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Serum midkine level might be a diagnostic tool for COVID19 disease in pregnancy: From the disease severity, hospitalization and disease progression respects

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ABSTRACT

Background: New biomarkers for diagnosis and monitoring the COVID-19 disease are the most important topics to be studied recently. We aimed to investigate the association between midkine levels and disease severity in pregnant women with COVID-19.

Methods: Totally 186 pregnant women were participated in this study. 96 of them were healthy pregnant women, 90 of them were pregnant women with COVID19. Pregnant women were evaluated according to their trimesters. Serum midkine level, biochemical profile clinical and disease severity outcomes of pregnant women were obtained.

Results: Our results showed that pregnant women with COVID19 have significantly increased serum midkine level compared to healthy pregnant women (1.801 ± 0.977 vs 0.815 ± 0.294 ng/dL). According to the data among each trimester, it was shown that there were significant increase in serum midkine level during all pregnancy trimesters (1st trimester Control Group: 0.714 ± 0.148, COVID-19 group 1.623 ± 0.824, $p < 0.0001$; 2nd trimester Control Group: 0.731 ± 0.261, COVID-19 group 2.059 ± 1.146, $p < 0.0001$; 3rd trimester Control Group: 1.0 ± 0.35, COVID-19 group 1.723 ± 0.907, $p = 0.001$). Serum midkine levels were significantly different between disease severity subgroups of pregnant women with COVID19; moderate and severe/critic groups had significantly higher serum midkine level than mild group. There was also significant correlation between serum midkine level and severity status (p:0.0001, r: 0.468). The most striking results of serum midkine levels were corelation between length of hospitalization (p: 0.01, r: 0.430) and O^2 saturation ($p < 0.0001$, r: −0.521). ROC curve analysis showed that serum midkine level might be a tool for predicting COVID-19 in pregnant women with COVID-19 (AUC: 0.912, 95% CI: [0.871, 0.952], $p < 0.0001$)

Conclusion: Our data showed that there is an obvious relation between COVID19 progression and serum midkine level for the first time which might be used for monitoring the disease process.

1. Introduction

Midkine was first identified in 1988 as the product of retinoic acid-responsive gene involved in embryogenesis [1,2]. It has been indicated that overexpression of midkine is associated with several biological processes such as differentiation, proliferation, carcinogenesis, adhesion, migration of cells and survival and it was considered as a heparin-binding growth factor or a cytokine [2,3]. Related to these

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physiological pathways, midkine plays an important role in multiple pathological conditions including inflammation, cancer, injury, autoimmune diseases, and neurodegenerative diseases [1–4].

Although midkine is rarely expressed in the tissues such as kidney, lung, lymphocytes and macrophages in adults in normal physiological conditions, its expression is stimulated by retinoic acid, nuclear factor kappa-β (NF-κβ), hypoxia, and reactive oxygen species (ROS). It has been shown that hypoxia induces the inflammatory responses in several tissues [1][3]. In the study of Reynolds et al., midkine expression was increased by hypoxia-inducible factor-1 (HIF-1) in respiratory epithelial cells under hypoxic conditions [5].

Previously, midkine roles on several mechanisms during pregnancy were investigated in the literature. Obama et al. showed the midkine expressions in the extraembryonic membranes and placenta during early gestation in the mice model, and the expression decreased during embryogenesis. Moreover, midkine was shown in amniotic fluid and cerebrospinal fluid, indicating that midkine might have a role in organogenesis [6].

Matsuura et al. demonstrated that midkine expression might be important for postnatal development of lungs and midkine level reached its maximum level on the 4th day of postnatal period [7]. Midkine was detected in the respiratory system between 9th and 14th days post-coitum. Midkine immunoreactivity was seen in the endoderm-derived tracheal epithelium and the adjacent mesenchyme on the 12th day of post-coitum. From 13th to 16th days of the post-coitum, midkine protein was detected on the surfaces of epithelial cells of the intrapulmonary segmental bronchi, bronchiole, alveolar ducts, and surrounding lung parenchyma. Additionally, midkine was also seen in central and peripheral nervous systems, sense organs, digestive, urogenital, and skeletal systems, indicating that midkine may have an important role in the differentiation and morphogenesis of the embryo [8].

