Does COVID-19 reduce anti-Mullerian hormone levels in women of reproductive age in late periods of infection?

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Abstract

Objective: The question of whether severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) infection influences ovarian function and oocyte quality has arisen as angiotensin converting enzyme-2 receptors, which facilitates viral infection, are found on reproductive system tissues, including the vagina, placenta, uterus, and ovaries. The primary objective of this prospective study was to evaluate the impact of SARS-CoV-2, on ovarian function, with a focus on anti-Mullerian hormone (AMH) and acute phase reactant levels in patients well after recovery from coronavirus disease-2019 (COVID-19).

Material and Methods: This prospective cohort study was conducted in the department of obstetrics and gynecology at a single center between October 2020 and June 2021. In order to investigate the impact of COVID-19 on ovarian reserve, 34 non-pregnant women of reproductive age (24-38 years) with COVID-19 polymerase chain reaction positivity were included.

Results: The difference between AMH levels measured 6 months after COVID-19 infection and baseline AMH levels was -0.31±0.80 ng/dL on average and -0.25 (-2.1-1.3) ng/dL on median. Significant correlations were observed between the change in AMH levels and white blood cell levels (r=-0.434, p=0.010), lymphocyte levels (r=-0.361, p=0.036), C-reactive protein levels (r=0.542, p=0.001), ferritin levels (r=0.570, p=0.001) and procalcitonin levels (r=0.598, p=0.001).

Conclusion: We believe this is the first study to examine whether there is a correlation between the late results of COVID-19 and ovarian function. In this cohort, AMH values decreased 6-months after recovery from COVID-19 and a correlation was found between measures of disease severity and the magnitude of decrease in AMH. However, the study was underpowered and future larger studies are required to validate these findings. (J Turk Ger Gynecol Assoc. 2024; 25: 231-7)

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Introduction

The severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), first detected in Wuhan, China in December 2019, caused a global coronavirus disease-2019 (COVID-19) pandemic. As of June 2022, 532,887,351 cases and 6,307,021 deaths have been detected worldwide (1).

SARS-CoV-2 exploits membrane bound angiotensin converting enzyme-2 (ACE2) in order to infect host cells. The fusion of the virus and the host cell occurs with the transmembrane serine protease 2 receptor (2). By targeting the vascular endothelium, SARS-CoV-2, known to cause severe harm to the respiratory system, can also lead to thrombosis, pulmonary embolism and high blood pressure. Immune system dysfunction contributes to the current condition by enhancing microvascular permeability and vascular inflammation (3).

Additionally, there is evidence that the heart, bowels, testicles, and ovaries may be target tissues for SARS-CoV-2 (4) ACE2 receptors on the ovaries have functions including gonadotropin response, modulation of steroidogenesis, follicle growth and angiogenesis (5,6). However, the current data on whether SARS-CoV-2 infection has any impact on the female reproductive system is quite limited.

Anti-Mullerian hormone (AMH) is an important biomarker of ovarian follicle reserve and quality (7). During the early 1990s, it was discovered that blood AMH concentration might serve as a measure of ovarian reserve by providing an indirect estimate of the total number of potential follicles (8).

The primary objective of this prospective study was to evaluate the impact of SARS-CoV-2 on ovarian function by measuring AMH and acute phase reactant levels in patients after complete recovery from COVID-19. The study also aimed to investigate the effect of severity of COVID-19 on ovulation and follicular function. We believe that this is the first study to investigate the relationship between severity of COVID-19 and ovarian function.

Material and Methods

After receiving University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital Local Ethics Committee approval (approval number: 2020-22-07, date: 02.11.2020), a prospective cohort study was conducted by the department of obstetrics and gynecology of a single center between October 2020 and June 2021. Written informed consent was obtained from all participants before starting the study.

In order to investigate the impact of COVID-19 on ovarian reserve, non-pregnant women of reproductive age (24-38 years) with COVID-19 polymerase chain reaction positivity and with regular (24 to 38 day) menstrual cycles were included in the study. Exclusion criteria were: pregnancy or lactation; pre-existing conditions that may affect ovarian function (ovarian surgery, pelvic region radiotherapy, systemic chemotherapy); endocrine disease (thyroid dysfunction, hyperprolactinemia or Cushing syndrome); diagnosis of premature ovarian failure; suspicion of adnexal malignancy; presence of ovarian endometrioma; history of infertility or pregnancy via assisted reproductive technique; and women with severe COVID-19 requiring intensive care.

