ÖZGÜN ARAŞTIRMA ORIGINAL RESEARCH

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THE IMPACT OF COVID-19 ON MORTALITY IN CANCER PATIENTS IN THE INTENSIVE CARE UNIT

COVİD 19'UN KANSER HASTALARINDA YOĞUN BAKIM MORTALİTESİ ÜZERİNE ETKİSİ

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Öz

Amaç

Yeni koronavirüs hastalığı (COVİD 19) Aralık 2019 yılında ortaya çıkan mortalitesi yüksek bir solunum sistemi hastalığıdır. Kalp hastalığı, hipertansiyon, diyabet ve kronik obstrüktif akciğer hastalığı olan ve bağışıklık sistemi zayıflamış kişiler, ciddi komplikasyonlar açısından daha yüksek risk altındadır. Kanser hastaları hem hastalığın hem de tedavilerinin getirdiği etkiler nedeniyle pandemi sürecinden olumsuz etkilendi. Bu çalışmada amacımız COVİD 19' un yoğun bakımda takip edilen kanser hastalarındaki mortalite üzerine etkisinin değerlendirilmesidir.

Gereç ve Yöntem

Ocak 2020- Nisan 2022 yılları arasında yoğun bakımda takip edilen 275 COVİD 19 hastası retrospektif olarak incelendi. Bu hasta grubunda kanser tanısı mevcut 72 hasta tespit edildi. Hastalar; grup 1 kanseri olmayan hastalar(n=203), grup 2 kanseri olan hastalar (n=72) olarak iki gruba ayrıldı. Tüm hastaların yaş, cinsiyet, ek hastalık, PCR test pozitiflikleri, laboratuvar parametreleri, APACHE II, SOFA skorları, yoğun bakım kalış süresi, mekanik ventilatör gereksinimi, mekanik ventilatör süreleri kaydedildi.

Bulgular

Hipertansiyon Grup 1 de Grup 2 ye kıyasla anlamlı olarak daha yüksekti [(sırayla 97 (%48) ve 24 (%33); p<0.05]. Serum C-reaktif protein (CRP) seviyeleri, Grup 2 de Grup 1 ile karşılaştırıldığında anlamlı olarak yüksekti [sırasıyla 144 (0.5-480) ve 112 (1.1-404) mg/L; p <0.01]. Grup 2' de serum albumin, serum platelet ve hemotokrit düzeyleri Grup 1 ile karşılaştırıldığında anlamlı olarak daha düşüktü [sırasıyla 2.7 ±0.4 ve 2.9 ±1.3; p <0.01], [sırasıyla 173 (11-557) ve 212 (14-624); p <0.01], [sırasıyla 31.4± 7.1 ve 35.8±6.6; p <0.01]. Grup 1'de mortalite oranı grup 2 ye kıyasla anlamlı olarak daha düşüktü [sırasıyla 114 (%56) ve 51 (%71); p:0.03].

Sonuç

Bu bulgular, yoğun bakımda takip edilen COVİD 19 olan kanser hastalarında mortalitenin, kanseri olmayan hasta grubuna göre daha yüksek olduğunu göstermektedir. Bu konuda yapılacak yeni çalışmalara ihtiyaç duyulmaktadır.

Anahtar Kelimeler: Covid 19, Kanser, Komorbidite, Yoğun Bakım

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Abstract

Objective
New corona virus disease (COVID-19) is a respiratory disease associated with high mortality that emerged in December 2019. Individuals with preexisting health conditions, such as heart disease, hypertension, diabetes, and chronic obstructive pulmonary disease, and those with weakened immune systems are at increased risk for severe complications. Cancer patients have been adversely affected by the pandemic, both due to the disease itself and its treatments. The aim of this study is to evaluate the impact of COVID 19 on mortality in cancer patients followed in the intensive care unit (ICU).

