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Impact of First-Trimester Vitamin D Levels on Pregnancy Complications

Birinci Trimester Vitamin D Düzeylerinin Gebelik Komplikasyonları Üzerine Etkisi

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ABSTRACT

Objective: Vitamin D deficiency during pregnancy is a global health issue, affecting a significant portion of pregnant women. It has been linked to various adverse maternal and fetal outcomes, yet studies offer conflicting results on its direct impact. This study aimed to evaluate the prevalence of vitamin D deficiency in the first trimester and its association with pregnancy complications.

Methods: This retrospective cohort study involved 1,999 pregnant women who attended Gazi University's Obstetrics and Gynecology Clinic and had their vitamin D levels measured during the first trimester between January 2018 and August 2023. Exclusions included incomplete data, multiple pregnancies, and significant comorbidities. Participants were categorized into four groups based on their vitamin D levels, and associations with fetal and adverse pregnancy outcomes

Results: When we grouped pregnant women according to their vitamin D levels, 36.3% were severely deficient (<10 ng/mL), 47.5% were deficient (10–19 ng/mL), and 13.1% were insufficient (20–30 ng/mL). Only 63 (3.2%) pregnant women had sufficient vitamin D levels (>30 ng/mL). A significant correlation was found between vitamin D levels and age, with older women showing higher levels ($p < 0.001$). There was no clear relationship between vitamin D levels and other pregnancy complications, such as preeclampsia, gestational diabetes, preterm labor, or adverse neonatal outcomes. The incidence of abortion in women with vitamin D levels >30 ng/mL was 18%, which was significantly higher than in lower vitamin D groups ($p = 0.029$). Vitamin D levels were significantly lower in pregnancies with term birth weight below 2500 grams ($p = 0.024$).

ÖZ

Amaç: Gebelikte vitamin D eksikliği, gebelerin önemli bir kısmını etkileyen küresel bir sağlık sorunudur. Çeşitli olumsuz maternal ve fetal sonuçlarla ilişkilendirilmiş olmakla birlikte, doğrudan etkisine ilişkin çalışmalar çelişkili sonuçlar bildirmektedir. Bu çalışmada, birinci trimesterde vitamin D eksikliği prevalansının ve bunun gebelik komplikasyonları ile ilişkisinin değerlendirilmesi amaçlandı.

Yöntemler: Bu retrospektif kohort çalışmasına, Ocak 2018 ile Ağustos 2023 tarihleri arasında Gazi Üniversitesi Kadın Hastalıkları ve Doğum Kliniğine başvuran ve birinci trimesterde vitamin D düzeyi ölçülen 1999 gebe dahil edildi. Eksik verisi olanlar, çoğul gebeliği bulunanlar ve önemli komorbiditeleri olanlar dışlandı. Katılımcılar vitamin D düzeylerine göre dört gruba ayrıldı ve fetal sonuçlar ile olumsuz gebelik sonuçları arasındaki ilişkiler değerlendirildi.

Bulgular: Gebeler vitamin D düzeylerine göre gruplandırıldığında, %36,3'ünde ciddi eksiklik (<10 ng/mL), %47,5'inde eksiklik (10–19 ng/mL) ve %13,1'inde yetersizlik (20–30 ng/mL) saptandı. Yalnızca 63 (%3,2) gebenin vitamin D düzeyi yeterliydi (>30 ng/mL). Vitamin D düzeyleri ile yaş arasında anlamlı bir ilişki bulundu ve ileri yaştaki kadınlarda vitamin D düzeylerinin daha yüksek olduğu görüldü ($p < 0,001$). Vitamin D düzeyleri ile preeklampsi, gestasyonel diyabet, preterm eylem veya olumsuz neonatal sonuçlar gibi diğer gebelik komplikasyonları arasında belirgin bir ilişki saptanmadı. Vitamin D düzeyi >30 ng/mL olan kadınlarda abortus oranı %18 olup, bu oran daha düşük vitamin D düzeylerine sahip gruplara göre anlamlı olarak daha yüksekti ($p = 0,029$). Termde doğum ağırlığı 2500 gramın altında olan gebeliklerde vitamin D düzeyleri anlamlı olarak daha düşüktü ($p = 0,024$).