Midkine was found to be a physiological mediator of renin angiotensin aldosterone system (RAAS) and it plays an important role in interaction between kidney and lung [9]. It has been shown that RAAS is one of the key factors for the regulation of the migration and proliferation of the smooth muscle cells, the production of extracellular matrix (ECM), the upregulation of the adhesion molecules expression, and the production of proinflammatory cytokines [4].

Many researchers have been trying to elucidate the critical mechanisms which play a role underlying the COVID-19 disease from the beginning of the pandemic. Studies showed that Spike (S) protein, was found to be related to the binding and entry of virus to target cells via angiotensin-converting enzyme 2 (ACE) receptor which is mainly located on the lung cell surface [10,11].

As it was mentioned before, midkine participates inflammatory processes through expression from injured tissues. Midkine induces inflammation by suppressing the regulatory T cell response, promoting the migration of inflammatory leukocytes and stimulating the synthesis of chemokines [12]. In our previous study, it was observed that midkine levels were correlated with proinflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) [13]. In another study, midkine was found to be associated with pulmonary fibrosis by regulating expression of transforming growth factor-β (TGF-β) and TNF-α, and inflammatory cell migration into lung [14]. These proinflammatory cytokines have also been reported to induce cytokine storm and severe lung injury by suppressing the functions of macrophages, dendritic cells and T lymphocytes in COVID-19 [15].

Our previous study showed that serum IFN γ, IL-6, erythrocyte sedimentation rate, C- reactive protein, procalcitonin, ferritin, D-dimer, lactate dehydrogenase and also pregnancy complication rate were significantly higher in pregnant women with COVID-19 disease compared to controls. Also, disease severity was correlated with IFN γ and IL-6. Moreover, serum IL-2, IL-10, and IL-17 levels were significantly higher in the control group [16]. As these studies showed cytokine levels changed significantly in pregnant women with COVID-19. Regarding the midkine relation with hypoxia and infection, the aim of this study was to investigate potential association between midkine levels, inflammation, and disease severity in pregnant women with COVID-19. To the best of our knowledge, this is the first study to show the relationship between midkine and COVID-19.

2. Material and Methods

2.1. Study groups and ethics

Pregnant women who applied to the Ministry of Health Ankara City Hospital Gynecology and Obstetrics Clinic between 14/06/2020 and 25/10/2020 were included in the study and divided into SARS-CoV-2 positive and control groups with similar clinical and demographic characteristics according to the results of the polymerase chain reaction (RT-PCR) tests. Inclusion criteria were singleton pregnancies with SARS-CoV-2 positivity in RT-PCR assay on the nasopharyngeal and oropharyngeal specimens and healthy controls. All patients were screened for diabetes mellitus in the first antenatal visit by measuring fasting blood glucose and HbA1c levels. Furthermore universal GDM screening was performed between 24 and 28 weeks of gestation [17]. As maternal glucose metabolism alterations may affect midkine levels, patients diagnosed as diabetes mellitus or GDM were excluded from the study [18]. Exclusion criteria were gestational diabetes, multiple pregnancies, pregnant women with clinical suspicion for COVID-19 but negative RT-PCR test. The other comorbidities such as preeclampsia, preterm birth, intrahepatic cholestasis of pregnancy, preterm prelabor rupture of membranes (PPROM) and oligohydramnios were determined according to the related guidelines:

- The diagnostic criteria for preeclampsia are elevated blood pressure (defined as systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg on two occasions at least 4 h apart after 20 weeks of gestation in a woman with a previously normal blood pressure or systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥110 mmHg confirmed within a short interval (minutes) to facilitate timely antihypertensive therapy) and proteinuria (defined as ≥300 mg per 24-hour urine collection or protein:creatinine ratio ≥0.3, or urine dipstick reading ≥2+) or, in the absence of proteinuria, new-onset hypertension with the new onset of any of the following; thrombocytopenia (platelet count < 100,000/microL), renal insufficiency (serum creatinine of >1.1 mg/dL or a doubling of the serum creatinine concentration in the absence of other renal disease), impaired liver function as indicated by liver transaminase levels at least twice the normal concentration, pulmonary edema, new-onset headache unresponsive to medication [19].
- The diagnosis of intrahepatic cholestasis of pregnancy (ICP) is based upon the presence of pruritus associated with elevated total serum bile acid levels (≥10 μmol/L), elevated aminotransferases, or both in the second and third trimesters of pregnancy [20,21].
- The diagnosis of preterm birth based upon clinical criteria of regular painful uterine contractions accompanied by cervical changes (dilation and/or effacement) and refers to a delivery that occurs between 20 0/7 and 36 6/7 weeks of gestation [22].
- PPROM is defined as a membrane rupture before the onset of uterine contractions before 37 weeks of gestation. The diagnosis of PPROM based on characteristic findings of both history and physical examination (presenting with a history of leaking fluid, and observing the pooling of amniotic fluid in the posterior vaginal vault on sterile speculum examination) and confirmed with commercial laboratory tests (placental alpha microglobulin-1 protein assay [PAMG-1]) [23].
- Oligohydramnios is defined as decreased amniotic fluid volume relative to gestational age. It is diagnosed by ultrasound examination and described quantitatively (eg, amniotic fluid index ≤5 cm, single deepest pocket <2 cm) [24,25].

Patients were grouped as mild, moderate or severe according to their disease stage based on the criteria in national guideline [26]:

- Mild: a. Patients with fever, muscle/joint pains, cough and/or sore throat but no respiratory distress (respiratory rate per minute < 24, SpO^2 > 93%). b. Patients with normal chest x-ray and/or tomography.
- Moderate: a. Patients with fever, muscle/joint pains, cough and/or sore throat, respiratory rate per minute < 30, SpO^2 level > 90%. b. Patients with mild to moderate pneumonia findings on chest X-ray or tomography.
- Severe: a. Patients with fever, muscle/joint pain, cough and sore throat, tachypnea (≥30/minute), low SpO^2 level (≤90%). b. Patients with bilateral diffuse pneumonia findings on chest X-ray or tomography.
- Critic: a. Patients with dyspnea and respiratory distress (Respiration rate ≥ 30/min, PaO2/FiO2 < 300, Oxygen requirement increasing in follow-up, SpO2 < 90% or PaO2 < 70 mmHg despite 5 L/min oxygen therapy)
  b. Hypotension (systolic blood pressure < 90 mmHg and a decrease in normal blood pressure>40 mmHg and mean arterial pressure < 65 mmHg, tachycardia > 100/min)
  c. Patients with acute kidney injury, acute liver function tests, confusion, acute organ dysfunction such as acute bleeding diathesis and immunosuppression
  d. Troponin elevation and arrhythmia
  e. High Lactate Level (>2 mmol)
  f. Presence of skin disorders such as capillary return disorder and cutis marmaratus

Both Turkey Ministry of Health as well as the institutional ethical commitee approved the study protocol (E1-20-1007), and informed consent was obtained from all patients. All COVID-19 cases were managed under the guidance of national guidelines.

2.2. Biochemical and clinical profile

Blood samples were taken from the patients along with their first laboratory tests at their first admission to the hospital. Demographic characteristics, clinical characteristics and laboratory parameters were analyzed. Maternal age, gravidity, parity, gestational age, hemoglobin (Hb), hematocrit (Hct), white blood cell&lymphocyte&neutrophil counts, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), procalcitonin, interleukin 6 (IL-6), ferritin, blood urea nitrogen (BUN), creatinine, total-direct-indirect bilirubine, Aspartate Aminotransferase, Alanine Amino Transferase, Gamma-Glutamyltransferase, Alkalen Phosphatase were obtained to determine the biochemical and clinical profile.

