Original Article

Evaluation of the Relationship between Early Clinical Manifestations and Changes in Biochemical, Inflammatory, and Coagulation Parameters and the Prognosis of Pregnant Women with COVID-19 Admitted to the ICU

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Abstract

Background: In the SARSCov2 virus epidemic, pregnant women are more susceptible to infectious diseases due to changes in biochemical parameters and are at higher risk of severe respiratory disease and pneumonia. This study aimed to evaluate the biochemical, inflammatory and coagulation parameters in pregnant women with severe disease conditions (as one of the high-risk groups) as well as prognosis and outcome.

Materials and Methods: This cross-sectional study was performed on 135 pregnant women with COVID-19 admitted to ICU. Demographic and clinical information and laboratory parameters of the patients were evaluated and recorded at the time of admission and in the next follow-up until discharge or death in addition to the outcome and also the pregnancy outcome.

Results: The mortality rate of pregnant women with COVID-19 was 9.6%. The mortality rate decreases with increasing Hb (OR (95% CI): 0.68 (0.47-0.99); *P* value = 0.043) and lymphocytes (OR (95% CI): 0.92 (0.85-0.96); *P* value = 0.028) and will increase significantly with increasing PT (OR (95% CI): 1.24 (1.01-1.51); *P* value = 0.037), INR (OR (95% CI): 1.89 (1.26-2.25); *P* value = 0.004), D-dimer (OR (95% CI): 1.68 (1.10-2.08); *P* value = 0.027), and LDH (OR (95% CI): 1.20 (1.01-1.61); *P* value = 0.010).

Conclusion: According to the results of the present study, inflammatory factors such as leukocytes, neutrophils, NLR, CRP have an increasing and lymphocytes have a decreasing trend, so that lymphocytopenia is more common in non-survivors. In addition, increase of PT, INR, D-dimer and LDH and decrease of Hb were significantly associated with increased chance of mortality. But fibrinogen, ferritin, ALT and AST were not significantly associated with mortality in these women.

Keywords: Mortality, pregnant women, SARS-CoV-2

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Introduction

The new coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a potentially life-threatening respiratory disease, also called coronavirus disease 2019 (COVID-19). The virus contains ribonucleic acid (RNA) that is isolated from the family Coronaviridae and belongs to Nidovirales. The virus generally causes respiratory and gastrointestinal infections that may range from mild self-limiting conditions to more severe cases, such as viral pneumonia with systemic dysfunction.[1,2]

Although pregnant women are generally more susceptible to infectious diseases than the general population and

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are particularly at risk for severe respiratory disease and pneumonia, they are considered a high-risk group in the epidemic because they have a weaker immune system; moreover, their upper respiratory tract is swollen with high levels of estrogen and progesterone, and the lungs' surface becomes restricted, making pregnant women more susceptible to such diseases.[3-5] Also, physiological changes during pregnancy cause intolerance to hypoxia.[6,7] In addition, cytokine storm can be one of the causes of severe and even fatal in infection pregnant women,[7] which together make pregnant women, their fetuses, and newborns more vulnerable to infectious epidemics.[8] For example, in the flu epidemic of 1918 or 2009, the mortality rate was 2.6% of the total population and 37% of pregnant women, and they were four times more likely to die than other hospitalized patients.[6] A major analysis in the United States about the COVID-19 pandemic reported that pregnant women are at greater risk of admission to the intensive care unit (ICU) and mechanical ventilation than nonpregnant women.[9]

It is also important to note that pregnancy, in addition to its effect on cardiopulmonary physiology, is associated with several changes in a woman's immunological profile and coagulation parameters. In pregnancy, a pro-inflammatory condition occurs with the migration of immune cells into the myometrium and high levels of pro-inflammatory cytokines found in both cervical tissue and peripheral blood.[10] Unfortunately, a unique feature of COVID-19 is the release of large amounts of inflammatory cytokines, which, in severe cases, is similar to macrophage activation syndrome. Some biomarkers, including D-dimer, C-reactive protein (CRP), lactate dehydrogenase (LDH), and ferritin, have been considered a factor to monitor the progression of COVID-19.[11-13] Changes in leukocyte counts (such as lymphocytopenia or increased ratio of neutrophil to lymphocyte (NLR)) also appear to be associated with disease severity.[12] Also, due to the increase in D-dimer, fibrinogen (Fgn), and hypercoagulability, severe coagulopathy due to COVID-19 may be more likely in pregnant women.[14]

However, there are many potential causes (such as direct liver injury, hepatic ischemia, drug-induced liver injury (DILI), muscle breakdown, inflammatory responses, and congestive hepatopathy) for elevated liver enzymes in SARS-CoV-2 patients.[15,16] Some studies have, however, reported a slight increase in alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) activity during the third trimester of pregnancy.[17,18] Therefore, the trend of changes in liver factors in pregnant women with COVID-19 can also be significant.