On the day of COVID-19 diagnosis, blood samples were taken from each participant (day 0). The following parameters were measured: plasma AMH (ng/dL); hemoglobin (Hb, g/dL); hematocrit (Htc, %); white blood cell count [(WBC), 10^3/uL]; lymphocyte proportion of WBC (%); neutrophil proportion of WBC (%); eosinophil proportion of WBC (%); C-reactive protein [(CRP), mg/L]; ferritin (ng/mL); procalcitonin (ng/mL); aspartate aminotransferase [(AST), U/L]; alanine aminotransferase [(ALT), U/L]; gamma glutamyl transferase [(GGT), IU/L]; lactate dehydrogenase [(LDH), U/L]; urea (mg/dL); and creatinine (mg/dL).

Patients were reviewed six months following infection, and blood tests were recollected to determine AMH levels. Plasma was centrifuged at 2500 rpm for 10 minutes and then stored at -80 °C. Serum AMH concentrations were measured by an enzyme immunoassay kit (EIA AMH/MIS; Immunotech, Chantilly, VA, USA) with a detection limit of 0.006 ng/mL. All hormone assays were processed by the same reference laboratory. Patients who experienced any adverse condition that could adversely affect AMH levels and/or ovarian reserve during this 6-month period were excluded. The effect of COVID-19 on ovarian reserve was evaluated by comparing day 0 and 6-month AMH levels.

Sample size and power analysis

The 2021 study by Kolanska et al. (9) provides comprehensive descriptive statistics for AMH levels. Specifically, the study reported initial median AMH levels of 2.87 ng/dL [interquartile range (IQR): 1.69-3.99] and subsequent levels of 1.51 (IQR: 0.82-2.38). In light of these values, a power analysis was conducted to assess the statistical significance of the difference between the initial and subsequent AMH measurements. This analysis was carried out under conditions of 80% power and 5% types 1 error rate.

Given the uncertainties regarding whether the data set follows a normal distribution, and considering that the study of Kolanska et al. (9) used non-parametric descriptive statistics, such as IQR, a non-parametric approach was adopted for the analysis. This methodology abstains from making any assumptions about the data distribution and offers a more robust alternative when parametric assumptions are not met.

In our initial sample size calculations, we anticipated achieving a power of 0.80 with 21 participants. However, our post-

hoc power calculations revealed a power of 0.618 with 34 participants. This discrepancy appears to be related to the observation of a smaller effect size than the one estimated based on previous studies, as well as an unforeseen variance. These findings emphasize that the expectations set for sample size and effect size in a study may not always match the actual outcomes. Nonetheless, considering the constraints imposed by the pandemic, our results can still be deemed noteworthy.

The analytic process was executed using the Python programming language and the SciPy statistical library, establishing a robust foundation for making more precise estimations of sample size in future research.

Statistical analysis

In order to perform statistical analysis, the Number Cruncher Statistical System 2007 (Kaysville, Utah, USA) program was used. Descriptive statistical methods (mean, standard deviation, median, range, frequency, and percentage) were used whilst evaluating the study data. The Shapiro-Wilk test and graphical analysis were used to assess normality of data distribution of the data sets. The Mann-Whitney U test was used to compare two data sets when at least one was non-parametric. The associations between the quantitative variables were examined using Spearman correlation analysis. The threshold for statistical significance was set at 0.05.

Results

In total, 34 women with a mean age of 26.79±4.87 years. The mean body mass index (BMI) was 23.35±2.98 kg/m^2. The parity was 0 in 22 (64.7%), 1 in 3 (8.8%), 2 in 7 (20.6%), and 3 in 2 (50.9%).

The distribution of Hb, Htc, WBC, lymphocyte, neutrophil, eosinophil, CRP, ferritin, procalcitonin, AST, ALT, GGT, LDH, urea, creatinine values of the patients participating in the study is shown in Table 1.

Table 2 shows the changes in AMH levels at baseline and at 6-months following SARS-CoV-2 infection. The mean decrease of 0.31±0.80 units in the month 6 measurements was significant compared to the day 0 AMH levels (p=0.025) (Table 2, Figure 1).