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ABSTRACT

Conclusion: Our study confirms a high prevalence of vitamin D deficiency among women in the first trimester of pregnancy and shows that vitamin D levels increase with advancing maternal age. Low vitamin D levels were not associated with adverse pregnancy outcomes.

Keywords: Vitamin D deficiency, pregnancy complications, first trimester, obstetric outcomes

ÖZ

Sonuç: Çalışmamız, gebeliğin birinci trimesterindeki kadınlarda vitamin D eksikliğinin yüksek prevalansta olduğunu ve vitamin D düzeylerinin maternal yaş arttıkça yükseldiğini göstermektedir. Düşük vitamin D düzeyleri, olumsuz gebelik sonuçları ile ilişkili bulunmamıştır.

Anahtar Sözcükler: Vitamin D eksikliği, gebelik komplikasyonları, birinci trimester, obstetrik sonuçlar

INTRODUCTION

Vitamin D deficiency, indicated by circulating low levels of 25-hydroxyvitamin (OH) D, affects approximately 40% of pregnant women (1). In Mediterranean countries, prevalence studies have showed that this rate can reach to 60-80% (2). As pregnancy progresses, the need for vitamin D increases, potentially exacerbating vitamin D deficiency. Severe vitamin D deficiency, defined as 25-OH vitamin D concentrations below 10 ng/mL, is associated with impaired bone homeostasis, rickets, and neonatal fractures (3). However, the effects of milder deficiencies on maternal and fetal health remain unclear.

The vitamin D plays an important role for fertilization, placental development, the pregnancy process, and infant health (4). Deficiency has been linked to increased risks of miscarriage, preeclampsia, preterm birth, gestational diabetes and intrauterine growth restriction (5). However, some observational and randomized studies have not found a consistent association between vitamin D levels and adverse obstetric outcomes (5). These inconsistencies may be due to racial and individual factors or the different gestational weeks when studies were conducted.

Most randomized studies on this topic focus on later gestational weeks or have small sample sizes. To address this gap, our study aims to investigate the relationship between baseline vitamin D levels measured in the first trimester–before vitamin supplementation begins, during the critical period of embryogenesis–and gestational morbidity and mortality outcomes.

MATERIALS AND METHODS

This retrospective cohort study was conducted at the Gazi University Obstetrics and Gynecology Clinic and included pregnant women who visited the clinic between January 2018 and August 2023. During this period, 4314 consecutive intrauterine pregnancies who had their vitamin D levels measured in the first trimester were included in the study. Medical records of pregnant patients were reviewed using the hospital information system. Women with incomplete data, those who were lost to follow-up at our clinic, those who were not examined in the first trimester, and those with comorbidities (history of phosphocalcic disorders, hypercalcemia, malabsorptive diseases, pregestational diabetes, preeclampsia, chronic hypertension, or renal disease) were excluded. Only singleton pregnancies were included in the study. A total of 1999 pregnant women were included in the study (Table 1).

The hospital records were used to collect information on maternal age, previous delivery methods, and Rh incompatibility. Pregnancy outcomes (miscarriage, ectopic pregnancy, stillbirth, preterm birth) and complications during pregnancy (vaginal bleeding, preterm premature rupture of membranes, threatened preterm labor, preeclampsia, gestational diabetes mellitus, cholestasis, placental anomalies, neural tube defects, oligohydramnios, or polyhydramnios) were documented. Delivery records were examined for delivery method, difficult labor, postpartum atony, meconium staining, and fetal distress. Additionally, records of the infants born from these pregnancies were reviewed, noting birth weight and length, 1st- and 5th-minute APGAR scores, and the infants' genders.

Women who participated in the study were divided into four groups based on their vitamin D levels: Group 1 (<10 ng/mL, severely deficient), Group 2 (10–19 ng/mL, deficient), Group 3 (20–30 ng/mL, insufficient), and Group 4 (>30 ng/mL, sufficient).

This study was approved by the Ethics Committee of Gazi University (approval number: 2023-1475, date: 19.12.2023).

Statistical Analysis

Data from the study were analyzed using IBM SPSS Statistics 23. Categorical variables are presented as percentages, and continuous variables are presented as mean (standard deviation) and median (maximum–minimum). Normality was assessed using the Shapiro–Wilk and Kolmogorov–Smirnov tests. Categorical variables were compared using the Pearson chi-square test or Fisher's exact test, as appropriate. For non-normally distributed continuous variables, the Mann–Whitney U test (two groups) and Kruskal–Wallis test (≥3 groups) were used. For normally distributed variables, the student's t-test (two groups) and one-way analysis of variance (≥3 groups) were used. A p value < 0.05 was considered statistically significant.