Material and Method
We conducted a retrospective analysis of 275 COVID-19 patients who were admitted to the ICU between January 2020 and April 2022. Among these patients, 72 had a cancer diagnosis and were classified into two groups: Group 1 (n=203) included patients without cancer, and Group 2 (n=72) included patients with cancer. We recorded age, gender, comorbidities, PCR test results, laboratory parameters, APACHE2 and SOFA scores, duration of ICU stay, mechanical ventilation requirement, and duration of mechanical ventilation for all patients.

Results
Hypertension was significantly more common in Group 1 compared to Group 2 [97 (48%) and 24 (33%), respectively); p<0.05]. Serum C-reactive protein levels were significantly higher in Group 2 compared to Group 1 [144 (0.5-480) and 112 (1.1-404) mg/L, respectively; p<0.01]. Serum albumin, serum platelet and hematocrit levels were significantly lower in Group 2 compared to Group 1 [respectively 2.7 ±0.4 and 2.9 ±1.3; p <0.01], [respectively; 173 (11-557) and 212 (14-624); p <0.01], [respectively; 31.4± 7.1 and 35.8±6.6; p <0.01]. Mortality ratio was significantly lower in Group 2 compared to Group 1 [51 (71%) and 114 (56%), respectively; p=0.03].

Conclusions
Our results suggest that mortality in cancer patients with COVID-19 who are admitted to the ICU is higher than in those without cancer. Further studies are needed to validate our results.

Keywords: Cancer, Comorbidity, Covid 19, Critical Care

Introduction

COVID-19 is a highly infectious disease that has been declared a pandemic since March 2020, affecting multiple organs and systems such as the respiratory, gastrointestinal, central nervous, and cardiovascular systems (1). Its rapid global spread has made it a significant public health concern, with economic and social implications. COVID-19 is associated with high mortality rates, particularly in patients who develop critical symptoms. While most people experience mild to moderate symptoms, severe complications such as Acute Respiratory Distress Syndrome (ARDS), myocarditis, widespread thromboembolism, and renal failure can occur (2-5). Consequently, COVID-19 represents much more than just a viral infection, and a clear cure for the disease, which has already claimed millions of lives, is yet to be identified.

Studies have consistently shown that COVID-19 patients with comorbidities, such as diabetes, chronic obstructive pulmonary disease (COPD), cardiovascular diseases (CVD), and hypertension, are at higher risk of mortality (6, 7). Cancer patients, who are already immunocompromised due to the disease and its treatments, are particularly vulnerable to COVID-19 infection and mortality (8). Furthermore, disruptions to cancer treatment services during the pandemic have delayed timely treatment and diagnosis, leading to worse clinical outcomes (9). Several studies have reported higher mortality rates in cancer patients infected with COVID-19 and hospitalized in the intensive care unit, which can be attributed to a range of factors, including comorbidities, age, mechanical ventilator requirement, type and stage of cancer, and presence of metastasis (10-12). This study aims to examine the impact of COVID-19 infection on cancer patients admitted to the intensive care unit, shedding light on the complex interplay between cancer and COVID-19 and identifying potential risk factors for mortality.

Material and Method

This retrospective study was conducted in the anesthesia intensive care unit of Suleyman Demirel University Faculty of Medicine. Ethics committee approval and necessary permissions for the study were obtained. The study included COVID-19 patients who were admitted to the intensive care unit between January 2020 and April 2022, with confirmed diagnoses by clinical and PCR testing. Of the 281 patients hospitalized with COVID-19, 6 were excluded due to PCR negativity, leaving 275

patients in the study. Among these patients, 72 had malignancies, with the type of cancer and metastasis recorded. The length of stay in the intensive care unit, mechanical ventilator requirement, and duration of mechanical ventilation were also recorded. Patients were categorized into two groups: Group 1 patients without cancer (n=203) and Group 2 patients with cancer (n=72). The hospital data processing system was used to extract information from the patient files, including variables such as age, gender, and comorbidities. Additionally, the PCR test results, biochemistry, hemogram, blood gas, and laboratory values such as CRP, Procalcitonin, Ferritin, D Dimer, and APACHE 2 and SOFA Scores at the time of admission to the intensive care unit were recorded. Patients without PCR positivity and those with masses but unclear pathology results were excluded from the study.