Given the unknown effects of COVID-19 on biomarkers and blood factor changes during pregnancy, evaluation of biochemical parameters, such as inflammatory, coagulation, and liver factors, can be very important. In this regard, some studies have investigated the changes in laboratory factors in patients with COVID-19 (pregnant or nonpregnant), which indicate leukopenia or leukocytosis, lymphopenia, and increase in CRP, LDH, AST, ALT, D-dimer, interleukin (IL)-6, and troponin.[3,4,19-21] However, limited studies have so far evaluated COVID-19 in pregnant women with severe disease conditions (as one of the high-risk groups) and followed the status of their biochemical parameters, as well as their prognosis and outcome.

Therefore, this study aimed to evaluate the initial clinical manifestations and changes in biochemical, inflammatory, and coagulation parameters and their role in the prognosis of pregnant women with COVID-19 admitted to the ICU.

Materials and Methods

This cross-sectional study was conducted from 2020 to 2021 in two educational–medical centers of Amin and Al-Zahra affiliated with the Isfahan University of Medical Sciences, Iran. The study population included all pregnant women with COVID-19 admitted to the ICU.

These patients had COVID-19 viral pneumonia based on the reverse transcription polymerase chain reaction test or chest computed tomography (CT) scan, and according to the national protocol classification, the disease level was moderate to severe, severe, or critical and required hospitalization in the ICU (with respiratory rate (RR) >24 bpm, oxygen saturation (SPO2) <90%, PaO2/FiO2 <300 mmHg, and more than 50% increase in lung involvement on CT). Due to the limited population of the study, all eligible people up to 135 people were included in the census.

Patients' medical histories were extracted from the hospital's archives after obtaining the code of ethics from the ethics committee of Isfahan University of Medical Sciences (approval code: IR.MUI.MED.REC.1400.306) and permission from Amin and Al-Zahra educational centers of Isfahan University of Medical Sciences. Then, the demographic information of patients, including maternal age, gestational age, trimester, history of abortion, and underlying diseases, such as hypertension, diabetes, cardiovascular diseases, rheumatism, and other diseases, were recorded. Also, the patients' clinical information was recorded at the ICU admission, including early signs of developing COVID-19 (such as fever, cough, shortness of breath, chest tightness, sore throat, myalgia, weakness or fatigue, nausea or diarrhea, and headache), the results of two tests of high-resolution computed tomography (HRCT), PCR, and vital signs, such as heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), RR, SPO2, and temperature. Also, laboratory information of patients was recorded at the time of ICU admission and subsequent follow-ups until the time of discharge (or death), including white blood cells (WBCs), lymphocytes, neutrophils, NLR, platelets (PLTs), prothrombin time (PT), activated partial thromboplastin time (aPTT), Fgn, D-dimer, LDH, CRP, ferritin (Fer), AST, ALT, and hemoglobin (Hb). Patients' follow-up time was recorded from the time of admission to the time of discharge (or death), as well as the complications and pregnancy outcomes.

It should be noted that the patients were discharged from the ICU with a decrease in respiratory distress, an increase in SPO2 >95%, RR <24, and a decrease in inflammatory factors (such as D-dimer, and CPR) according to the doctor's final diagnosis.

Finally, the collected data were analyzed by Statistical Package for the Social Sciences (SPSS) version 26. The data were displayed as *n* (%) or mean ± standard deviation (SD) and median (interquartile region (IQR)). In addition, the Chi-square and Fisher's exact tests were used to examine the qualitative data. The independent *t*-test and the Mann–Whitney test were used to detect the mean of quantitative data between the non-survivor and survivor groups. Logistic regression was used to examine factors associated with mortality in pregnant women with COVID-19, and the odds ratio of mortality was shown with odds ratio (95% confidence interval (CI)). In all analyses, a significance level of less than 0.05 was considered significant.

Results

This study was performed on 135 pregnant women with COVID-19 admitted to the ICU. Of these, 122 (90.4%) survived and 13 (9.6%) were dead. The duration of ICU hospitalization in the non-survivor group, with a mean of 8.38 ± 5.60 days, was significantly longer than that in the survived group, with a mean of 5.44 ± 5.00 days (*P* value = 0.039). The gestational age of the non-survivors, with a mean of 26.00 ± 6.51 weeks, was significantly lower than that in survivors, with a mean of 29.00 ± 6.24 weeks. In fact, with increasing pregnancy trimester, the mortality rate of patients decreased significantly (*P* value = 0.001). The most common symptoms were cough, shortness of breath, fever, and fatigue or weakness with 74.8%, 71.9%, 52.6%, and 27.4%, respectively, but only two symptoms of shortness of breath and myalgia in non-survivors were significantly higher than that in survivors (*P* value <0.05). SPO2 at the time of admission to the ICU in the non-survivor group had a mean of 86.76 ± 5.98%, which was less than that in survivors, with a mean of 90.17 ± 5.73%, and HR in the non-survivor group, with a mean of 112.46 ± 11.38 bpm, was higher than that in survivors, with a mean of 103.81 ± 18.29 bpm (*P* value <0.05). Finally, there was no significant difference between the two groups in terms of delivery (vaginal and cesarean sections) (*P* value >0.05). However, the number of primary thyroid lymphoma (PTL) cases in non-survivors was significantly higher than that in survivors. In addition, the incidence of intrauterine fetal demise (IUFD) in non-survivors (38.5%) was significantly higher than that in survivors (4.1%), respectively (*P* value = 0.001). Also, only two cases of abortion were reported in non-survivors (*P* value <0.05) [Table 1].