2.3. Measurement of midkine

Measurements of midkine level were performed following the instructions for use of commercial kit with the immune-based ELISA method (Human Midkine Elisa Kit, Bioassay Technology Laboratory).

2.4. Statistical analysis

IBM SPSS Statistics 25 (Armonk, NY, USA) software was used for statistical analysis and the data were expressed as mean ± standard deviation. Student's T test was used to analyze differences between study groups, and Pearson correlation was used for correlation analysis between data. $p < 0.05$ was considered statistically significant. Graphpad PRISM 6.0 (La Jolla, CA, USA) was used for visualization of the data.

Table 1
Characteristics of study groups.

	Control (n:90)		COVID19 (n:96)	
	Mean/ Median/n (%)	Std. Deviation/ Min-Max	Mean/ Median	Std. Deviation/ Min-Max
Age (years)	27	19–41	28	18–40
Gestational Age (weeks)	25	0–40	30	4–40
Body Mass Index (kg/m^2)	27.26	5.42	27.60	3.99
Gravidity	2	0–5	2	1–8
Parity	1	0–3	1	0–3
WBC (/μL)	8840	3630–15330	7195	2760–18820
Neutrophil (/μL)	6360	2150–12280	5485	1710–15790
Lymphocyte (/μL)	2185	460–3030	1335	530–3090
Monocyte (/μL)	420	170–1140	360	110–1140
CRP (mg/L)	7.67	6.5	14.54	0.5–597
IL-6 (pg/mL)	3.48	1.65	16.96	19.63
Procalcitonin (ng/mL)	0.02	0.01	0.10	0.06
Ferritin (ng/mL)	19.71	20.33	60.13	193.5
Hemoglobin (g/dL)	12.08	1.152	13.38	12.93
Hematocrit %	36.84	3.60	41.04	41.21
Platelet per mL	251.553	58.227	317.395	887.408
Blood Urea Nitrogen (mg/dL)	17.11	5.415	16.11	5.507
Creatinine (mg/dL)	0.50	0.11	1.285	7.242
ALT (IU)	18.86	13.82	22.16	16.67
AST (IU)	14.74	6.716	25.56	15.84
Direct Bilirubin mg/dL	0.08	0.136	0.190	0.178
Indrect Bilirubin mg/dL	0.243	0.352	0.434	0.526
Total Bilirub mg/dL	0.326	0.483	0.573	0.574
LDH (IU)	92.96	116.0	230.5	52.98
GGT (IU)	2.833	4.890	17.0	15.71
ALP (IU)	32.06	63.48	109.2	65.49
D-Dimer mg/L	0.7647	0.840	2.289	3.949
Fibrinogen g/L	2.982	2.014	4.834	1.084
APGAR 1 Score	8	0–8	9	2–8
APGAR 5 Score	10	0–10	9	3–10
Serum Midkine Level ng/mL	0.815	0.294	1.801	0.977

Table 2
Maternal-Fetal Complications/Comorbidities of COVID-19 group and control group.

Complication	COVID-19 Group n (%)	Control Group n (%)	p
Intrahepatic Cholestasis of Pregnancy	2 (2.08%)	0	0.59
Preeclampsia	1 (1.04%)	1 (1.1%)	0.96
Preterm Birth	3 (3.12%)	6 (6.6 %)	0.26
Preterm Premature Rupture of Membrane (PPROM)	3 (3.12%)	0	0.34
Oligohydramnios	1 (1.04%)	2 (2.2%)	0.52
Multiple Anomalies	1 (1.04%)	0	0.96

3. Results

Totally 186 pregnant women were participated in this study. 96 of them were healthy pregnant women, 90 of them were COVID19 patients. Characteristic of participants were given in Table 1. Maternal and fetal complications/comorbidities of the control and COVID-19 groups were given in Table 2.