Statistical Analyses

Data were analyzed with the SPSS software version 23.0 for Windows (SPSS, Chicago, Il, USA). Continuous variables were expressed as means ± standard deviation or medians and 25th–75th percentile values (normally and not normally distributed, respectively). To compare continuous variables, the Student's t-test or Mann-Whitney U test was used, as appropriate. Categorical variables were compared using the Chi-square test. Using Cox's proportional hazards model, univariate and multivariate analyses for survival differences were performed. Survival was calculated from the diagnosis of the patient to either the date of death from any cause or the date of the last follow-up. Median cumulative survival probability was calculated using the product-limit method of Kaplan–Meier. Differences in survival between groups were determined using the log-rank test. A P-value less than 0.05 was considered statistically significant.

Results

The study included 281 patients who were admitted to the intensive care unit with a diagnosis of COVID-19. Among them, six patients were excluded due to the absence of confirmed PCR positivity. Group 1 comprised 203 patients without cancer, while Group 2 consisted of 72 patients with cancer. The mean age of patients in Group 1 was 70±13, while in group 2, it was 69±13. In Group 1, there were 129 men and 74 women, and in Group 2, there were 53 men and 19 women. No significant differences were observed between the two groups concerning age and gender. Table 1 shows the demographic characteristics of the groups. All patients presented with dyspnea as the initial symptom, and radiological examination showed lung involvement in all cases.

In Group 2, pathological diagnoses of 72 patients with cancer were recorded. The most common cancer types observed in this group were lung (n=23), hepatobiliary (n=11), hematological (n=11), prostate (n=9), breast (n=4), bladder (n=4), brain tumor (n=2), gynecological (n=2), thyroid (n=2), stomach (n=2), colon (n=1), and esophageal (n=1). Among them, 50 patients had distant metastases. Mortality was significantly higher in patient with metastases compared to without metastases [40 (80%) and 10 (50%), respectively; p=0.02].

Table 1 displays the comorbidities observed in the patients. Hypertension was significantly more prevalent in Group 1 compared to Group 2 [97 (48%) and 24 (33%), respectively; p<0.05]. Chronic renal failure was not significantly different between the two groups [62 (31%) for Group 1 and 18 (25%) in Group 2; p=0.1], There was no significant difference prevalence rates of other comorbidities [37 (18%) and 11 (15%) for diabetes, p=0.72, and 22 (10%) and 3 (0.4%) for cerebrovascular disease, p=0.1]. There was no significant difference in the requirement for mechanical ventilation between Group 1 and Group 2 [133 (66%) and 55 (76%), respectively; p=0.1]. The ICU length of stay was also not significantly different between the two groups [11.1 days (range 1-50) for Group 1 and 11.2 days (range 2-36) for Group 2; p=0.98]. The APACHE II and SOFA scores were not significantly different between Group 1 and Group 2 [18.4±6.5 and 17.5±7.5 for APACHE score, p=0.38, and 7.4±3.1 and 7.6±3.3 for SOFA score, p=0.68]. However, mortality was significantly higher in Group 1 compared to Group 2 [114 (56%) and 51 (71%), respectively; p=0.03]. See table 1 for further details.