Examinations of inflammatory factors (including lymphocytes, neutrophils, NLR, CRP, and WBC) revealed that, at the time of admission to the ICU, the WBC in the non-survivor group (median (IQR): 9.35 (6.10–14.90); × 109/L) was significantly higher than that in survivors (median (IQR): 7.30 (6.00–9.52); × 109/L) (*P* value <0.05). From days 4 to 13, an increase was observed in WBC, which was still higher than in the survivor group. In the deceased group, there were fewer lymphocytes and more neutrophils than in the survivor group, although there was no significant difference at the beginning of admission to the ICU (*P* value >0.05), but from day 6 onward, this difference was obvious (*P* value <0.05). Furthermore, NLR on days 4 to 13 of hospitalization in the non-survivor group was significantly higher than that in the survivor group (*P* value <0.05). CRP declined over time although it was higher in the non-survivor group than the survivor group. Coagulation factors, such as PLT, PT, PTT, international normalized ratio (INR), LDH, Fgn, and D-dimer, did not differ significantly between the two groups at the time of admission to the ICU (*P* value >0.05), but over time in the ICU, blood coagulation time in the non-survivor group had a significant increase compared with the survivor group (*P* value <0.05). LDH at the time of admission to the ICU in the non-survivor group (median (IQR): 685.00 (541.00–1061.00) U/L) was significantly higher than that in the survivor group (median (IQR): 579.00 (437.00–706.00) U/L) (*P* value <0.05). The level of D-dimer in the non-survivor group significantly increased over time (since mid-ICU hospitalization) compared with the survivor group. At the time of death, the level of D-dimer in the non-survivor group (median (IQR): 1745.00 (1122.00–2676.00) (μg/ml) was significantly higher than that in the survivor group (median (IQR): 1250.00 (682.75–1918.75) (μg/ml) (*P* value <0.05). Other biochemical and hepatic parameters, such as Hb, Fer, ALT, and AST, did not differ significantly between the two groups (*P* value >0.05). However, the AST upon entry to the study in the non-survivor group (median (IQR): 51.50 (37.50–83.70) U/L) was significantly higher than that in survivors (median (IQR): 40.50 (31.00–62.75) U/L) (*P* value <0.05); this difference became insignificant over time (*P* value >0.05) [Figure 1].

The evaluation of factors related to the mortality chance of pregnant women with COVID-19 is presented in Table 2. For this purpose, each of the factors of significant differences with mortality was included in the logistic regression model and the results showed that the chance of mortality increased with ICU length of stay, myalgia, and HR, while increasing gestational age and high SPO2 at the time of ICU admission reduced mortality. However, none of these factors played a statistically significant role in the mortality of pregnant women (*P* value >0.05). In contrast, considering the studied biochemical factors, the mortality rate decreases with increasing Hb (odds ratio (OR) (95% CI): 0.68 (0.47–0.99); *P* value = 0.043) and lymphocytes (OR (95% CI): 0.92 (0.85–0.96); *P* value = 0.028) and will increase significantly with increasing PT (OR (95% CI): 1.24 (1.01–1.51); *P* value = 0.037), INR (OR (95% CI): 1.89 (1.26–2.25); *P* value = 0.004), D-dimer (OR (95% CI): 1.68 (1.10–2.08);

Table 1: Basic and clinical characteristics between two groups of survivor and non-survivor pregnant women with COVID-19