No significant correlation was found between the first and second AMH concentrations of the patients and WBC, lymphocyte, neutrophil, eosinophil, CRP, ferritin and procalcitonin measurements (p>0.05). There was no relationship between neutrophil and eosinophil levels of women participating in the study and the changes in the AMH values (p>0.05) (Table 3).

A weak negative correlation (r=-0.361; p=0.036) was identified between the baseline lymphocyte measurements and the value of the difference between the baseline and 6-month

Table 1. Summary of baseline hematological parameters and biochemical markers in COVID-19 patients

	Mean ± SD	Median (min.-max.)
Hematological parameters		
Hb (g/dL)	12.86±0.96	13 (10.9-15)
Htc (%)	38.61±2.95	38.9 (31-44)
WBC (10^3/uL)	11.12±4.05	9.8 (5.9-21.4)
Lymphocyte (10^3/uL)	2.18±1.00	2.1 (0.1-4.5)
Neutrophil (10^3/uL)	6.11±2.68	5.4 (3.3-16.3)
Eosinophil (10^3/uL)	0.21±0.17	0.2 (0-0.6)
Inflammation and infection markers		
CRP (mg/L)	11.09±11.87	4.1 (0.5-43)
Ferritin (ng/mL)	61.94±43.66	59.8 (6.6-157)
Procalcitonin (ng/mL)	0.06±0.09	0 (0-0.5)
Liver function tests		
AST (U/L)	18.24±9.94	16 (10-68)
ALT (U/L)	19.18±16.72	14 (8-91)
GGT (U/L)	19.38±6.42	18 (11.4-41)
LDH (U/L)	200.21±45.57	200 (139-338)
Renal function parameters		
Urea (mg/dL)	24.03±7.31	24.3 (10-43)
Creatinine (mg/dL)	0.63±0.09	0.6 (0.4-0.9)

Hb: Hemoglobin, Htc: Hematocrit, WBC: White blood cell, CRP: C-reactive protein, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, GGT: Gamma-glutamyl transferase, LDH: Lactate dehydrogenase, SD: Standard deviation, min.: Minimum, max.: Maximum

AMH concentrations. Similarly, a moderate negative correlation (r=-0.434; p=0.010; p<0) was found between WBC and the variation of difference between baseline and 6-month AMH measurements (Figure 2). This finding is perhaps not unexpected, as a major proportion of the WBC will consist of lymphocytes.

In terms of acute phase reactants, moderate positive correlations were found for CRP (r=0.542; p=0.001; Figure 3), ferritin (r=0.570; p=0.001; Figure 4) and procalcitonin (r=0.598; p=0.001; Figure 5) and the differences in baseline and 6-month AMH values.

Table 2. Evaluation of variation between AMH measurements

		Day 0	Month 6	Difference	Test statistic/p-value
AMH	Mean ± SD	3.58±1.51	3.27±1.53	-0.31±0.80	Z: -2.248
	Median (min.-max.)	3.01 (1.94-8.41)	3.01 (1.4-9.74)	-0.25 (-2.1-1.3)	[a]**0.025***

[a]Wilcoxon signed-ranks test, *p<0.05, min.-max.: Minimum-maximum, SD: Standard deviation, AMH: Anti-Mullerian hormone

Table 3. Correlation between change in AMH at baseline and at 6-months and parameters of inflammation

		1. Measurement AMH	2. Measurement AMH	Change in AMH
WBC (10^3/uL)	r	0.170	-0.005	-0.434
	p	0.336	0.978	**0.010**
Lymphocyte (%)	r	-0.152	0.034	-0.361
	p	0.392	0.849	**0.036**
Neutrophil (%)	r	-0.136	-0.007	-0.116
	p	0.443	0.968	0.515
Eosinophil (%)	r	0.047	0.158	-0.111
	p	0.793	0.371	0.531
CRP (mg/L)	r	0.254	0.080	0.542
	p	0.147	0.652	**0.001**
Ferritin (ng/mL)	r	0.312	0.015	0.570
	p	0.072	0.934	**0.001**
Procalcitonin (ng/mL)	r	0.151	-0.154	0.598
	p	0.393	0.385	**0.001**

r: Spearman correlation coefficient, WBC: White blood cell, CRP: C-reactive protein, AMH: Anti-Mullerian hormone