Our results showed that pregnant women with COVID-19 have

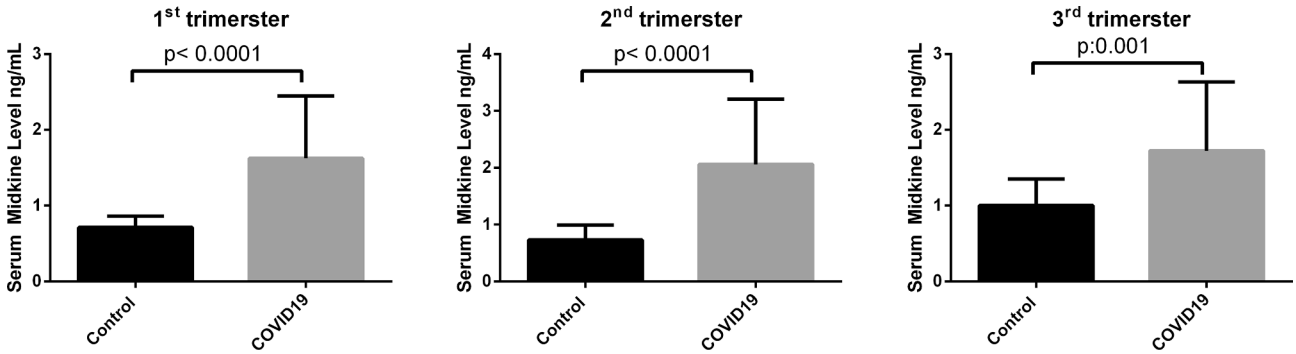

Fig. 1. Serum Midkine Level of pregnant women with COVID19 disease and healthy pregnant women in each trimester.

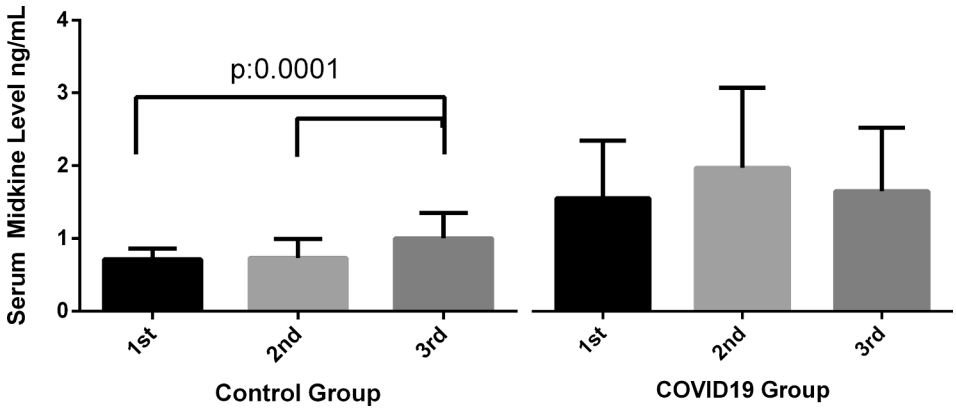

Fig. 2. The changes in Serum Midkine Levels of pregnant women with COVID19 disease and healthy pregnant women during pregnancy.

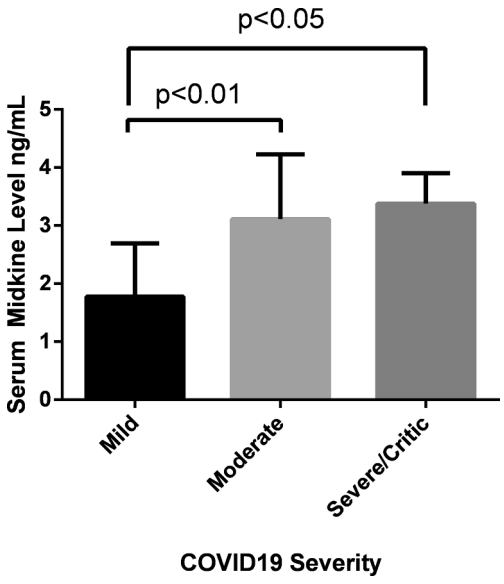

Fig. 3. Serum Midkine Levels of infected pregnant women in each severity status.