Characteristics	Total (*n*=135)	Non-survivors (*n*=13)	Survivors (*n*=122)	*P*
Hospital length of stay (day)	10.62±6.80	10.45±6.77	12.23±7.18	0.408
ICU length of stay (day)	5.72±5.12	8.38±5.60	5.44±5.00	0.039
Age (year)	31.57±5.71	31.64±5.69	30.84±6.06	0.632
PCR positive	135 (100%)	13 (100%)	122 (100%)	-
HRCT positive	127 (94.1%)	13 (100.0%)	114 (97.4%)	0.559
Gravidity				
Primigravida	5 (3.7%)	1 (7.7%)	4 (3.3%)	0.753
Multigravida	130 (96.3%)	12 (92.3%)	118 (96.7%)	
Abortion history				
Non	96 (71.1%)	8 (66.7%)	88 (72.7%)	0.596
1–2	33 (24.5%)	3 (25%)	30 (24.8%)	
>2	6 (4.4%)	2 (15.4%)	4 (3.3%)	
Gestational age (week)	28.71±6.31	26.00±6.51	29.00±6.24	0.041
Trimester 1	1 (0.7%)	1 (7.7%)	0 (0%)	0.001
Trimester 2	42 (31.1%)	5 (38.5%)	37 (30.3%)	
Trimester 3	92 (68.1%)	7 (53.8%)	85 (69.7%)	
Comorbidities				
Diabetes mellitus	37 (27.4%)	2 (15.4%)	35 (28.7%)	0.546
Rheumatism	3 (2.2%)	0 (0.0%)	3 (2.5%)	0.567
Hypertension	9 (6.7%)	0 (0%)	9 (7.4%)	0.598
Cardiovascular disease	4 (3%)	1 (7.7%)	3 (2.5%)	0.336
Symptoms				
Fever	71 (52.6%)	7 (53.8%)	64 (52.5%)	0.924
Cough	101 (74.8%)	12 (92.3%)	89 (73.0%)	0.126
Shortness breath	97 (71.9%)	13 (100.0%)	84 (68.9%)	0.018
Chest pain	9 (6.7%)	1 (7.7%)	8 (6.6%)	0.876
Chills	24 (17.8%)	2 (15.4%)	22 (18.0%)	0.812
Hyposmia or anosmia	3 (2.2%)	0 (0.0%)	3 (2.5%)	0.567
Abdominal pain	1 (0.7%)	0 (0.0%)	1 (0.8%)	0.743
Sore throat	4 (3%)	0 (0.0%)	4 (3.3%)	0.507
Weakness or fatigue	37 (27.4%)	2 (15.4%)	35 (28.7%)	0.307
Headache	15 (11.1%)	2 (15.4%)	13 (10.7%)	0.606
Nausea or diarrhea	2 (1.5%)	0 (0.0%)	2 (1.6%)	0.642
Myalgia	6 (4.4%)	2 (15.4%)	4 (3.3%)	0.044
Treatment				
Remdesivir	108 (80%)	13 (100%)	95 (77.9%)	0.070
Tocilizumab	13 (9.6%)	2 (15.4%)	11 (9%)	0.363
Dexamethasone	87 (64.4%)	9 (69.2%)	78 (63.9%)	0.705
Prednisolone	85 (63.0%)	8 (61.5%)	77 (63.1%)	0.911
Betamethasone	8 (5.9%)	2 (15.4%)	6 (4.9%)	0.129
Antibiotics	132 (97.8%)	12 (92.3%)	120 (98.4%)	0.264
Vital signs				
Systolic blood pressure (mmHg)	113.48±14.33	112.99±14.42	118.15±13.10	0.201
Diastolic blood pressure	69.63±10.05	69.58±9.93	70.15±11.54	0.846
Oxygen saturation	89.84±5.82	86.76±5.98	90.17±5.73	0.045
Respiratory rate (breaths/min)	24.94±9.37	24.55±9.18	28.53±10.72	0.146
Heart rate (beats/min)	104.64±17.90	112.46±11.38	103.81±18.29	0.025
Temperature	38.76±17.14	38.93±18.03	37.20±0.89	0.297
Outcome of pregnancy				
Vaginal delivery	3 (2.2%)	1 (7.7%)	2 (1.6%)	0.264
Preterm delivery GA <37 w	1	1	0	
Term delivery ≥37 w	2	0	2	

Contd...

Table 1: Contd...

Characteristics	Total (*n*=135)	Non-survivors (*n*=13)	Survivors (*n*=122)	*P*
Cesarean delivery	39 (28.9%)	5 (38.5%)	34 (27.9%)	0.521
Preterm delivery GA <37 w	31	5	26	
Term delivery ≥37 w	8	0	8	
Continuation of pregnancy	81 (60%)	0 (0%)	81 (66.4%)	0.001
Intrauterine fetal demise	10 (7.4%)	5 (38.5%)	5 (4.1%)	0.001
Abortion	2 (1.5%)	2 (15.4%)	0 (0.0%)	0.096

Table 2: Logistic regression in assessing factors associated with mortality in pregnant women with COVID-19

