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An evaluation of maternal serum dynamic thiol-disulfide homeostasis and ischemia modified albumin changes in pregnant women with COVID-19

COVID-19 olan gebe kadınlarda maternal serum dinamik tiyol-disülfit dengesinin ve iskemi modifiye albümin değişikliklerinin değerlendirilmesi

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Abstract

Objective: It is thought that oxidative stress, free radicals, reactive oxygen species and reactive nitrogen species affect the pathophysiology of coronavirus disease-2019 (COVID-19). This study aimed to evaluate the oxidative status in pregnant patients with COVID-19 infection according to the changes seen in the levels of maternal serum thiol-disulfide and ischemia-modified albumin (IMA).

Materials and Methods: A study group was formed of 40 pregnant women with confirmed COVID-19 infection (study group) and a control group of 40 healthy pregnant women with no risk factors determined. In this prospective, case-controlled study, analyses were made of the maternal serum native thiol, total thiol, disulfide, IMA, and disulfide/native thiol concentrations.

Results: The maternal serum native thiol and total thiol concentrations in the study group were determined to be statistically significantly lower (p=0.007 and p=0.006, respectively), and the disulfide/native thiol ratio was higher but not to a level of statistical significance (p=0.473). There was no difference between the two groups regarding IMA levels (p=0.731).

Conclusion: The thiol-disulfide balance was seen to shift in the oxidant direction in pregnancies with COVID-19, which might support the view that ischemic processes play a role in the etiopathogenesis of this novel disease.

Keywords: COVID-19, ischemia-modified albumin, pregnancy outcomes, thiol-disulfide homeostasis

Öz

Amaç: Koronavirüs hastalığı-2019 (COVID-19) patofizyolojisinde oksidatif stres, serbest radikaller, reaktif oksijen türleri ve reaktif nitrojen türlerinin rol oynadığı düşünülmektedir. Bu çalışmanın amacı, maternal serum tiyol-disülfit ve iskemi modifiye albümin (İMA) düzeylerinde görülen değişikliklere göre COVID-19 enfeksiyonu olan gebe hastalarda oksidatif durumu değerlendirmektir.

Gereç ve Yöntemler: COVID-19 enfeksiyonu tanısı konulan 40 gebe kadın (çalışma grubu) ve risk faktörü olmayan 40 sağlıklı gebe kadından oluşan kontrol grubu şeklinde gruplar belirlendi. Bu prospektif, olgu-kontrol çalışmasında, maternal serum native tiyol, total tiyol, disülfit, İMA ve disülfit/native tiyol konsantrasyonlarının analizleri yapıldı.

Bulgular: Çalışma grubunda maternal serum native tiyol ve total tiyol konsantrasyonlarının istatistiksel olarak anlamlı daha düşük (p=0,007 ve p=0,006, sırasıyla), disülfit/native tiyol oranının ise daha yüksek olduğu ancak istatistiksel olarak anlamlı düzeyde olmadığı belirlendi (p=0,473). IMA düzeyleri açısından iki grup arasında fark izlenmedi (p=0,731).

PRECIS: The thiol-disulfide balance was seen to shift in the oxidant direction in pregnancies with COVID-19.

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Sonuç: Gebelikte COVID-19 varlığında tiyol-disülfit dengesinin oksidan yöne kaydığı görülmüştür. Bu durum, bu yeni hastalığın etiyopatogenezinde iskemik süreçlerin varlığını desteklemektedir.

Anahtar Kelimeler: COVID-19, iskemi modifiye albümin, gebelik sonuçları, tiyol-disülfit dengesi