The laboratory parameters were mostly similar between the two groups. However, some differences were observed. In Group 2, serum CRP levels were significantly higher compared to Group 1 [144 (0.5-480) and 112 (1.1-404) mg/L, respectively; p <0.01]. Additionally, serum albumin levels were significantly lower in Group 2 compared to Group 1 [2.7 ± 0.4 and 2.9 ± 1.3, respectively; p <0.01]. Serum platelet levels were also significantly lower in Group 2 compared to Group 1 [173 (11-557) and 212 (14-624), respectively); p <0.01]. Moreover, hematocrit levels were significantly lower in Group 2 compared to Group 1 [31.4±7.1 and 35.8±6.6, respectively; p <0.01]. Other laboratory parameters did not differ significantly between the groups. The laboratory results of the patients can be found in table 2.

Table 1 Comparison of demographic and clinical parameters.

	Group 1 Cancer - n= 203	Group 2 Cancer+ n= 72	P value
Mean age, year	70±13	69±13	0.55
Male / Female, n/n	129/74	53/19	0.15
Metastases (-/+)		22/50	
Hypertension, n(%)	97 (%48)	24 (%33)	0.04
Diabetes Mellitus, n(%)	77 (%38)	30 (%42)	0.67
Heart failure, n(%)	37 (%18)	11 (%15)	0.72
Chronic renal failure, n(%)	62 (%31)	18 (%25)	0.10
COPD, n(%)	38 (%19)	7 (%10)	0.08
Thyroid n(%)	3(%0.1)	3 (%0.4)	0.19
Rheumatological disease n(%)	3 (%0.1)	2 (%0.2)	0.61
CVD, n(%)	22 (%10)	3(%0.4)	0.10
Mechanical ventilation, n(%)	133 (%66)	55 (%76)	0.10
Mechanical ventilation time, day	5.2 (0-32)	5.6 (0-16)	0.62
Hospitalized time, day	11.1 (1-50)	11.2 (2-36)	0.98
SOFA score, n	7.4±3.1	7.6±3.3	0.68
APACHİ II score, n	18.4±6.5	17.5±.7.5	0.38
Mortality, n (%)	114 (%56)	51 (%71)	**0.03**

COPD; Chronic obstructive pulmonary disease, CVD; Cardiovascular diseases, SOFA; Sequential Organ Failure Assessment, APACHE; Acute Physiology and Chronic Health Evaluation

Survival and Prognostic Factors

In the last control, the number of patients who died in the group with malignancy was higher than in the group without malignancy [(51 (71%) vs 114 (56%), p: 0.03, table 1]. In Kaplan Meier analysis, survival tended to be lower in patients with malignancy [13.7 vs 17.0 days; HR, 1.32;0.95-1.85, p: 0.06]. Additionally, prognostic risk factors were evaluated by univariate analysis (Table 3). According to this analysis need for mechanical ventilation (MV, p: <0.001), MV duration (<P: 0.001), SOFA score (P:0.03), APACHI score (P:0.005), neutrophil-lymphocyte ratio (P: 0.03), the presence of DM (P:0.02), lactate level (P< 0.001) and serum albumin level (P:0.04) were significantly associated with survival. Subsequently, all significant prognostic factors were evaluated via multivariate analysis and used Cox's proportional hazards model. Need for MV (HR 8.60; 95% CI 3.79-19.51; P: <0.001), MV time (HR 0.84; 95% CI 0.80-0.88; P <0.001), APACHI score (HR 1.03; 95% CI 1.01-1.06;

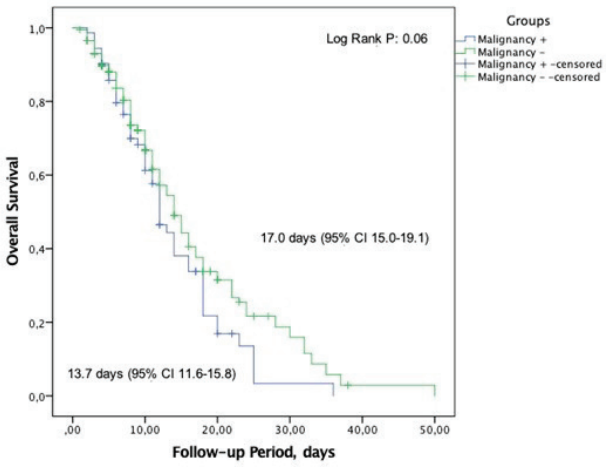

Figure 1
Survival analysis. Kaplan-Meier curves reflect the difference in survival rates in COVID-19 patients with and without malignancy.