Factors	Odds ratio (95% CI)	*P*
ICU length of stay (day)	1.08 (0.99-1.17)	0.067
Gestational age	0.61 (0.18-2.04)	0.423
Myalgia	1.16 (0.88-2.65)	0.068
SPO2 (%)	0.92 (0.85-1.01)	0.055
Heart rate (beats/min)	1.03 (0.99-1.07)	0.093
Change in inflammation parameters		
WBC (×10^9/L)	1.96 (0.77-1.19)	0.713
Lymphocytes (%)	0.92 (0.85-0.96)	0.028
Neutrophil (%)	1.07 (1.01-1.14)	0.037
NLR	1.14 (0.98-1.31)	0.084
CRP (mg/L)	1.07 (0.98-1.03)	0.519
Change in coagulation parameters		
PLT (×10^9/L)	0.99 (0.89-1.01)	0.418
PT (s)	1.24 (1.01-1.51)	0.037
aPTT (s)	1.00 (0.99-1.01)	0.550
INR	1.89 (1.26-2.25)	0.004
D-dimer (µg/ml)	1.68 (1.10-2.08)	0.027
Fgn (mg/Dl)	0.99 (0.98-1.02)	0.650
Fer (µg/L)	0.99 (0.99-1.01)	0.213
LDH (U/L)	1.20 (1.01-1.61)	0.010
Change in liver or biochemical parameter		
AST (U/L)	1.01 (0.99-1.01)	0.165
ALT (U/L)	0.99 (0.98-1.01)	0.401
Hb (g/dL)	0.68 (0.47-0.99)	0.043

WBC=White blood cells, NLR=Neutrophil-to-lymphocyte ratio, PLT=Platelet, PT=Prothrombin time, aPTT=Activated partial thromboplastin time, Fgn=fibrinogen, LDH=Lactate dehydrogenase, CRP=C-reactive protein, Fer=ferritin, AST=Aspartate aminotransferase, ALT=Alanine aminotransferase, Hb=Hemoglobin

P value = 0.027), and LDH (OR (95% CI): 1.20 (1.01–1.61); *P* value = 0.010) [Table 2].

Discussion

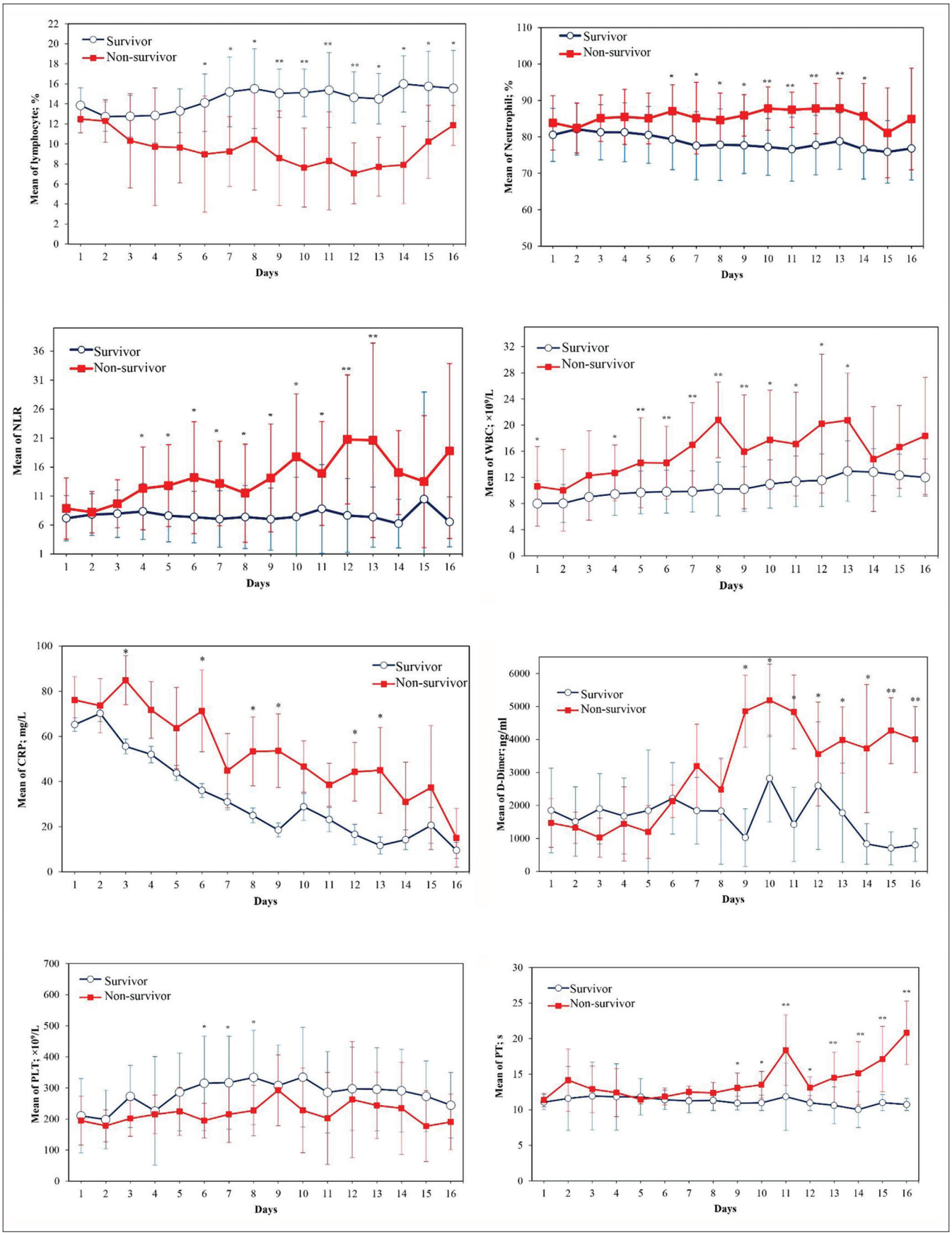
In the present study, the mortality rate in pregnant women with COVID-19 was 9.6%. The majority of critically ill patients were in the second and third trimesters of pregnancy. One patient in the first trimester of pregnancy died. The mortality rate in the second and third trimesters of pregnancy was reported as 38.5% and 53.8%, respectively. In addition, the most common symptoms of COVID-19 at the time of admission included cough, shortness of breath, and fever. The highest prevalence of pregnancy outcomes in non-survivors was IUFD and preterm labor, which was significantly higher than in survivors. The majority of survivors have been discharged from the hospital as their pregnancies continue.