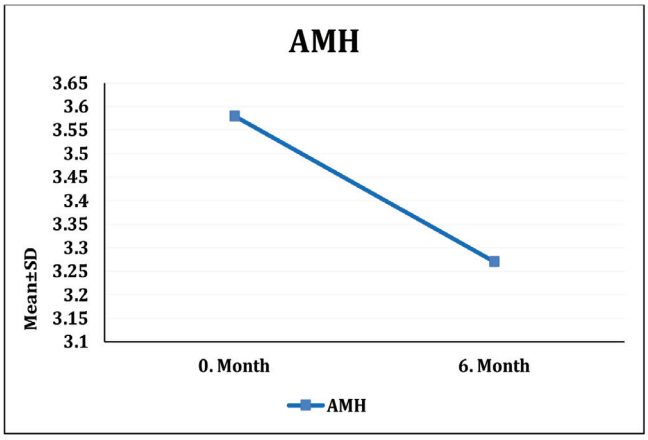

Figure 1. Evaluation of variation between AMH measurements
AMH: Anti-Mullerian hormone

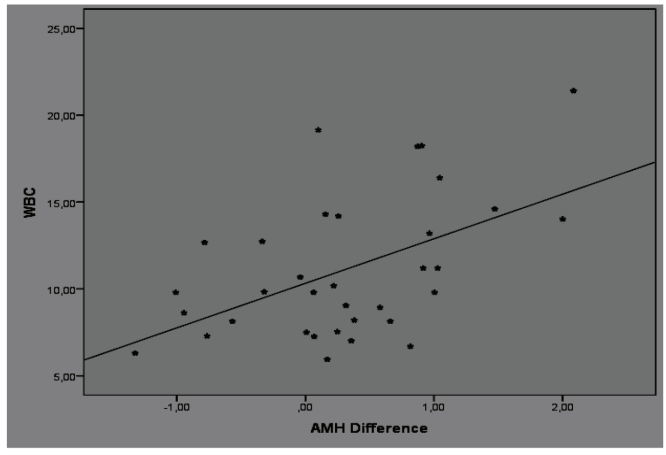

Figure 2. Distribution of the relationship between WBC values and the changes in 1st and 2nd AMH measureme
WBC: White blood cell count, AMH: Anti-Mullerian hormone

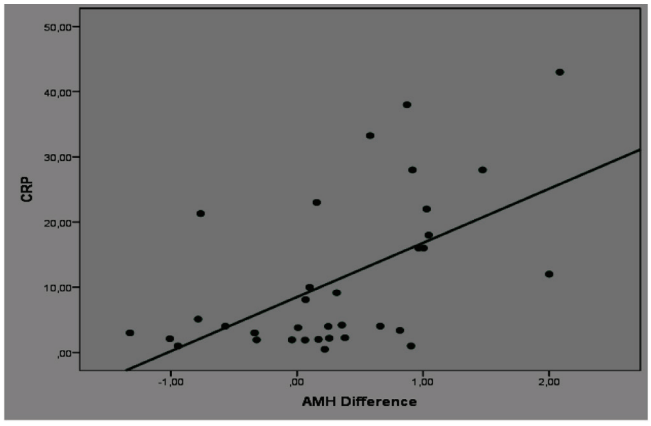

Figure 3. Distribution of the relationship between CRP concentrations and the differences in 1st and 2nd AMH measurements
CRP: C-reactive protein, AMH: Anti-Mullerian hormone

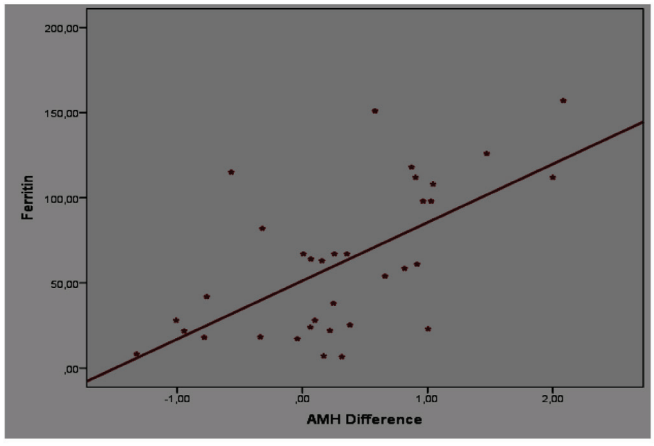

Figure 4. Distribution of the relationship between ferritin levels of participants and the variations in 1st and 2nd AMH measurements
AMH: Anti-Mullerian hormone

