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Comparison of antenatal care and pregnancy outcomes in pregnant women diagnosed with fetal death between the COVID-19 pandemic period and pre-pandemic period

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Abstract

Aim: To reveal the preventable complications related to fetal loss more clearly by hypothesizing that the negative effects of the pandemic on antenatal follow-up and daily habits in pregnancies resulting in fetal loss may increase compared to the pre-pandemic period.

Materials and Methods: In this question-based study, 80 pregnant women who were diagnosed with fetal death during the pre-pandemic period(September 1, 2019- February 28, 2020) were compared with 80 pregnant women diagnosed with fetal death during the pandemic period (March 1,2020-September 1,2020). Antenatal screening tests, dietary, exercise, smoking, medications, low-income status, fetal anomalies, coexisting medical disorders and, adverse outcomes have been comparatively analyzed between the groups.

Results: There was no statistical difference between the periods in terms of the number of antenatal visits ($p = 0.52$). However dietary modification and physical exercise rates were lower during the pandemic ($p=0.03$, and $p<0.01$), respectively. The use of vitamin D has increased during the pandemic period ($p = 0.02$). Maternal complication rates in women diagnosed with stillbirth were 20% in the pre-pandemic period and 30% in the pandemic. The stillbirth rates were 1.4%(87/6277) and 1.3%(87/6936), in pre-pandemic and pandemic periods, respectively ($p>0.05$).

Conclusion: In particular, we demonstrated that the pandemic process negatively affected the daily routine such as physical exercise and dietary in women diagnosed with fetal loss. However, we found the stillbirth rates similar between the periods.

Introduction

Coronavirus disease 2019 (COVID-19) is a global pandemic that has caused many deaths worldwide since March 11, 2020 [1]. During this period, COVID-19 epidemiology continues to evolve and shows rapid change [2]. As a result of the rapid spread of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the health system was insufficient even in developed countries. With the increased risk of complications in pregnant women with SARS-CoV-2, pregnant women are considered a high-risk group because of the important impacts of COVID-19 disease on pregnancy, postpartum period, and on their neonates[3]. The World Health Organization defines fetal death as the intrauterine death of the fetus at any time during pregnancy [4]. Today, there are concerns that inadequate antenatal follow-up may lead to an increase in more severe outcomes, such as stillbirth and neonatal death. In a recent study, Khalil et al. found that the incidence of stillbirth during the pandemic was significantly higher possibly due to reduced antenatal visits and concern for contracting infection [5]. Related to this situation, one possible explanation for the higher decrease in triage participation than at births is that women perceived triage participation as avoidable, but that birth was not[6]. At the same time, the emotional status, physical exercise and eating habits of pregnant women have changed with the pandemic. Especially the decrease in daily routines and social interactions has a negative emotional impact on pregnant women. [7-9]. The prolongation of the sedentary process during pregnancy can lead to an increase in adverse pregnancy outcomes considering its relationship with advanced maternal age, increased body mass index, and pre-existing

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comorbidities, which are among the risk factors for severe COVID-19 disease [3]. Stillbirth is the result of the complex mechanisms between maternal, fetal, and placental disorders. Today, comorbid chronic diseases such as diabetes, hypertensive disorders, chronic kidney disease, uncontrolled thyroid disease, systemic lupus erythematosus, antiphospholipid syndrome, and obesity are considered as the main known risk factors for fetal demise [10]. However, a significant proportion of stillbirths are still unexplained even after a through evaluation [11]. In this study, we aimed to reveal the preventable complications related to fetal loss more clearly by hypothesizing that the negative effects of the pandemic on antenatal follow-up and daily habits in pregnancies resulting in fetal loss may increase compared to the pre-pandemic period. We focused on how the physical exercise and eating habits of pregnant women have changed with the pandemic. We also aimed to examine factors reflecting social life and economic status such as smoking, monthly income, and antenatal follow-up.