In a large retrospective cohort study, Lombardi *et al*. reported a mortality rate of 1.6% in pregnant women with COVID-19.[14] Di Toro *et al*. in their systematic review reported an ICU admission rate of 8%, a stillbirth rate of 3, and a maternal mortality rate of 5.[22] It should be noted that our study population was pregnant women with COVID-19 in severe or moderate-to-severe disease condition (admitted to the ICU), so it seems logical that the mortality rate in this sample was higher.

According to some studies in the recent epidemic, the prevalence of preterm delivery, low birth weight, cesarean section, and neonatal ICU (NICU) admissions was higher in COVID-19 pregnant women than in general subjects.[23-25] In addition, although the majority of mothers will be discharged from the hospital without any serious complications, severe maternal morbidity and COVID-19-related prenatal deaths have been reported.[26] In general, there is little information on the consequences of maternal infection in the first and second trimesters of pregnancy.[27] There is some evidence that hyperthermia or fever during the first trimester of pregnancy, when organogenesis occurs, may be an environmental risk factor for fetal abnormalities, especially neural tube defects and miscarriage,[28] but in our study there was only one case of the first trimester that died after 5 days in the ICU.

It is also important to note that in our study the history of underlying diseases and the treatment protocol used for the patients, such as antibiotics, antivirals, and corticosteroids, were the same and there was no significant difference between the deceased and survivors. In fact, it can be said that the COVID-19 infection has played a significant role in the fate of these women that can also be due to the adverse effects of this virus on maternal blood parameters. For this purpose, the inflammatory, coagulation, hepatic, and other parameters of these patients during ICU admission are studied and interpreted.

In the study of inflammatory factors in our study, it was found that at the time of admission to the ICU, only the WBC of non-survivors was significantly higher than that of the survivors and the percentage of leukocytes has increased significantly by time. Other factors, such as neutrophils, lymphocytes, NLR, CRP, and D-dimer, did not differ between



