pregnancy tends to cause hypervolemia in the mother due to fluid retention, resulting in lower sodium levels in pregnant females than in non-pregnant females.[58] This theory is in line with the results of our study, which showed that pregnant female's sodium levels were lower. COVID-19 can cause a state of dysmetria, where hyponatremia is common and can increase

mortality.[59] Although hyponatremia is associated with COVID-19 infection, the results of normonatremia in this study are in agreement with those of other studies, which showed that 68% of study subjects had normal sodium levels and only 29.10% of them had hyponatremia.[60] One research also showed a similar situation where hyponatremia only occurred in 20.50% of cases of COVID-19 pneumonia infection.[59] Meanwhile, this study showed no significant difference in potassium levels. A study by Diourgu, 2020 showed that sodium, potassium, chloride, and bicarbonate remained unchanged in the three trimesters of pregnancy.[61] This happens because pregnant females have the opposite mechanism between aldosterone and progesterone. Subsequently, Calcium levels did not show a significant difference between pregnant and non-pregnant females, possibly due to calcium levels that tended to be low during pregnancy and hypocalcemia caused by COVID-19 infection.[62] Expansion of intravascular fluid causes gestational hypoalbuminemia, resulting in a decrease in total calcium concentration.[63] COVID-19 infection can also cause increased levels of unsaturated fatty acids and cytokine storms, leading to hypoalbuminemia and low serum calcium concentration.[62]

In addition, serum creatinine levels were also not significantly different. The mean value of creatinine in pregnant females in this study was still within normal limits (0.52 mg/dl), and creatinine in non-pregnant females was still at the highest limit of normal values (1.10 mg/dl). With advancing gestational age, the glomerular filtration rate during pregnancy may increase physiologically, and serum creatinine levels decrease.[64] The absence of an increase in creatinine in non-pregnant females infected with COVID-19 indicated that the mean of our study subjects was not at a severe level.

This study also has limitations that should be mentioned. The study's design is retrospective, exposing our results to potential bias. Our study population is relatively small; therefore, generalizability may limit. This study included pregnant females of different gestational ages and trimesters but did not analyze the differences. Additionally, this study did not expose data concerning other examinations, such as gas blood analysis, management, and complications. The strength of our research should also be acknowledged. All patients were diagnosed in a single medical center and evaluated by the same team and laboratory during the same period.

Conclusion

Considerations regarding clinical and laboratory features of COVID-19 are important in COVID-19 in terms of diagnosis and management. Significant differences between pregnant and non-pregnant female inpatient patients hospitalized with COVID-19 were found, especially in laboratory features. Laboratory features were also discovered to significantly predict the length of stay. This can be the basis for the development of further studies and decision-making in the management of COVID-19 infection, especially during pregnancy.

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Conflicts of interest

Nothing to declare.

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