RESULTS

A total of 1999 pregnant women were included in the study. The study flow diagram of patient selection is presented in Figure 1. The demographic data and general characteristics for the four groups, including patients' age, parity, duration of gestation, and characteristics of infants born from these pregnancies, are presented in Table 1. When we grouped pregnant women according to their, vitamin D levels, 36.3% of pregnant women were severely deficient (<10 ng/mL) 47.5% were deficient (10–19 ng/mL), 13.1% were insufficient (20–30 ng/mL). Only 63 (3.2%) pregnant women were found to have sufficient vitamin D levels (>30 ng/mL). A significant difference in age was observed between the groups, with the vitamin D–sufficient group being older ($p < 0.001$). Gestational age at birth, newborn weight and 1st and 5th minutes Apgar scores were similar between vitamin D groups ($p = 0.44$, $p = 0.99$, $p = 0.15$, $p = 0.46$ respectively)

When the population was categorized into three maternal age groups (<26, 26–35, and >35), a significant difference was observed among the groups (p < 0.001) (Table 2). Vitamin D levels were found to increase with advancing maternal age (Figure 2).

When pregnancy complications were compared among the patients, no statistically significant relationship was observed between vitamin D levels and complications such as preeclampsia, gestational diabetes, and preterm labor (p = 0.07, p = 0.49, p = 0.64, respectively) or adverse fetal outcomes such as stillbirth and fetal distress (p = 0.82, p = 0.91). The incidence of abortion in women with vitamin D levels >30 ng/mL was 18%, significantly higher than in lower vitamin D groups (p = 0.029) (Table 3). Due to the absence of a gradual trend among the groups, a subgroup analysis was performed. For abortion, statistically significant differences were identified between Group 1 and Group 4, as well as between Group 2 and Group 4 (p = 0.008 and p = 0.006, respectively).

The birth weights of the patients whose pregnancies ended at term (>37 gestational weeks) were analyzed separately. A statistically significant difference was found between vitamin D levels and birth weights below 2500 grams small-for-gestational-age (SGA) (p = 0.024) (Table 4). The mean and standard deviation of vitamin D levels in term SGA infants were 12.9 (±4.8), while the mean and standard deviation of the group with birth weights over 2500 grams were 14.2 (±5.9).

DISCUSSION

Our study used data from a tertiary center in Türkiye to evaluate the relationship between first-trimester vitamin D levels and adverse pregnancy outcomes and to describe vitamin D status in the reproductive population. The screening of women at low risk for pregnancy complications and the large patient population distinguish our study from other published studies. In our study, vitamin D levels increased with age, but no clear relationship was found between these levels and pregnancy-related complications.

Our study showed that vitamin D deficiency is a common health problem among women of reproductive age in Türkiye. Our prevalence of vitamin D insufficiency was 96.8%. The prevalence of vitamin D insufficiency ranges from 22% to 77% in northern countries (such as Germany and The Netherlands) and from 46% to 97% in Asian countries (6-9). When comparing prevalence studies conducted in different countries, researchers should consider racial and geographical differences. Nevertheless, the consistently high prevalence reported across various regions, irrespective of ethnic and geographical variations, underscores that vitamin D insufficiency is a global issue. Prevalence studies use varying cut-off values for vitamin D levels. For instance, some studies define insufficiency at thresholds of 15 ng/mL or 20 ng/mL, leading to differences in reported prevalence (6,10-12). The findings revealed a high prevalence of vitamin D deficiency, particularly among younger age groups. In our study, vitamin D deficiency was more severe among younger women, and vitamin D levels tended to normalize with age. This normalization may be associated with better dietary habits, increased sun exposure, or improved awareness of vitamin D supplementation among older age groups.

This study, which involved a large patient population and identified high rates of vitamin D insufficiency and deficiency, found no significant overall increase in pregnancy complications. Although the Endocrine Society recommends routine vitamin D supplementation for all pregnant women to prevent intrauterine mortality, preeclampsia, preterm labor, and SGA complications, our study,

Table 1. Characteristics of patients according to vitamin D levels.