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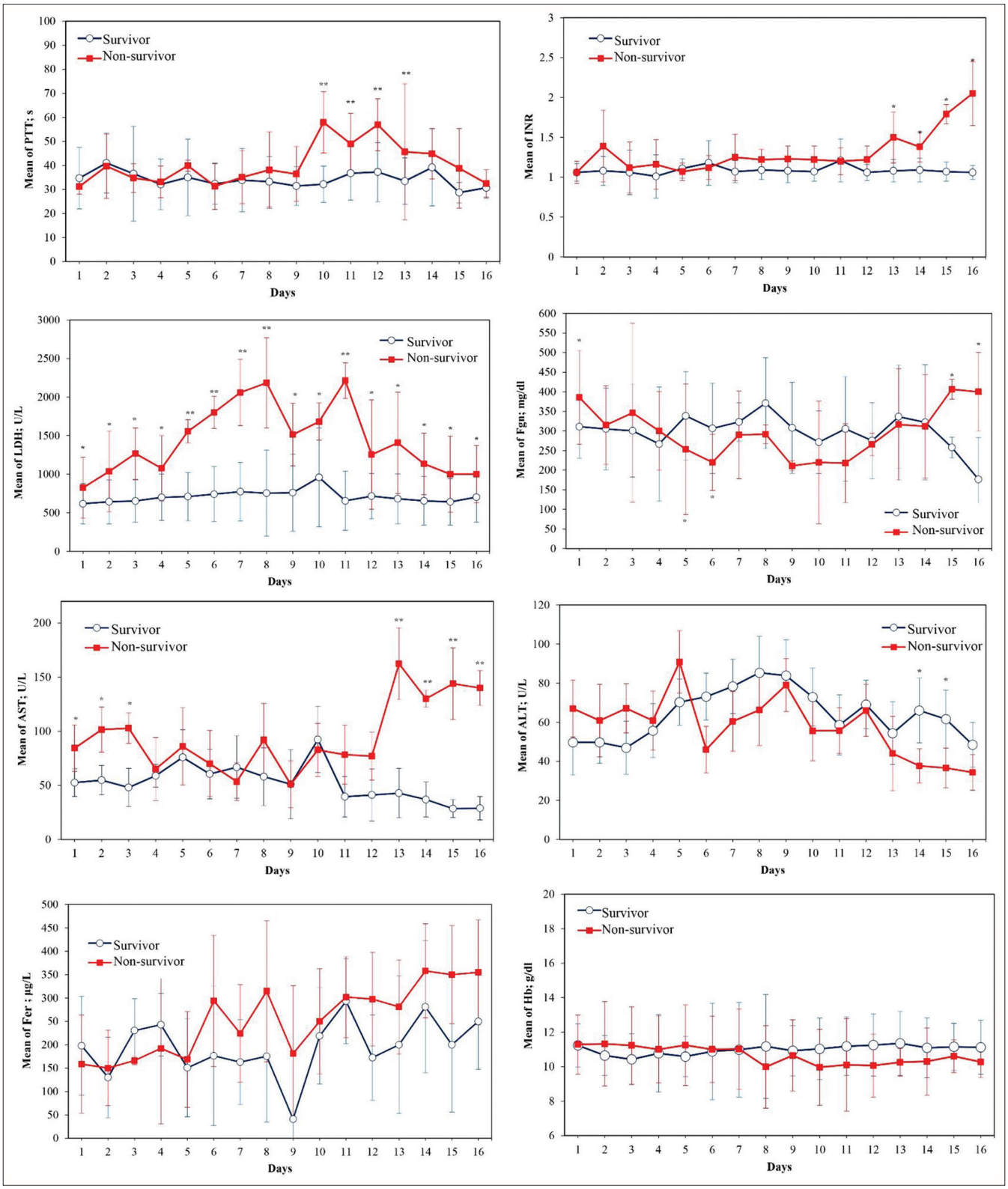

Figure 1: Changes in inflammatory, coagulation, hepatic, and other biochemical factors among two groups of survivor and non-survivor pregnant women with COVID-19

the two groups at the time of admission to the ICU. The difference in inflammatory factors was significant from the fourth day onward. Lymphocytes in non-survivors were associated with a significantly decreasing trend compared with the survivors, and in contrast, neutrophils and NLR had an upward trend in non-survivors compared with the survivors.

In fact, we have seen lymphocytopenia in non-survivors. Confirming the trend of changes in these factors, the results of logistic regression showed that the increase in lymphocytes and neutrophils significantly reduced the chance of mortality in pregnant women with COVID-19 (OR = 0.92) and increased (OR = 1.07), respectively. Although CRP was higher in non-survivor women than survivors, in the process of patients' ICU admission, the results were not stable and were associated with fluctuations, which eventually had a declining trend.

Consistent with the present study, Wang *et al*. in a study on nonpregnant patients with severe COVID-19 showed that the number of leukocytes has increased the chance of ICU admission by 1.5-fold, the absolute neutrophil count by 1.7-fold, and lymphopenia by 0.9-fold.[29] Similar results have been reported in other studies based on the association of laboratory factors with hospitalization, COVID-19 severity, ICU hospitalization, and mortality[30-32] as the inflammatory biomarkers have been introduced as a tool to assess the progress of COVID-19.[29,33,34] In their study, Servante *et al*. reported very different CRP levels during the disease in pregnant women, as well as the association of these high levels with disease severity.[12] They also stated that homocytometric parameters, leukocytes, neutrophils, lymphocytes, and NLRs are the markers whose values have changed significantly. In line with our study, they also stated that the lower the lymphocyte count at admission, the greater the likelihood of receiving oxygen supplementation during hospitalization, suggesting that additional care should be considered for the patients referred with decreased levels of these blood cells.

In fact, lymphocytopenia,[35] high NLR,[36] and high CRP[37] have all been related to disease severity or mortality. In the study of Yu *et al*., the number of absolute lymphocytes decreased significantly during the infection with this virus.[3] Therefore, our research confirms that these variables represent abnormal values even in pregnant women and reflect the course of disease.

However, the presence of hypercoagulable in patients with COVID-19 is another prominent clinical feature of patients with increased mortality and more severe disease. In this regard, the results of the present study showed that the D-dimer level of the studied women was more than 1000 μg/ml from the time of ICU admission with an upward significant increase in non-survivors in the ninth day of hospitalization compared with the survivors, while this factor has been controlled in the survived women and showed a downward slope. In this regard, there is evidence of an increasing trend of this factor, which supports the role of vascular endothelial and thrombosis factors in the pathogenesis of COVID-19.[38-43]

In addition, the results of the present study showed that although PLT levels were very slightly different between the two groups and could not be significantly associated with mortality in these patients, PT and PTT have been increasing over time in the second week of hospitalization in non-survivor pregnant women. The results of logistic regression showed that the increase in PT, INR, D-dimer, and LDH significantly affected the chance of mortality in pregnant women with COVID-19. LDH was one of the most important factors that increased significantly in non-survivor pregnant women compared with survivors, but Fgn was not significantly different between the two groups.