Introduction

The emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in China in December 2019, as the agent of coronavirus disease-2019 (COVID-19), affected the whole world. This highly contagious infectious disease was declared a pandemic on 11.02.2020 by the World Health Organization (WHO)[1]. Researchers worldwide have been studying to reveal the complex pathophysiological mechanisms behind this deadly disease at the beginning of the pandemic. However, knowledge of this disease is still very limited and there is no efficient treatment at present. SARS-CoV-2 infects the host respiratory epithelium by cleaving to angiotensin-converting enzyme 2 (ACE-2) receptors. ACE-2 is preponderantly expressed in type II alveolar cells in the lungs[2]. The invasion of the respiratory epithelium usually results in acute respiratory distress syndrome (ARDS). As there is an incremental effect on the permeability of the alveolar-capillary membrane, microthrombus, refractory hypoxemia, and bilateral pulmonary infiltrates can be seen in ARDS[3]. Hypoxia and impaired perfusion seem to be the main factors responsible for most systemic complications of COVID-19. Therefore, it has been suggested that oxidative stress (OS), free radicals, reactive oxygen species (ROS), and reactive nitrogen species (RNS) affect the pathophysiology of COVID-19. Moreover, as it has been shown that viral infections could activate the free radical production and could deplete antioxidants, SARS-CoV-2 may trigger OS, in the same way as other RNA viruses[4,5].

During pregnancy, there is a physiological increase in the oxygen consumption of tissues due to the needs of both mother and fetus. Physiological immune tolerance is maintained, thereby allowing the growth of the semi-allograft fetus[6]. Although concerns have been raised by physicians about the potential effects of COVID-19 on pregnancy, the above-mentioned adaptive changes may be of benefit to pregnant women as an increased pro-inflammatory cytokine response (cytokine storm) in the host has been reported to be the main pathological event in severe and critical COVID-19 cases[7].

Thiols are organic compounds, which contain a sulfhydryl group that can oxidate to covalent disulfide bonds in OS states. This dynamic balance of thiol-disulfide is essential for the antioxidant defense system, critical cell functions such as cellular transcription, cellular signal transmission, detoxification, enzymatic and apoptotic pathways[8-10]. Furthermore, the thiol-disulfide homeostasis is a good reflection of the cellular redox system[11]. ACE-2 and SARS-CoV-2 spike proteins have been shown to be highly disrupted when all disulfide molecules are reduced to thiol groups. Hence, it has been concluded that this computational result may provide molecular principle for discriminative COVID-19 cellular signaling through OS[12]. A recent study showed that COVID-19 patients had depleted thiol status, and therefore concluded that this could be an effective biomarker in the prediction of the severity of COVID-19[11].

Ischemic conditions activate substantial modifications in the metal-binding capability of albumin, resulting in the altered oxidized form known as ischemia-modified albumin (IMA)[13]. Although OS has generally been examined in ischemic cardiac pathologies, ischemia and reperfusion in different tissues may result in elevated IMA levels. Normal trophoblast evolution is related to ischemic conditions and increased IMA concentrations. Higher IMA levels have also been reported in pregnancies with perinatal hypoxia, fetal growth restriction and fetal distress[9,14].

Although the course of pregnancy in women with COVID-19 infection is similar to that of female adult patients of the same age group, there have been reports in literature of increased rates of obstetric complications such as fetal distress, preterm labor and higher cesarean section rates[7]. These complications could be explained by OS in COVID-19 infection. No previous study could be found in the literature that has evaluated the oxidative status of pregnant women with COVID-19 infection, through the examination of the maternal serum thiol-disulfide balance and IMA levels.

Therefore, this study aimed to evaluate the oxidative status of pregnant women with COVID-19 by analyzing the changes in maternal serum dynamic thiol-disulfide homeostasis and IMA levels.

Materials and Methods

This prospective, case-control study was approved by the Ethics Committee of The Republic of Turkey Ministry of Health Ankara City Hospital (E1-20-954). This hospital is a tertiary-level reference hospital, which has played a leading role in COVID-19 management throughout the pandemic[15]. All the pregnant women included in the study provided informed consent for participation. The study included pregnant women who presented at the Department of Obstetrics and Gynecology between June 19-July 16, 2020. The required data were collected from patient records.

For the calculation of the sample size required by the study, power analysis was performed using G*Power 3.1.9.4 statistical software on the basis of previous study results. Target alpha (α) and 1-beta (β) error levels were taken as 0.05 and 0.95, respectively, and to obtain 95% power, a minimum of 34 patients were required in each group (total 68)[16,17].