Materials and Methods

This study was a retrospective cohort study. In this question-based study, 160 patients were diagnosed with fetal death in the early second trimester ($\geq$ 14 weeks of gestation) and after 20 weeks of gestation and hospitalized in Ankara City Hospital between September 1, 2019, and September 1, 2020, were included. 80 pregnant women who were diagnosed with fetal death during the pre-pandemic period (September 1, 2019 - February 28, 2020) were compared with 80 pregnant women diagnosed with fetal death during the pandemic period (March 1, 2020 - September 1, 2020). The study was approved by our Institutional Ethical Committee (E1-20-1073 on 16 September 2020). In admissions to obstetrics emergency service and outpatient clinics, pregnant women diagnosed with fetal death in the early second trimester ($\geq$ 14 weeks of gestation) and after 20 weeks of gestation were evaluated. Pregnant women who were diagnosed with fetal death above 14 weeks and participated in the questionnaire were included in the study. Patients diagnosed with fetal death in the pre-pandemic period participated in the questionnaire by phone. During the pandemic, patients diagnosed with fetal death participated in the questionnaire while in the hospital or by phone after discharge. Patients who could be reached in two six-month periods and agreed to participate in the questionnaire were included in the study. At the time of the study, no vaccine has yet been found for COVID-19. The number of antenatal visits, dietary modification in pregnancy (evaluated with dietitian consultation at least once during pregnancy), physical exercise (those who read the brochure with home exercise recommendations from the pregnant school serving within the hospital and have the opportunity to practice at home at least 3 times a week), folic acid intake, oral anti-anaemic medication, vitamin D and multivitamin supplementations, smoking and monthly income status (according to Turkey's economic statistics, the poverty level is defined as the living cost of two people with an income below 5920 TL) were evaluated in the questionnaire [12]. In addition, first-trimester aneuploidy screening test, second-trimester anatomic ultrasound scan between 18 and 22 weeks of gestation, 50 g glucose challenge test (GCT) or 75 g oral glucose tolerance test (OGTT), and structural fetal and/or neonatal anomalies (cardiac anomalies, neuroanatomic abnormalities, and other major structural abnormalities) were recorded. The results of the patients who underwent the prenatal chromosomal diagnostic tests (chorion villus biopsy, amniocentesis, or cordocentesis) were also recorded. A stillbirth occurs after 20 weeks of pregnancy and before or during delivery which is defined as fetal death or loss by the United States National Center for Health Statistics[13]. Fetal death diagnosis was confirmed by ultrasound in all patients. Maternal characteristics and obstetrical histories in pregnant women with the diagnosis of fetal death were recorded. Also, body mass index, gestational age at diagnosis, and coexisting medical disorders were recorded. Maternal complications such as preeclampsia, placental abruption, preterm premature rupture of membranes, HELLP (hemolysis, elevated liver enzymes, low platelet count) syndrome, and disseminated intravascular coagulation (DIC) were evaluated. The diagnosis of SARS-CoV-2 infection was made by a real-time polymerase chain reaction (RT-PCR) test of nasopharyngeal and oropharyngeal swabs. Antenatal care visits in our center, include viability ultrasound scan at 6-9 gestational age (wk), aneuploidy screening at 11-14 wk, anatomy ultrasound scan at 18-22 wk, 50 g GCT or 75 g OGTT at 24-28 wk, fetal heart rate monitoring every two weeks after 32 weeks of gestation, group B streptococcus (GBS) screening, and evaluation of fetal presentation at 35 weeks of gestation. Inclusion criteria for this study were the following: gestational age $\geq$ 14 weeks of gestation, the diagnosis of fetal death, and the participation of patients in the questionnaire. First trimester miscarriages, incomplete abortions, inductions of labor for pre-viable premature rupture of membranes, anatomic abnormalities of the uterus, and termination for fetal abnormalities were exclusion criteria for this study.

Data analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS.22; IBM SPSS Statistics for Windows, Version 22.0, IBM Corp., Armonk, NY, USA). Visual (histograms, probability plots) and analytical methods (Kolmogorov-Smirnov test) were used to determine the normality of distribution. When comparing between the groups, we used the Mann-Whitney U test. Categorical data were presented as percentages. Data were analyzed with a chi-square-based comparison of proportion testing. $p < 0.05$ was considered statistically significant.