	Vitamin D Level (ng/mL) n (%)				
All	**<10 725 (36.3%) Mean ± SD**	**10-19 949 (47.5%) Mean ± SD**	**20-30 262 (13.1%) Mean ± SD**	**>30 63 (3.2%) Mean ± SD**	**p**
Age	28 ± 5	29 ± 5	30 ± 5	32 ± 5	<0.001
Pregnancy outcome (days)	256 ± 50	256 ± 50	256 ± 49	233 ± 83	0.443
Infant weight (gr)	3169 ± 533	3173 ± 532	3172 ± 497	3160 ± 447	0.994
Infant height (cm)	48 ± 3	48 ± 3	48 ± 3	48 ± 2	0.578
APGAR score at 1 minute	8 ± 1	8 ± 1	9 ± 1	9 ± 1	0.147
APGAR score at 5 minutes	10 ± 4	9 ± 1	9 ± 1	10 ± 1	0.458
	n (%)	**n (%)**	**n (%)**	**n (%)**	**p**
Parity					0.740
Nulliparous	285 (39.3%)	358 (37.7%)	107 (40.8%)	27 (42.9%)	
Multiparous	440 (60.7%)	591 (62.3%)	155 (59.2%)	36 (57.1%)	
Vaginal	191 (43.4%)	221 (37.4%)	47 (30.3%)	13 (36.1%)	
Cesarean	249 (56.6%)	370 (62.6%)	108 (69.7%)	23 (63.9%)	
Infant gender					0.260
Male	362 (49.9%)	502 (52.9%)	145 (55.3%)	40 (63.5%)	
Female	363 (50.1%)	447 (47.1%)	117 (44.7%)	23 (36.5%)	

SD: Standard deviation.

Table 2. Vitamin D levels by age.

	Age (n)			
	≤25 (541)	26-35 (1181)	>35 (277)	p-value
Vitamin D level (ng/mL) mean (±SD)	12.8 ± 4.6	14.6 ± 6.1	15.8 ± 7.3	<0.001

SD: Standard deviation.

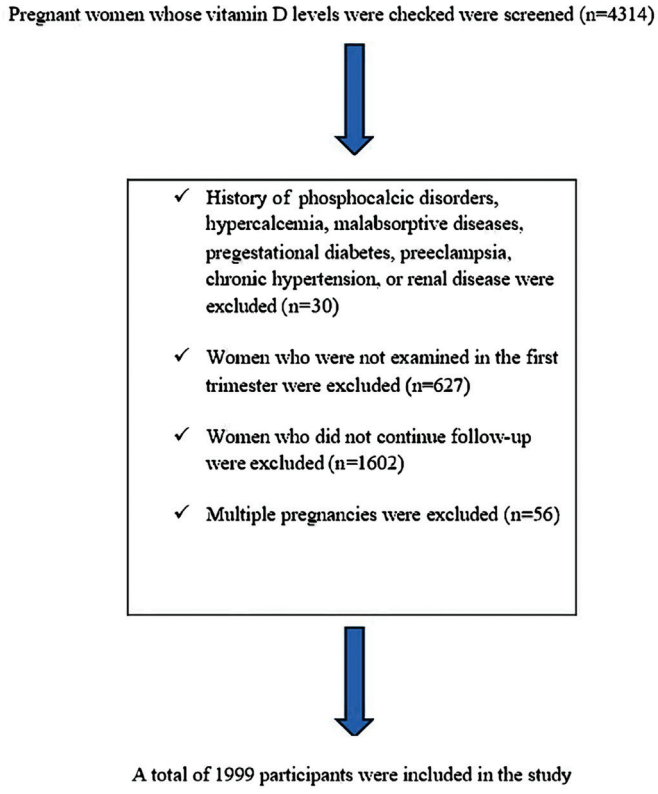

Figure 1. Flow diagram of patient eligibility.

which included a large patient population with a high prevalence of vitamin D deficiency, did not identify a significant increase in these pregnancy complications (13).