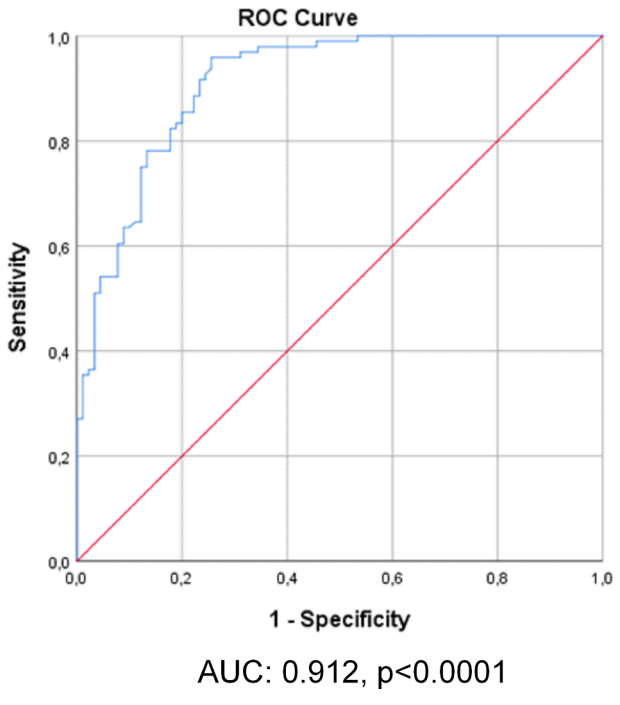

Fig. 4. ROC curve analysis of serum midkine level for predicting COVID-19 in pregnant women. (AUC: Area Under Curve).

significantly increased serum midkine level compared to healthy pregnant women (1.801 ± 0.977 vs 0.815 ± 0.294 ng/dL) (given in Table 1). According to the data among each trimester it was shown that there were significant increase in serum midkine level during all pregnancy period (previously 1st trimester Control Group: 0.714 ± 0.148 ng/dL, COVID-19 group 1.623 ± 0.824 ng/dL, $p < 0.0001$; 2nd trimester Control Group: 0.731 ± 0.261 ng/dL, COVID-19 group 2.059 ± 1.146 ng/dL, $p < 0.0001$; 3rd trimester Control Group: 1.0 ± 0.35 ng/dL, COVID-19 group 1.723 ± 0.907 ng/dL, $p = 0.001$) (Fig. 1).