Results

A total of 160 patients were included in this study. 80 pregnant women who were diagnosed with fetal death during the pre-pandemic period (September 1, 2019 - February 28, 2020) were compared with 80 pregnant women diagnosed with fetal death during the pandemic period (March 1, 2020 - September 1, 2020). Median maternal age, body mass index, and parity were not different between groups (p=0.12, p=0.79, and p=0.12), respectively (Table 1). It was found that dietary changes and physical exercise rates decreased significantly in cases with fetal loss during the pandemic period (p=0.03, and p<0.01),

Table 1. Comparison of the demographic and clinical characteristics of pregnant women diagnosed with fetal death at or after 14 weeks of gestation between the pre-pandemic and pandemic periods.

Variables	Pre-pandemic Period (n=80)	Pandemic period (n=80)	*p*
Maternal age (years) (median, IQR, range)[a]	34 (10) (19-46)	31.5 (11) (20-44)	0.12
BMI (kg/m2) (median, IQR, range)[a]	25.9 (2.1) (19.5-57.3)	25.8 (6.2) (20.2-42.8)	0.79
Gravidity (median, IQR, range)[a]	3 (3) (1-11)	3 (3) (1-8)	0.03
Parity (median, IQR, range)[a]	2 (2) (0-4)	1 (1) (0-5)	0.12
Gestational age at diagnosis (weeks) (median, IQR, range)[a]	21 (14) (14-38)	25 (13) (14-40)	0.21
First trimester screening test (n, %)[b]	46 (61%)	44 (57%)	0.60
Dietary modification in pregnancy (n, %)[b]	34 (43%)	21 (27%)	0.03
Physical exercise (n, %)[b]	55 (69%)	32 (40%)	<0.01
Folic acid intake (n, %)[b]	54 (68%)	55 (69%)	0.86
Vitamin D supplementation (n, %)[b]	10(13%)	22 (28%)	0.02
Multivitamin supplementation (n, %)[b]	34 (43%)	32 (40%)	0.71
Oral anti-anaemic medication (n, %)[b]	37 (46%)	29 (36%)	0.19
Smoking (n, %)[b]	8 (10%)	13 (16%)	0.23
Low Income (n, %)[b]	9 (12%)	16 (20%)	0.12

Data are presented as median, interquartile range (IQR), minimum, and maximum. BMI: Body mass index, Dietary modification in pregnancy: evaluated with dietitian consultation at least once during pregnancy, physical exercise (those who read the brochure with home exercise recommendations from the pregnant school serving within the hospital and have the opportunity to practice at home at least 3 times a week), Low income (according to Turkey's economic statistics, the poverty level is defined as the living cost of two people with an income below 5920 TL in May 2020).

[a]Statistical analysis was performed by Mann-Whitney U test.

[b]Statistical analysis was performed by Chi-square test $p < 0.05$ was considered statistically significant.

respectively (Table 1). However, no significant differences were observed in the first-trimester screening test and gestational age at diagnosis between the two groups (p=0.60, and p=0.21), respectively (Table 1). We also observed that the use of vitamin D has increased significantly during the pandemic period (p = 0.02)(Table 1). When we evaluated the other drugs between the groups, no statistical difference was found in terms of folic acid, anti-anaemic, and multivitamin intake (p=0.86, p=0.19, and p=0.71), respectively (Table 1). In addition, smoking and low-income status were comparable between the groups (p=0.23, and p=0.12) respectively.(Table 1). When pregnancies undergoing 75g OGTT were examined, gestational diabetes mellitus (GDM) was detected in one of 16 cases (6%) during the pre-pandemic period and in four of 12 cases (33%) during the pandemic period. Figure 1 shows a flow diagram for the numbers of patients in our health system, including the number with fetal demise. While the total number of applications to the obstetrics emergency service and the outpatient clinic was 33,297 in the six months before the pandemic, this number was 25,160 in six months during the pandemic period (Figure 1). When we compare the periods retrospectively in terms of fetal losses; in the pre-pandemic period, 66 patients between 14-20 weeks and 87 patients above 20 weeks were detected. During the pandemic period, 69 patients between 14-20 weeks and 87 patients above 20 weeks were detected. The stillbirth rates were 1.4%(87/6277) and 1.3%(87/6936), in pre-pandemic and pandemic periods, respectively (p>0.05). The gestational age at diagnosis, number of antenatal visits, and maternal complication rates were comparable between the stillbirth groups (>20 weeks of gestation) (p=0.93, p=0.52, and p=0.40), respectively (Table 2). Preeclampsia, placental abruption and HELLP syndrome cases were seen in both groups (Table 2). Differently, there was one case each diagnosed with diabetic ketoacidosis, DIC, and chorioamnionitis during the pandemic (Table 2). Maternal mortality was not observed in both groups. Second trimester ultrasound screening between 18-22 gestational weeks was 25/28 (90%) in the pre-pandemic period and 24/39 (62%) in the pandemic period. Hydrops fetalis, cystic hygroma, ventricular septal defect, and hydronephrosis were fetal anomalies detected in both periods (Table 3). COVID-19 infection RT-PCR tests were performed on 30 patients diagnosed with fetal death during the pandemic. RT-PCR positivity was de-