The incidence of abortion in women with vitamin D levels >30 ng/mL was significantly higher than in women with lower vitamin D levels. This higher risk may be associated with the older age of this cohort. Contrary to our finding, the literature includes studies reporting that vitamin D deficiency predisposes to miscarriage and threatened miscarriage (4,14,15). Furthermore, women with a history of at least one pregnancy loss have lower vitamin D levels than those without such a history. A recently published meta-analysis on recurrent pregnancy loss reported that preconception vitamin D levels play a role in preventing miscarriage (16). However, this study did not include a subgroup analysis regarding maternal age and supplementation. As our findings highlight, the importance of considering maternal age in studies of miscarriage is another critical factor that needs to be emphasized Considering the tendency for vitamin D levels to be higher in older mothers, increasing vitamin D in this group may not be effective in preventing miscarriages.

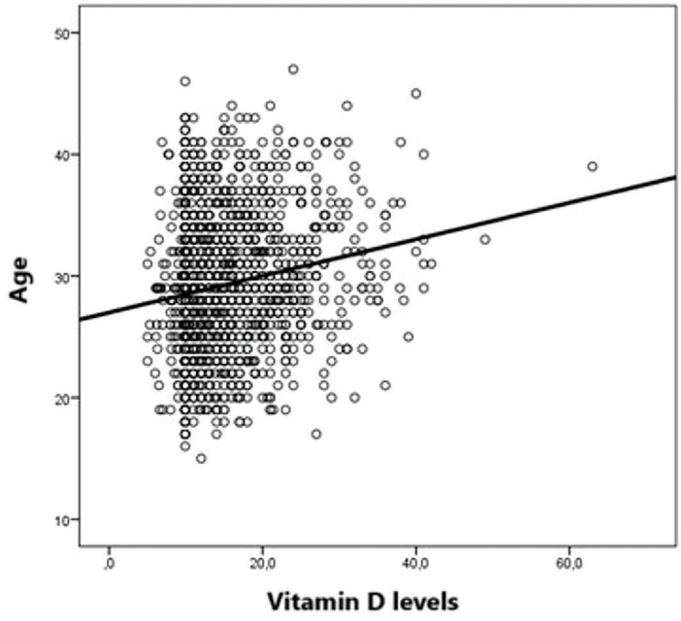

Figure 2. Vitamin D levels by age.

Low birth weight was significantly associated with lower vitamin D levels. This finding suggests that adequate vitamin D levels may be important for optimal fetal growth. A randomized controlled trial conducted in Bangladesh initiated supplementation at three different doses between the 17th and 24th gestational weeks and found no significant correlation with birth weight (17). In contrast, a prospective cohort study published in Sweden identified an association between vitamin D deficiency and SGA (18). A meta-analysis also reported that vitamin D levels below 12 ng/mL increased the risk of SGA by 1.5 times (odds ratio 1.58; 95% confidence interval: 1.14, 2.22) (19). A positive correlation between vitamin D supplementation and infant weight was observed. Infants whose mothers received supplementation had higher weights at 3, 6, and 12 months of age. A six-year follow-up randomized controlled trial conducted in Denmark, starting supplementation from the 24th gestational week, reported no effect on infant weight but found that vitamin D levels below 12 ng/mL were associated with growth retardation (20). These findings from various geographic locations suggest that maintaining sufficient first-trimester serum vitamin D levels is crucial for supporting fetal development.

Our study demonstrated that vitamin D insufficiency and deficiency did not lead to a significant increase in obstetric complications. The relationship between vitamin D levels and adverse obstetric outcomes remains unclear. This uncertainty may stem from conflicting results in the literature, variations in gestational age at screening, differing cut-off levels, small sample sizes, and most studies focusing on a single obstetric outcome. Therefore, our study, with its large sample size and examination of multiple outcomes within the same cohort, will help clarify the relationship between vitamin D levels and adverse obstetric outcomes in the scientific literature. The primary strengths of our study are its large sample size and homogeneous ethnic background of the patient population, which enhance the reliability of the findings. Additionally, measuring vitamin D levels during the first trimester provides critical

Table 3. Pregnancy complications according to vitamin D levels.