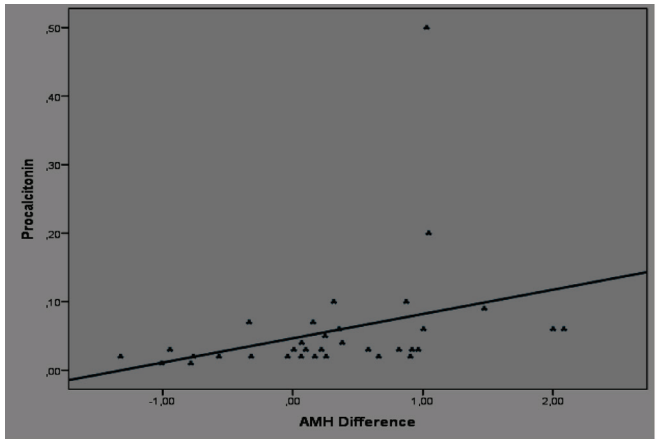

Figure 5. Distribution of the correlation between procalcitonin levels of the patients and the changes in AMH concentrations measured at day 0 and month 6
AMH: Anti-Mullerian hormone

Discussion

COVID-19 continues to affect tens of thousands of individuals worldwide, causing severe morbidity and mortality in certain cases. However, limited data exist regarding the early and long-term impacts of COVID-19 on ovarian function.

AMH is the most sensitive indicator of ovarian reserve, recognized as an early marker during its assessment (10,11).

In our study group, while some women saw their AMH levels rise and others fall, we observed a clear trend towards decreased AMH levels 6-months after COVID-19 infection compared to initial measurements. This suggests a significant effect of COVID-19 on ovarian reserve over time. A correlation was identified between decreased AMH values and increased acute phase reactants, suggesting an effect of severity of COVID-19 on ovarian function and/or reserve. This suggests a relationship between the severity of disease and thus impact of systemic inflammation on ovarian reserve in the chronic process, as well as in the acute infection period. We speculate that this may be due to severe oophoritis or multisystem inflammatory syndrome in some cases of COVID-19.

In a study of 78 female patients, COVID-19 positive patients had significantly lower serum AMH levels (0.19 vs. 1.12 ng/mL, $p=0.003$) and higher serum testosterone (0.38 vs. 0.22 ng/mL, $p<0.001$), FSH (FSH ≥10 mIU/mL: 53.8% vs. 34.7%, $p=0.041$) and prolactin levels (25.43 vs. 12.12 ng/mL, $p<0.001$). Changes in menstrual characteristics, such as menstrual irregularities and increased premenstrual symptoms, were also observed in this study (12). Furthermore, an animal study reported that SARS-CoV-2 infection of the ovarian granulosa cells via ACE2 receptors may lead to loss of ovarian reserve and adverse outcomes (13).

In studies, SARS-CoV-2 RNA was not detected in the follicular fluids of COVID-19 positive cases, while SARS-CoV-2 immunoglobulin G (IgG) was positive (14) IgG positivity can be interpreted as evidence of inflammation, which may cause tissue damage and hence a decrease in ovarian reserve. A study conducted by Herrero et al. (15) documented lower interleukin-1 and vascular endothelial growth factor (VEGF) levels in follicular fluid (14). In previous studies higher IL-1 and VEGF levels were associated with higher IVF success rates (16,17). Thus, oocyte quality may have deteriorated due to COVID-19. However, in a study by Li et al. (18), the concentrations of sex hormones [follicle-stimulating hormone (FSH), luteinizing hormone (LH), estrogen, progesterone, testosterone and AMH] in women of childbearing age with COVID-19 were compared to those of age-matched controls. These authors found no difference between the groups, although some of the women with COVID-19 exhibited a menstrual volume decrease or cycle prolongation (17).