Table 2. Comparison of antenatal visit numbers and maternal complications and gestational age at diagnosis after 20 weeks of gestation in pregnant women diagnosed with fetal death between the pre-pandemic and pandemic periods.

Variables	Pre-pandemic period >20 gestational week (n=45)	Pandemic period >20 gestational week (n=47)	*p*
Gestational age at diagnosis (weeks) (median, IQR, range)[a]	29 (11) (22-38)	29 (9) (21-40)	0.93
Number of antenatal visits (median, IQR, range)[a]	2 (2.5) (0-6)	2 (2) (0-5)	0.52
Maternal complication rates (n, %)[b]	9 (20%)	14 (30%)	0.40
Preeclampsia (n)	4	4	
Chronic hypertension with superimposed preeclampsia (n)	1	1	
Placental abruption (n)	2	3	
HELLP syndrome (n)	2	3	
DIC (n)	-	1	
Diabetic ketoacidosis (n)	-	1	
Chorioamnionitis (n)	-	1	

Data are presented as median, interquartile range (IQR), minimum, and maximum. Maternal complications include the following diseases: preeclampsia, chronic hypertension with superimposed preeclampsia, placental abruption, HELLP syndrome: hemolysis, elevated liver enzymes, low platelet count, DIC: disseminated intravascular coagulation, diabetic ketoacidosis and chorioamnionitis.
[a]Statistical analysis was performed by Mann-Whitney U test.
[b]Statistical analysis was performed by Chi-square test $p < 0.05$ was considered statistically significant.

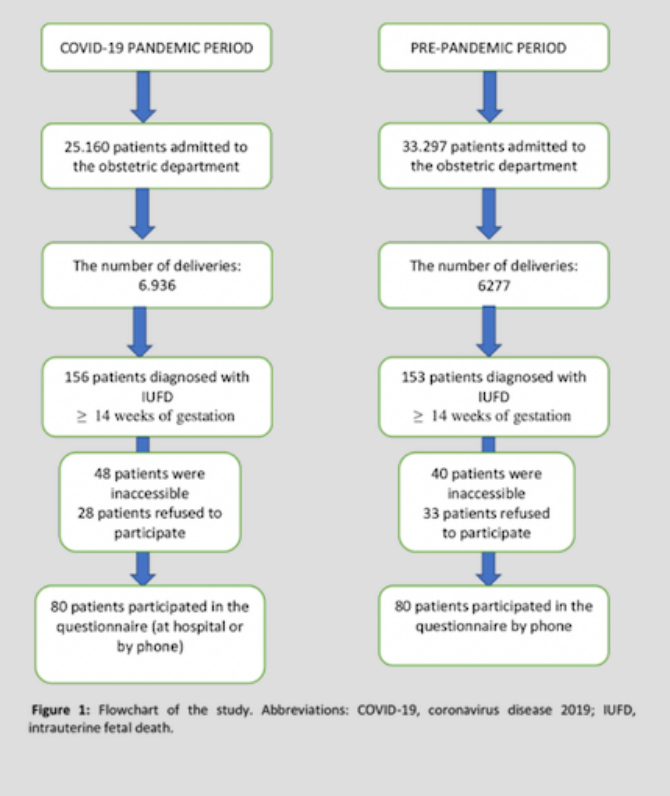

Figure 1: Flowchart of the study. Abbreviations: COVID-19, coronavirus disease 2019; IUFD, intrauterine fetal death.