To investigate nature of the pregnancy period effect on serum

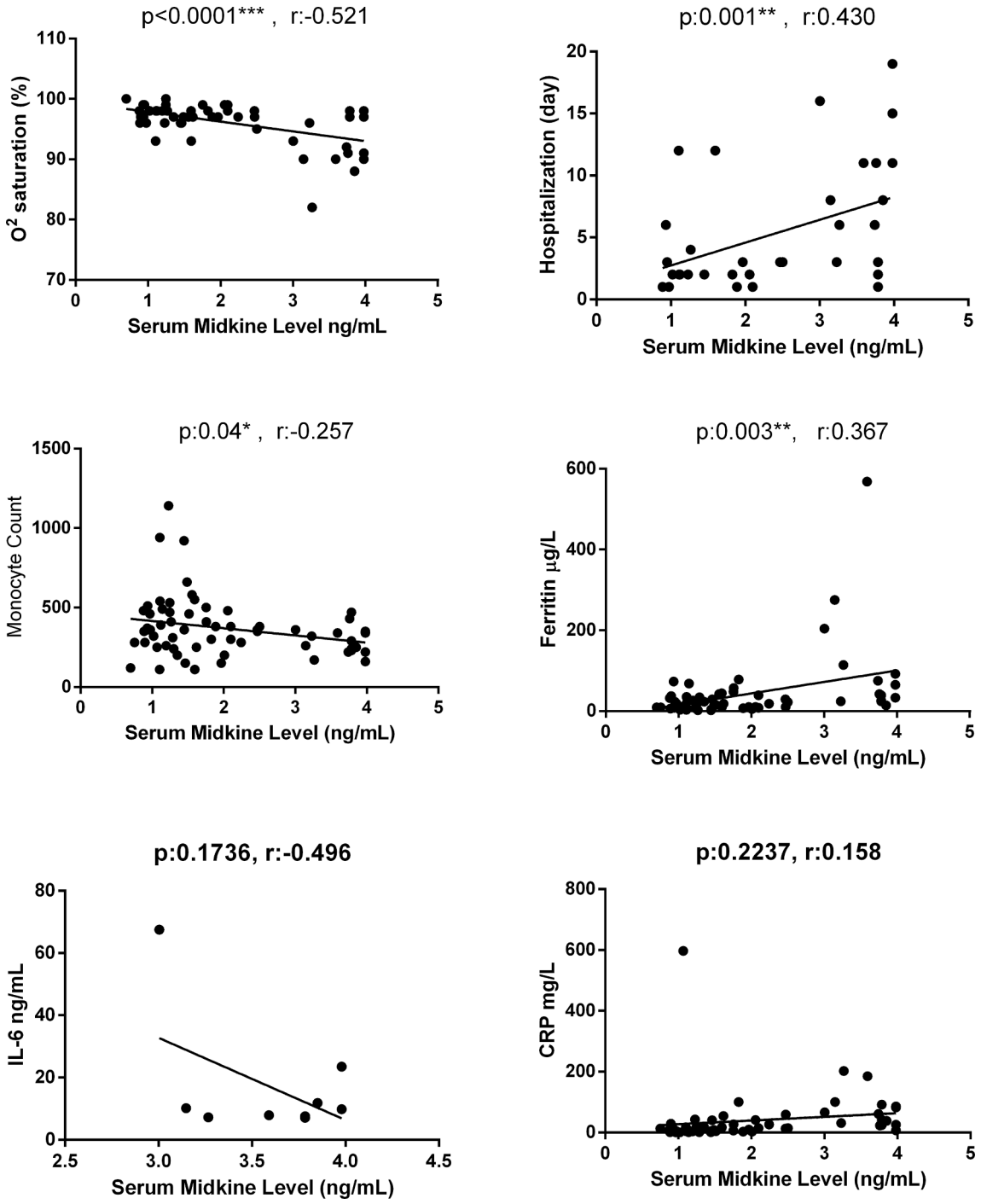

Fig. 5. Serum Midkine Level relation with oxygen saturation, hospitalization (day), monocyte count, serum ferritin level, IL-6 level and CRP level in pregnant women with COVID19.

midkine level, it was shown of the serum midkine changes during pregnancy in each control and COVID-19 group. According to our results, it might be mentioned that natural progress of the pregnancy has impact on serum midkine level increase; however, there was exaggerated increase in COVID-19 group compared to control group during pregnancy (Fig. 2).

As an important result, serum midkine level were significantly different between disease severity subgroups of pregnant women with COVID19. Moderate and severe/critic groups had significantly higher serum midkine level than mild group (Fig. 3). There was also significant correlation between serum midkine level and severity status (p: 0.0001, r: 0.468).

According to ROC curve analysis, it was shown that serum midkine level might be a tool for predicting COVID-19 in pregnant women with COVID-19 (AUC: 0.912, 95% CI: [0.871, 0.952], $p < 0.0001$) (Fig. 4).

Our further correlation analyses of the data obtained from COVID19 group pointed out that serum midkine level is related with COVID19 disease. The most striking results of serum midkine level were correlation between length of hospitalization and O^2 saturation. It was shown that pregnant women with COVID19 which had higher level of serum midkine level had longer hospitalization period (p: 0.01, r: 0.430) and lower O^2 saturation ($p < 0.0001$, r: −0.521). Also according to serum biochemical analyses, there were significant negative correlation between monocyte count and serum midkine level (p: 0.04, r: −0.257) but

not with white blood cell, neutrophil and lymphocyte counts. One of the acute phase reactants, serum ferritin level was positively correlated with serum midkine level (p: 0.003, r: 0.367) however there wasn't any correlation between IL-6 or C-Reactive protein level (Fig. 5).