Similarly, in another study by Madendag et al. (19) on 132 patients with COVID-19 examining the blood levels of AMH, FSH, LH, and estradiol following disease, at 3 months after recovery from COVID-19 no negative impact on the ovarian reserve was reported. Yet, irregular menstruation and decrease in bleeding volume were identified on review of patients' menstrual cycles. The cause of these changes was attributed to the immune response and inflammation (19).

Same study also assessed serum and follicular fluid samples for anti-COVID IgG as well as estrogen, progesterone and heparan sulfate proteoglycan 2 concentration in three study groups, women recovering from confirmed COVID-19, vaccinated women and uninfected, non-vaccinated controls suggested that SARS-CoV-2 had no influence on ovarian functions on hospitalized patients with moderate symptoms of the disease (18).

One study represented that a mild COVID-19 infection did not significantly alter ovarian reserve in women undergoing assisted reproductive technology (ART) treatment, as measured by AMH levels. AMH levels were comparable among COVID-19 positive and negative groups, before and during ART treatment. This suggests that mild COVID-19 infection may not have a detrimental effect on ovarian reserve (20).

The common feature of these studies, and ours, is the investigation of ovarian reserve and quality 3-9 months following infection. However, if it is acknowledged that inflammation is a mechanism of injury, longer-term studies are needed and may yield different results. Many studies have shown that oxidative stress may increase due to inflammation and adversely affect oocyte quality, female fertility and the number of healthy embryos (21). SARS-CoV-2 also triggers a systemic inflammatory response, which may cause oxidative stress. Even though the harmful effects of COVID-19 on the human body have not been fully elucidated, there is a clear need for further research with more cases and longer follow-up is to evaluate the influence of COVID-19 on both the menstrual cycle and ovarian reserve.

Study limitations

Our study found a post-hoc power value of 0.62, which is lower than the often-recommended value of 0.8. According to fundamentals of statistical analysis (22), while higher power is preferred, lower power can still be meaningful, especially in early-stage or constrained research. Our study's design, a before-and-after approach conducted during the challenging times of the COVID-19 pandemic, faced unique hurdles, such as difficulties in recruiting participants and collecting data. These challenges mean we should interpret our results carefully, recognizing they still contribute valuable insights despite the lower power value. This situation highlights the need to be flexible and realistic about what can be achieved under less-than-ideal research conditions. Another limitation of our study is the short follow-up period. In assessing the long-term effects of COVID-19 on health outcomes, a longer follow-up period would have been ideal to understand the persistence or evolution of impact over time fully. The rapid emergence of the pandemic and the urgent need for timely data contributed to the decision to use a shorter observation window. Future research should aim for longer follow-up periods to capture the full range of effects of COVID-19 and allow a more detailed assessment of its long-term health consequences.

Conclusion

Reflecting on the outcomes of our investigation and considering the broader spectrum of research, our study delves into the consequences of COVID-19 on ovarian reserve, acknowledging that while some reports indicate minimal impact, particularly in cases of mild infection, our observations point towards a discernible decrease in AMH levels post-infection. This trend is particularly pronounced in more severe instances of the disease, suggesting that the extent of systemic inflammation could play a significant role in this outcome. Such variability underscores the intricate ways in which COVID-19 can affect reproductive health, highlighting the critical need for more comprehensive, long-term studies to unravel the complex interplay between infection severity, inflammation, oxidative stress, and reproductive function.

Ethics Committee Approval: *The study protocol was reviewed and approved by University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital Ethics Committee (approval number: 2020-22-07, date: 02.11.2020).*

Informed Consent: *Written informed consent was obtained from all participants before starting the study.*

Author Contributions: *Surgical and Medical Practices: K.D., İ.Ö.A., A.E., M.G., M.C.D., M.E.; Concept: K.D., A.K., İ.Ö.A., M.E.; Design: K.D., A.K., İ.Ö.A., M.E.; Data Collection or Processing: K.D., İ.Ö.A., A.E., M.G., N.H.; Analysis or Interpretation: K.D., A.K., N.H., M.C.D.; Literature Search: K.D., İ.Ö.A., M.G., M.C.D., Writing: K.D., İ.Ö.A., A.E., M.C.D., M.E.*

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