Figure 1. Flowchart of the study. Abbreviations: COVID-19, coronavirus disease 2019; IUFD, intrauterine fetal death.

tected in 5/30 (16%) patients in this period. Before the pandemic, chorionic villus sampling (CVS) was performed in 1 case, amniocentesis in 3 cases, and cordocentesis in 1 case. In the pandemic, CVS and amniocentesis were performed in one case each. The fetal karyotype result of the pregnant woman who was diagnosed with fetal death waiting for the result of amniocentesis in the pre-pandemic period was reported as trisomy 18.

Discussion

To our knowledge, with this question-based study, we had the opportunity to better evaluate the antenatal care and adverse pregnancy outcomes between the COVID-19 pandemic period and pre-pandemic period in pregnant women diagnosed with fetal death. Stillbirth is frequently idiopathic in fetuses without malformations. Early ultrasound examination and screening tests in antenatal care might help us to assess the risk of stillbirth. Detailed maternal obstetrical history, second-trimester ultrasound between 18 and 22 weeks of gestation, glucose challenge test, and the frequency of antepartum monitoring can reduce the risk of adverse perinatal outcomes. In our study, we observed that the number of antenatal visits and maternal complication rates were comparable between the stillbirth groups. In parallel with this result, gestational age at diagnosis and complication rates were similar between the periods. As Khalil et al. stated the high incidence of stillbirth during the pandemic might be associated with reduced antenatal visits [5]. Despite study limitations, these findings indicated changes in patients' attitudes during the pandemic, which may also be associated with higher stress in antenatal period. Similarly, De Curtis et al. found a statis-

Table 3. Comparison of fetal anomalies detected at or after 14 weeks of gestation in pregnant women diagnosed with fetal death between the pre-pandemic and pandemic periods.

Fetal Anomalies	Pre-pandemic Period (n = 80)	Pandemic Period (n = 80)	*p*
Hydrops fetalis (n, %)	3 (3.7%)	1 (1.3%)	
Cystic Hygroma (n, %)	1 (1.3%)	1 (1.3%)	
Myelomeningocele (n, %)	-	1 (1.3%)	
Vermian hypoplasia (n, %)	-	1 (1.3%)	
Anencephaly (n, %)	-	1 (1.3%)	
Micrognathia (n, %)	-	1 (1.3%)	
Ventricular septal defect (n, %)	1 (1.3%)	2 (2.5%)	
Congenital pulmonary airway malformation (n, %)	1 (1.3%)	-	
Intestinal atresia (n, %)	-	2 (2.5%)	
Single umbilical artery (n, %)	-	1 (1.3%)	
Umbilical vein varix (n, %)	1 (1.3%)	-	
Hydronephrosis (n, %)	1 (1.3%)	1 (1.3%)	
Posterior urethral valves (n, %)	2 (2.5%)	-	
Skeletal dysplasia (n, %)	1 (1.3%)	2 (2.5%)	
Clubfoot (n, %)	1 (1.3%)	-	
Total	12 (15%)	14 (17.5%)	0.63

*Statistical analysis was performed by Chi-square test. $p < 0.05$ was considered statistically significant.