The study group was formed of 40 pregnant women with a confirmed diagnosis of COVID-19 infection during clinical follow-up and a control group was formed of 40 healthy pregnant women, selected to be similar in terms of demographic

characteristics. The inclusion criteria were defined as pregnant women with confirmed COVID-19 infection positivity, who were hospitalized in the relevant period. Patients were excluded from the study if they had any systemic comorbidities or were smokers. The COVID-19 diagnosis was made according to the results of real-time polymerase chain reaction (RT-PCR) test applied to nasopharyngeal and oropharyngeal smears[18]. Gestational age was calculated according to the last date of menstruation or ultrasonography in the first trimester. Patients with ongoing pregnancy were followed up, and their neonatal results were recorded.

Study Parameters

Comparisons were made between the groups of maternal age, body mass index (BMI), gravida, parity, previous miscarriage, gestational age at diagnosis, pregnancy status, initial laboratory tests, gestational age at birth, the type of delivery, labor anesthesia, birth weight, Apgar scores at 1 and 5 mins, neonatal outcomes, admission to neonatal intensive care unit (NICU), clinical characteristics and obstetric outcomes.

A record was made of the laboratory parameters on hospital admission, including hemoglobin, hematocrit, leukocyte, neutrophil, lymphocyte, neutrophil- lymphocyte ratio, platelets, erythrocyte sedimentation rate, C-reactive protein, procalcitonin interleukin 6 (IL-6), blood urea nitrogen, creatinine, alanine aminotransferase, and aspartate aminotransferase.

At the time of hospital admission, blood samples were taken from all patients. For the maternal blood serum sample, 5-10 cm^3 of blood was taken into a biochemistry tube. Following centrifugation at 3,500 rpm for 10 min, sera were obtained, and the samples were transferred into Eppendorf tubes and stored at -80 °C until assay. When the number of patients required for the study was reached, analysis was made of the specimens in the biochemistry laboratory of our institution.

The thiol-disulfide levels were determined using the spectrophotometric procedure defined by Erel and Neselioglu[8]. The albumin-cobalt binding test was used to determine the presence of IMA[19].

Statistical Analysis

Statistical analysis of the study data was performed using IBM SPSS Statistics 22.0 software (IBM Corp., Armonk, NY, USA). Whether or not the data conformed to the normal distribution was assessed with the Kolmogorov-Smirnov test and histograms. As the data were seen to be normally distributed, descriptive numerical statistics were stated as mean and standard deviation values, and categorical variables as number (n) and percentage (%). The Student's t-test was applied to comparisons between groups of numerical data, and the chi-square test was used to compare categorical variables. The level of statistical significance was set at $p<0.05$.

Results

The neonatal results and demographic data of maternal age, BMI, gestational age at diagnosis, gravida, parity, gestational status, delivery mode, birthweight, Apgar scores, and NICU admission rates are presented in Table 1. The results of the analyses of IMA, native thiol, total thiol, disulfide, and disulfide/native thiol ratio are shown in Table 2. Inflammatory and other laboratory parameters are presented in Table 3.

The clinical course in the study group of pregnant women diagnosed with COVID-19 was seen to be similar to that of the general population [mild n=31 (77.5%), moderate n=5 (12.5%), severe n=4 (10%)[20,21]. There was seen to be no difference between the two groups in terms of demographic features and neonatal outcomes ($p>0.05$). The rate of admission to NICU was seen to be higher (23.1%) in the study group of pregnant patients with COVID-19, but not to a statistically significant level ($p=0.142$).

There was determined to be a statistically significant difference between the groups in terms of the thiol-disulfide homeostasis parameters and IMA levels. Significantly lower native thiol and total thiol values were observed in the COVID-19 group than in the control group ($p=0.007$ and $p=0.006$, respectively). A higher but not statistically significant disulfide/native thiol ratio was determined in the COVID-19 group ($p=0.473$). IMA levels were seen to be similar in the two groups ($p=0.731$) (Table 2). Inflammation parameters were determined to be statistically significantly higher in the COVID-19 group than in the control group ($p<0.001$, $p=0.047$ and $p=0.020$, respectively) (Table 3).

Discussion

This study aimed to evaluate the role of OS in pregnant women with COVID-19 infection. The study results demonstrated a significant decrease in native thiol and total thiol concentrations in the study group supporting the tendency of thiol-disulfide homeostasis shifting to oxidant status. OS is associated with various conditions such as diabetes mellitus, hypertensive disorders, ischemic coronary artery diseases, premature aging, and different types of cancers[9,22]. Increased free radical production and antioxidant consumption can be observed in viral infections, and thus infections caused by RNA viruses, including Herpes, HIV 1, Hepatitis B, C, D, respiratory viruses and coronaviruses could trigger OS[23,24].