4. Discussion

As it was observed in our study, serum midkine level was found to be related with COVID19 infection. According to control group results it might be mentioned that increase in serum midkine level during pregnancy might be the natural changes in pregnancy; however, it can be easily seen that there were dramatically increase in COVID19 group compared to controls in each trimesters. Our data showed that there is an obvious relation between COVID19 progression and serum midkine level as there were correlations between serum midkine level, COVID19 severity, O2 saturation, and hospitalization length.

It is the first study indicating the serum midkine level and COVID19 relation in the literature. Due to this limitation, to discuss potential mechanism of midkine on COVID19 infection, it should be mentioned midkine role on general immunity, inflammatory status and infectious disease. Also midkine should be evaluated as an important cytokine which related to pulmonary fibrosis, endothelial cell proliferation, vasodilatation and arteriogenesis in COVID19 disease perspective. Krzystek-Korpacka et al. showed that circulating midkine level significantly appraised with the systemic inflammatory response syndrome (SIRS) and it was seen at the highest level in septic patients compared to SIRS and healthy patients. It was shown that 63% of septic patients had high midkine level (>1,000 ng/L). There was persistently high midkine level in patients with cardiac insufficiency and in mechanically ventilated patients; however, midkine levels were decreased in patients without cardiac insuffeciency and not requiring mechanic ventilation. Also, it was observed that midkine levels were persistant in the septic shock patients; however, it was decreased in severe sepsis patients with the hospitalization [27].

Also, midkine role on HIV pathogenesis was shown with its enhanced expression in lymphocytes [28].

Our findings showed that increased serum midkine level negatively correlated with monocyte count. Recent studies in the literature discuss the monocyte dynamics of COVID-19 patients. Qin et al. mentioned that monocyte levels were decreased with disease severity; critical COVID-19 patients had lower monocyte levels than mild or severe patient groups. However CD16+ subtype were increased in critical patients [29]. In another study dysregulation of immune response in COVID-19 patients was investigated. They observed that while monocyte and lymphocyte percentage were decreased in severe COVID-19 patients compared to non-severe patients, neutrophil percentage was increased with disease severity [30]. According to these results, correlation between monocyte count and serum midkine level might be based on severity stage of patients.

It was mentioned that midkine synthesis in endothelial cells was elevated under hypoxic conditions [31]. Studies have indicated that plasma midkine concentration significantly increased in patients with acute respiratory distress syndrome (ARDS) [32]. It was also shown that midkine was associated with induction of ACE level in the lung [9,33]. Xu et al. found that plasma midkine level was significantly increased in septic patients and plasma midkine levels was found to be associated with the increase in ACE expression and the severity of lung injury [34].

Jee et al. evaluated plasma midkine concentrations in pregnant women and non-pregnant healthy controls. There was not a significant difference among non-pregnant healthy women, normal mid-term pregnancy, preterm in labor, term without labor, and term with labor groups. They also examined midkine levels in amniotic fluid in healthy and complicated pregnancies. They observed midkine level decreased with gestational age and midkine concentrations was lower in pregnancies complicated by chorioamnionitis but these results were insignificant [35]. However, our results showed important differences with COVID19 group and also between trimesters during healthy pregnancy. It has to be specifically mentioned that midkine role in pregnancy complications is not clear in the literature and there is limited information about how midkine levels changes in pregnancy problems. Therefore, further studies to evaluate midkine role in pregnancies with infection or complications are needed.

5. Conclusion

There is an important relation between serum midkine level and COVID19 progression which might be used for monitoring the disease process. Our study is the first study which shows the changes in midkine levels in pregnant women with COVID-19 with regards to disease severity. According to these results, serum midkine level might be thought as a promising biomarker for COVID-19 disease.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Ethical approvement

Republic of Turkey Ministry of Health and the institutional ethical committee approved this study (Protocol Number: E1-20-1007).

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