	<10 ng/mL 725 (36.3%) n (%)	**10-19 ng/mL 949 (47.5%) n (%)**	**20-30 ng/mL 262 (13.1%) n (%)**	**>30 ng/mL 63 (3.2%) n (%)**	**p**
Vaginal bleeding	41 (5.7%)	65 (6.8%)	14 (5.3%)	4 (6.3%)	0.708
PPROM	19 (2.6%)	35 (3.7%)	4 (1.5%)	0 (0.0%)	0.115
Preterm labor	33 (4.6%)	46 (4.8%)	14 (5.3%)	1 (1.6%)	0.640
Dystocia	48 (6.6%)	58 (6.1%)	18 (6.9%)	4 (6.3%)	0.962
Postpartum hemorrhage	2 (0.3%)	7 (0.7%)	4 (1.5%)	0 (0.0%)	0.157
Atony	1 (0.1%)	2 (0.2%)	0 (0.0%)	0 (0.0%)	0.867
Fetal distress	23 (3.2%)	28 (3.0%)	6 (2.3%)	2 (3.2%)	0.911
Meconium staining	1 (0.1%)	4 (0.4%)	2 (0.8%)	0 (0.0%)	0.462
Preeclampsia	22 (3.0%)	14 (1.5%)	9 (3.4%)	3 (4.7%)	0.070
GDM	47 (6.5%)	70 (7.4%)	15 (5.7%)	2 (3.2%)	0.494
Abortion	58 (8%)	69 (7.3%)	20 (7.7%)	11 (18%)	0.029
Stillbirth	10 (1.4%)	12 (1.3%)	3 (1.1%)	0 (0 %)	0.821
Ectopic pregnancy	1 (0.1%)	0 (0 %)	1 (0.4%)	0 (0 %)	0.363
Cholestasis of pregnancy	7 (1.0%)	11 (1.2%)	4 (1.5%)	0 (0.0%)	0.732
Thrombotic event	20 (2.8%)	30 (3.2%)	8 (3.1%)	2 (3.2%)	0.971
Oligohydramnios	4 (0.6%)	7 (0.7%)	3 (1.1%)	0 (0%)	0.697
Polyhydramnios	7 (1.0%)	5 (0.5%)	1 (0.4%)	0 (0.0%)	0.564
Neural tube defect	2 (0.3%)	2 (0.2%)	0 (0.0%)	1 (1.6%)	0.155
Placental anomaly	10 (1.4%)	10 (1.1%)	2 (0.8%)	0 (0.0%)	0.680
SGA (<2500g)	65 (8.9%)	84 (8.8%)	23 (8.7%)	4 (6.3%)	0.983

SGA: Small-for-gestational-age, PPROM: Preterm premature rupture of membranes, GDM: Gestational diabetes mellitus.

Table 4. Infant weight at term births.

	Infant weight (n)		
	< 2500 (97)	**> 2500 (1555)**	**p-value**
Vitamin D level mean (±SD)	12.9 ± 4.8	14.2 ± 6	0.024

SD: Standard deviation.

baseline data before supplementation begins. However, the lack of information on vitamin D supplementation and the absence of follow-up measurements in later trimesters are notable limitations. This restricts the ability to assess changes in vitamin D status throughout pregnancy. Despite these limitations, our study offers valuable insights into the relationship between early pregnancy vitamin D levels and obstetric outcomes.

CONCLUSION

In our comprehensive study of first-trimester pregnant women, we identified a high prevalence of vitamin D deficiency, and vitamin D levels increased with advancing maternal age. There was no clear relationship between vitamin D levels and most pregnancy-related complications, except for a modest association with term low birth weight and a higher abortion rate in the vitamin D–sufficient group, which may reflect confounding by maternal age. Prospective studies incorporating supplementation data and serial measurements are warranted.

Ethics

Ethics Committee Approval: This study was approved by the Ethics Committee of Gazi University (approval number: 2023-1475, date: 19.12.2023).

Informed Consent: Because of the retrospective design of the study, individual informed consent was waived.

Footnotes

Authorship Contributions

Surgical and Medical Practices: S.F., B.M.S., Ş.D.Y., C.K., P.T.Ç., D.K., Concept: S.F., B.M.S., Ş.D.Y., C.K., P.T.Ç., D.K., Design: S.F., B.M.S., Ş.D.Y., C.K., P.T.Ç., D.K., Data Collection or Processing: S.F., B.M.S., Ş.D.Y., C.K., P.T.Ç., D.K., Analysis or Interpretation: S.F., B.M.S., Ş.D.Y., C.K., P.T.Ç., D.K., Literature Search: S.F., B.M.S., Ş.D.Y., C.K., P.T.Ç., D.K., Writing: S.F., B.M.S., Ş.D.Y., C.K., P.T.Ç., D.K.

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