Cytokine storm related to the release of several cytokines such as interleukin 2 (IL-2), interleukin 6 (IL-6), interleukin 7 (IL-7) and tumor necrosis factor-alpha has been defined in the etiopathogenesis of COVID-19[25]. However, ROS and RNS can also cause an oxidative storm that may cause lipid peroxidation, hyalinization, and alterations in the pulmonary alveolar membranes leading to fatal respiratory consequences[4]. In elderly patients and those with comorbid conditions, a poor prognosis has also been reported to be associated with exacerbation of pre-existing OS by viral infections[26].

Because of physiological adaptations in the cardiorespiratory system and the immune system during pregnancy, pregnant women may become more vulnerable to infections in general. Resistance to hypoxia is lower during pregnancy because of an increase in the transverse diameter of the thorax and elevation of the diaphragm. Because of lung volume changes and vasodilation, mucosal edema may develop with increased secretions in the respiratory tract. Moreover, susceptibility to infection caused by intracellular organisms such as viruses is increased with changes in cellular immunity. Although there is a

Table 1. Demographic features, clinical characteristics and obstetric outcomes of the study and control groups[a]

Parameters	Group 1 COVID-19 (n=40)	Group 2 Control (n=40)	p-value[b,c]
Maternal age (years)	28.6±6.7 (15-45)	27.3±5.1 (17-41)	0.353[b]
BMI (kg/m^2)	27.8±5.7 (21.4-43.9)	27.5±4.7 (16.6-39.2)	0.764[b]
Gravidity	2.7±1.5 (1-7)	2.52±1.4 (1-6)	0.594[b]
Parity	1.3±1 (0-4)	1±1.14 (0-5)	0.261[b]
Previous miscarriage	0.2±0.5 (0-2)	0.3±0.5 (0-2)	0.692[b]
Gestational age at diagnosis (weeks)	27.9±11.1 (5-40)	27.3±10.7 (6-40)	0.870[b]
Pregnancy status Ongoing pregnancy (n=57) (72.2%) Delivered (n=21) (26.6%) Miscarriage (n=1) (1.3%)	 (n=26) (65%) (n=13) (32.5%) (n=1) (2.5%)	 (n=31) (79.5%) (n=8) (20.5%) (n=0) (0%)	0.221[c]
Gestational age at birth (weeks)	37.0±3.6(28-41)	38.2±1.1 (36-40)	0.263[b]
Route of delivery (n=21) Vaginal (n=7) (33.3%) Cesarean Section (n=14) (66.7%)	 (n=5) (38.5%) (n=8) (61.5%)	 (n=2) (25%) (n=6) (75%)	0.525[c]
Labor anesthesia (n=14) Regional (n=12) (57.1%) General (n=2) (9.5%)	 (n=7) (53.8%) (n=1) (7.7%)	 (n=5) (62.5%) (n=1) (12.5%)	0.797[c]
Birth weight (g)	2923±798 (1200-3780)	3249±275 (2900-3700)	0.197[b]
1st minute Apgar score	8.0±1.15 (6-9)	7.75±0.7 (7-9)	0.546[b]
5th minute Apgar score	9.4±0.8 (8-10)	9.3±0.5 (9-10)	0.779[b]
Neonatal intensive care unit (NICU) admission rate (n, %)	3/13 (23.1%)	0/8 (0%)	0.142[c]

BMI: Body mass index, NICU: Neonatal intensive care unit, COVID-19: Coronavirus disease-2019
[a]Values are given as number (percentage) or mean ± standard deviation (range)
[b]Statistical analysis was performed using the Independent sample test (t-test)
[c]Statistical analysis was performed using the chi-square test

Table 2. Comparisons of thiol-disulfide homeostasis parameters and IMA levels between the groups[a]