Consistent with the present study, the majority of studies also showed a significant increase in LDH and D-dimer.[44] In addition, another study reported an increase in ferritin levels due to secondary hemophagocytic lymphohistiocytosis (sHLH) and cytokine release syndrome in severe COVID-19 patients.[45] Based on body temperature, organomegaly, blood cell cytopenia, triglycerides, Fgn, AST, and ferritin levels, they proposed a predicted H-score to estimate the risk of sHLH.

In explaining the above results, it can be said that SARS-CoV-2 infects host endothelial cells through angiotensin-converting enzyme 2 (ACE2) (an integral membrane protein).[46] Patients with COVID-19 tend to show more ACE2-positive endothelial cells.[47] Therefore, vascular endothelial damage is commonly seen in patients with COVID-19 that leads to the formation of microvascular microthrombi, which causes the expression of trigger active tissue factor in macrophages and endothelial cells.[48]

Our study also found that ferritin did not play a significant role in the mortality of pregnant women with COVID-19. In contrast, the mortality rate decreases with increasing Hb. AST at the time of ICU admission until the third day of hospitalization and also in the last days of hospitalization was significantly higher in non-survivor pregnant women than in survivors and generally had a growing trend in the course of the disease, although ALT and AST could not play a significant role in the increase in mortality chance.

Contrary to the present study, Wang *et al*. indicated that ALT and AST increase the chance of ICU hospitalization (worsening of disease severity) by 1.5 and 1.8 times, respectively.[29] Qin *et al*. also reported that with an increase in white blood cell (WBC), Neutrophils, NLR, platelet-to-lymphocyte ratio (PLR), procalcitonin (PCT), erythrocyte sedimentation rate (ESR), CRP, ferritin, or serum amyloid A protein (SAA), coagulation disorders (including abnormal D-dimer, Fgn, aPTT, and PT), and myocardial, liver, or kidney damage (including increased Creatine kinase (CK), cardiac troponin I (cTnI), myoglobin (MYO), LDH, ALT, AST, total bilirubin (TBIL), albumin (ALB), creatinine (CRN), and blood urea nitrogen (BUN)), the main clinical abnormalities of patients with severe COVID-19 infection increase.[49]

The study by Velavan *et al*. also found that patients with severe COVID-19 had more common symptoms of liver dysfunction than patients with milder types. They have reported increased levels of ALT, AST, and total bilirubin in these patients.[45]

In fact, hepatocellular infection with SARS-CoV-2 cannot be ruled out, as diarrhea is also a relatively common symptom

in these patients and viral RNA can be detected in both stool and blood samples, which indicates the presence of hepatic virus.[50] It is also possible that any inflammation caused by the immune system, especially cytokine storms, as well as pneumonia associated with hypoxemia, may lead to liver damage in patients with COVID-19.[51]

Therefore, considering the changes in inflammatory, coagulation, myocardial, and hepatic parameters during COVID-19 infection and also considering the specific physiological condition of pregnant women, it can be very important to evaluate the changes in laboratory parameters to determine the prognosis. Thus, the evaluation of 16 blood factors in pregnant women with severe COVID-19 (admitted to the ICU) in this study can be considered as its strengths. However, due to the unknown nature of this new virus, more studies are needed. The factors studied in this study can be evaluated separately for different pregnancy trimesters and pregnant women can be divided into high- and low-risk groups based on their gestational stages. It is also possible to calculate the cutoff point in each trimester from the evaluated parameters in predicting the mortality of these patients, which can be one of the limitations of this study, and we intend to address this issue in future studies and encourage other researchers to evaluate it. Also, the lack of evaluation of neonates' condition can be one of the weaknesses of our study. Because our study was retrospective and therefore we did not have access to this information, the study of the outcome of infants and fetuses in this group of mothers can also be very interesting and is recommended for future studies.

Conclusion

According to the results of the present study, inflammatory factors, such as leukocytes, neutrophils, NLR, and CRP, have an increasing trend and lymphocytes have a decreasing trend, so lymphocytopenia is more common in non-survivors. In addition, although the concentration of D-dimer at the time of ICU admission did not differ between the two groups of patients, in general, the level of this factor has been more than 1000 μg/ml at this time as the upward increase in the non-survivor group was significant compared with the survivors. In addition, the increase in PT, INR, D-dimer, and LDH was significantly effective in the chance of mortality in pregnant women with COVID-19. LDH is also one of the most important factors that has increased significantly in non-survivors compared with survivors, but Fgn, ferritin, ALT, and AST did not play a significant role in the mortality of these patients.

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Conflicts of interest

There are no conflicts of interest.

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