tical significant increase of about three times in stillbirths which was determined in the lockdown period (comparing three months in the same period of 2019) [14]. We also observed that the number of births at our center increased during the pandemic period. The fact that our hospital is a referral center with high-capacity maternal and neonatal intensive care units may be associated with increased birth numbers. However, when compared to the pre-pandemic period, we found the stillbirth rates comparable (Figure-1). Similarly, Berghella et al. found the incidences of perinatal death were similar between pre-pandemic and pandemic periods[15]. In another study, Janssen et al. showed that there was no increase in the number of stillbirths during the peak period of the pandemic [16]. Additionally, McDonnell et al. showed that there were no significant changes in perinatal deaths and preterm births [17]. In a European region study, there was no relation between prematurity and lockdown, nor between stillbirths and lockdown[18]. A limitation of these studies is that they do not differentiate between spontaneous and iatrogenic preterm birth. Besides, the lack of a consensus in terms of the severity of the disease and the timing of delivery explains the differences in studies on serious fetal complications such as preterm birth or stillbirth. When we evaluated the supplementation drugs between the groups, the use of vitamin D has increased significantly during the pandemic period. Several studies showed the role of vitamin D in reducing the risk of acute viral respiratory tract infections and pneumonia with a mechanism of inhibition with viral replication, anti-inflammatory or immunomodulatory ways [19]. Vitamin D use in a pandemic may have increased due to more frequent use in antenatal care and due to the news. Moreover, we found that dietary changes and physical exercise rates decreased significantly in cases with fetal loss during the pandemic period in our study. Regarding this situation, a sedentary lifestyle may increase adverse pregnancy outcomes in high-risk pregnancies accompanied by obesity and gestational diabetes. Therefore, understanding the impact of quarantine on the physical activity of pregnant women is particularly important for women with GDM. However, the change in maternity care may have affected women's physical activity levels as well as the decrease in face-to-face appointments. On the other hand, smoking and low-income status were similar between the groups. Also, no significant changes were observed in the first-trimester screening test and gestational age at diagnosis between the two groups. Some serious maternal complications such as HELLP syndrome, disseminated intravascular coagulation (DIC), and diabetic ketoacidosis were seen in one case each in the third trimester during the pandemic. Preeclampsia and placental abruption were observed in both groups. Diabetic ketoacidosis and hypertensive disorders seem preventable if adequate antenatal visits were performed. Therefore, reducing preventable stillbirths and newborn deaths should be a global priority[20]. Gestational diabetes mellitus (GDM) was detected in one of 16 cases during the pre-pandemic period and in four of 12 cases during the pandemic period. Simmons et al. stated that undiagnosed GDM potentially increases adverse pregnancy outcomes during the SARS-CoV-2 pandemic[21]. In addition, Deprest et al. reported that most fetal therapies are time-sensitive and any invasive procedure such as chorionic villus sampling, amniocentesis, fetal blood transfusion, thoraco-amniotic shunting, laser for twin-to-twin transfusion syndrome and spina bifida closure should also be continued due to maternal and fetal benefits during the COVID-19 pandemic. In our study, chorionic villus biopsy and amniocentesis procedures were performed in one case each in pregnant women diagnosed with fetal death during the pandemic period. The association of infection with stillbirths is approximately 10-20% in developed countries and this rate is even higher in devel-

oping countries. The pathological mechanisms include direct fetal infection, placental dysfunction, severe maternal disease, or stimulating spontaneous preterm birth. Cytomegalovirus, parvovirus, and Zika virus are associated with stillbirth [10]. Although the vertical transmission of SARS-CoV-2 through the placenta remains controversial, viral factors might affect the rates of in utero transmission [22]. Among the patients hospitalized for fetal death during the pandemic period, there were 5 patients diagnosed with COVID-19 in our study. SARS-CoV-2 infection during pregnancy may have different effects according to trimesters such as rubella virus infection which causes more adverse outcomes in the first and second trimesters. As a result of viral infection, more adverse perinatal outcomes such as miscarriage, preterm birth, fetal growth restriction, and stillbirth can occur [1]. However, in a recent study involving 533 pregnant women diagnosed with SARS-CoV-2 disease, the course of COVID-19 was mild in the majority of the cases [23]. In our opinion, apart from the vertical transmission of the disease, excessive inflammation, vascular injury, and impaired perfusion may lead to pregnancy loss in pregnant women with COVID-19 [24]. The strengths of this study were the large number of cases, question-based and unique study design. Limitations of the study were retrospective, single- center experience, and lack of information about the causes of stillbirths. In addition, the participation in the questionnaire was around 52% in both groups.

Conclusion

In particular, we demonstrated that the pandemic process negatively affected the daily routine such as physical exercise and dietary in women diagnosed with fetal loss in our study. In some cases, such as uncontrolled diabetes, hypertension, or a poor obstetric history, antenatal assessment should continue [25]. We found that the stillbirth rates similar between the pre-pandemic and pandemic periods. Detailed evaluation of maternal obstetrical history, first and second-trimester ultrasound screening, and glucose challenge tests are simple methods that can reduce fetal losses. In conclusion, the antenatal process should not be interrupted in terms of maternal-fetal morbidity and mortality in national and global emergencies such as pandemics.

Author contributions

All the authors have accepted responsibility for the entire content of this manuscript and approved submission.

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Competing interests

The authors declare that they have no conflicts of interest. The funding organization(s) played no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the report for publication.

Ethics approval

The study was approved by Ankara City Hospital Clinical Research Ethics Committee (E1-20-1073 on 16 September 2020) and the COVID-19 Scientific Research Evaluation Commission of the TR Ministry of Health.

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