Parameters	Group 1 COVID-19 (n=40)	Group 2 Control (n=40)	p-value[b]
IMA (U/mL)	0.67±0.02 (0.63-0.74)	0.68±0.01 (0.66-0.71)	0.731
Native thiol (µmol/L)	356.6±42.87 (260-452)	381.45±37.45 (309-461)	**0.007**
Total thiol (µmol/L)	396.15±43.13 (293-487)	421.87±38.31 (333-511)	**0.006**
Disulfide (µmol/L)	19.77±5.6 (7.5-31)	20.21±6.01 (2.5-30)	0.737
Disulfide/native thiol (%)	5.63±1.78 (0.60-8.10)	5.35±1.66 (2.51-9.54)	0.473

IMA: Ischemia-modified albumin, COVID-19: Coronavirus disease-2019
[a]Values are given as number (percentage) or mean ± standard deviation (range)
[b]Statistical analysis was performed using the Independent sample test (t-test)

lack of data, current literature supports the view that the course of COVID-19 in pregnant women is not different to that of non-pregnant women[27]. The most common symptoms in pregnant women are mild or moderate cold/flu-like symptoms[7,28]. However, it has also been reported that poor prognosis can also be observed in pregnant women, especially in those with comorbid diseases[29]. There have also been reported to be higher rates of obstetric complications such as preterm birth, pre-labour rupture of membranes, pre-eclampsia and cesarean delivery due to fetal distress[30].

Thiols are organic molecules including sulfhydryl groups, which play a critical role in oxidation-reduction reactions and redox balance. Thiols can be oxidized and transformed into disulfides, which may reduce to thiols, thereby maintaining dynamic thiol-disulfide homeostasis. The new automated process improved by Erel and Neselioglu[8], has enabled the measurement of native thiol, total thiol, and disulfide levels. It has been previously reported that disulfide levels are increased in inflammatory diseases and are decreased in malignant diseases[31]. Therefore, it has been stated that the increase in disulfide concentrations is related to OS and the increase in native thiol levels could be a marker of a reaction to the oxidative environment[9,32].

Any disturbance in the thiol-disulfide balance dissuades viruses from entering target cells. Alterations in pH and the reduction of the disulfide viral spike protein to thiol molecules restore these conformational modifications. Under severe OS, the cell surface receptor ACE-2 and receptor-binding domain of the penetrating viral spike protein can be present in the oxidant model with mostly disulfide bonds. In a computational analysis, the absence of a reducing medium under OS caused the viral protein to bind significantly to the cell surface ACE-2, and the reduction of all disulfides to sulfhydryl groups entirely disrupted the process of the SARS-CoV-2 spike protein binding to ACE-2[12]. In a recent study evaluating thiol status in patients with COVID-19 infection, thiol levels were found to be significantly lower in 517 COVID-19-positive patients compared to the control group (n=70). It has also been reported that these low thiol levels were correlated with the severity of COVID-19 (area under the curve: 0.949, sensitivity 98.6%, specificity 80.4%). Therefore, it was concluded that thiol status could be a potential biomarker for prediction of the severity of COVID-19[11]. In this study, a similar decrease in native thiol and total thiol concentrations was observed in the COVID-19 group, consistent with findings in the literature.

Table 3. Comparisons of laboratory parameters between the groups[a]

Parameters	Group 1 COVID-19 (n=40)	Group 2 Control (n=40)	p-value[b]
Hb (g/dL)	11.44±1.33 (8.3-14.1)	11.96±1.21 (9.7-14.7)	0.461
Hct (%)	35.03±3.56 (26.9-43.8)	36.65±3.65 (28.6-44.0)	**0.048**
Leukocyte (10^3/mm^3)	11146.75±1423.15 (4900-21600)	8562.00±1927.65 (3630-12420)	**<0.001**
Neutrophil (10^3/mm^3)	6151.00±1504.32 (2610-9940)	4686.25±1953.22 (1810-10580)	**<0.001**
Lymphocyte (10^3/mm^3)	1146.75±423.15 (490-2160)	1710.50±475.79 (770-3230)	**<0.001**
Neutrophil to lymphocyte ratio	4.66±2.41 (0.98-10.57)	3.79±1.24 (1.93-6.79)	**0.047**
Platelet (10^3/mm^3)	208.0±720.48 (82-354)	241.25±65.66 (147-373)	**0.034**
ESR (mm/h)	45.25±12.01 (23-73)	29.52±16.58 (3-66)	**<0.001**
CRP (mg/dL)	14.3±16.6 (3.1-95)	7.0±9.9 (0.4-64)	**0.020**
Procalcitonin (ng/mL)	0.25±0.17 (0.03-0.73)	0.02±0.01 (0.01-0.03)	**<0.001**
IL-6 (pg/mL)	8.71±5.42 (1-19.4)	3.71±1.05 (1.7-6.1)	**<0.001**
Ferritin (ng/mL)	28.47±33.44 (5-204)	14.67±11.05 (2-43)	**0.017**
BUN (mmol/mL)	14.80±3.79 (9-26)	17.72±6.71 (9-41)	**0.019**
Creatinine (mg/dL)	0.50±0.10 (0.29-0.81)	0.48±0.08 (0.30-0.65)	0.347
ALT (IU/L)	16.67±5.77 (9-32)	18.92±15.48 (8-106)	0.393
AST (IU/L)	19.37±9.90 (7-53)	16.60±6.64 (8-43)	0.146

ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, BUN: Blood urea nitrogen, COVID-19: Coronavirus disease-2019, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, Hb: Hemoglobin, Hct: Hematocrit, IL-6: Interleukin 6, LDH: Lactate dehydrogenase

[a]Values are given as number (percentage) or mean ± standard deviation (range)

[b]Statistical analysis was performed using the Independent sample test (t-test)

IMA is a sensitive biomarker in the identification of suspected myocardial ischemia. OS is triggered by ischemia, resulting in changes in the N-terminal part of albumin, and thus metal-binding cannot occur. Therefore, IMA is an oxidatively altered albumin form that develops a reaction to ROS due to ischemia. There have been reported to be high IMA levels in several clinical pathological conditions when the oxidative status is affected[9,33]. Within minutes of the onset of ischemia, the IMA level in the blood begins to rise, reaches a peak within 6 h and maintains a high level for up to 12 hours[34]. The fact that no difference was found between maternal serum IMA levels in the current study suggests the presence of underlying non-acute ischemic oxidant processes in COVID-19.

One of the most striking of the COVID-19 laboratory findings is high serum ferritin levels. In this study, high ferritin values were determined in the COVID-19 group. Iron can increase virulence and pro-oxidant responses and contribute to OS in the lungs. Increased molecular iron levels in bronchoalveolar lavage fluid have been demonstrated in patients with ARDS. In viral infections, the presence of extracellular iron in healthy lungs creates a predisposition to oxidative damage and infection[35].

Prevention and treatment strategies for COVID-19 also include supportive antioxidant therapy to reduce OS. Selenium is a co-factor in glutathione peroxidase, and it has been stated that the thiol groups in the virus protein disulfide Isomerase are oxidized by the chemical form, sodium selenite, so that the virus cannot penetrate the healthy cell membrane. Thus, selenite could be used in the fight against the coronavirus pandemic[36].

Study Limitations

The strong aspects of this study were the prospective design and the evaluation of a high number of parameters. However, there were also some limitations, primarily the relatively small number of patients, and that the fetal serum thiol-disulfide balance and IMA levels were not evaluated.

Conclusion

With the limited data available on the etiopathogenesis of COVID-19, the oxidative status in pregnant women with COVID-19 was evaluated together with the maternal serum thiol-disulfide balance and IMA levels, for the first time in the literature. The results of the study showed that the thiol-disulfide balance had shifted in the oxidant direction. In addition to supporting previous evidence that OS is characterized by ROS and RNS production, these findings demonstrate an antioxidant deficiency in patients with COVID-19 and that ischemic processes are present in the etiopathogenesis of the disease.

Ethics

Ethics Committee Approval: This prospective, case-control study was approved by the Ethics Committee of The Republic of Turkey Ministry of Health Ankara City Hospital (E1-20-954).
Informed Consent: All the pregnant women included in the study provided informed consent for participation.
Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Supervision: Ö.E., Ö.M.T., D.Ş., Critical Review: H.L.K., D.Ş., Concept: S.A.E., D.Ş., Design: S.A.E., A.T., H.L.K., S.N., D.Ş., Data Collection or Processing: S.A.E., A.T.A., H.S., Analysis or Interpretation: A.T., S.N., Literature Search: S.A.E., A.T., D.Ş., Writing: S.A.E., A.T.A., A.T., S.N., D.Ş.

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