Table 2 Laboratory characteristics between the patients the patients with cancer and without cancer.

	Cancer - n= 203	Cancer + n= 72	P value
Glucose, mg/dl	178±82	163±59	0.16
Creatinine, mg/dl	1.49 (0.3-7.8)	1.65 (0.2-9.6)	0.43
Sodium, mg/dl	140±7	136±18	**0.03**
Potassium, mg/dl	4.2±0.7	4.3±0.8	0.48
Hemoglobin, g/dl	12.3±8.0	10.4±2.4	**0.05**
Hematocrit (%)	35.8±6.6	31.4±7.1	**<0.01**
Platelet count x10^3/mm^3	212 (14-624)	173 (11-557)	**<0.01**
Ddimer, mg/mL	2097 (20-36524)	2215 (153-11890)	0.80
Ferritin, mg/L	799 (0.3-2991)	972 (49-2000)	**0.04**
White blood cell, x10^3/mL	12.8 (0.9-46)	15 (0.1-93.3)	0.11
Lymphocytes count, 10^3/mL	0.88 (0.1-9.7)	1.8 (0.1-73.1)	0.12
Neutrophil count, 10^3/mL	11.1 (0.3-41.8)	11.0 (0.1-41.4)	0.99
Neutrophil lymphocyte ratio	22.5 (0.2-157)	25.0 (0.1-172)	0.45
Procalcitonin, ng/ml	3.0 (0.0-100)	5.2 (0.1-100.2)	0.25
Albumin, g/dL	2.9±1.3	2.7±0.4	**<0.01**
C-Reactive Protein, mg/L	112 (1.1-404)	144 (0.5-480)	**<0.01**
Hs TnT, pg/dl	0.07 (0.001-2.40)	0.11 (0.001-1.20)	0.16
pH	7.36±0.30	7.36±0.13	0.90
Lactate	2.7±1.7	3.1±2.1	0.19

Hs TnT; high sensitive troponine T

Table 3 Results of Univariate and Multivariate Cox's Proportional Hazard Models Regarding OS.

Characteristics	Univariate Analysis		Multivariate Analysis	
	OS HR (95% CI)	P Value	OS HR (95% CI)	P Value
MV	3.27 (1.51-7.10)	<0.001	8.60 (3.79-19.51)	<0.001
MV duration	0.92 (0.89-0.95)	<0.001	0.84 (0.80-0.88)	<0.001
SOFA score	1.05 (1.00-1.09)	0.03		
APACHI II	1.03 (1.01-1.05)	0.005	1.03 (1.01-1.06)	0.007
Diabetes Mellitus	1.44 (1.05-1.98)	0.02	1.68 (1.21-2.33)	0.002
NLR	1.007 (1.001-1.013)	0.03		
Albumin	0.70 (0.47-1.03)	0.04	0.62 (0.42-0.94)	0.02
Lactate	1.19 (1.11-1.28)	<0.001	1.18 (1.10-1.26)	<0.001

APACHE: Acute Physiology and Chronic Health Evaluation, SOFA: Sequential Organ Failure Assessment Score,
MV: Mechanical Ventilation, NLR: Neutrophil/Lymphocyte

P:0.007), the presence of DM (HR 1.68; 95% Cl 1.21-2.33; P: 0.002), serum albumin level (HR 0.62; 95% Cl 0.42-0.94; P:0.02), and lactate level (HR 1.18; 95% Cl 1.10-1.26; P< 0.001) were independent prognostic factors, and predicted poor in-hospital survival cancer and without cancer patients. All multivariate survival analyses were presented in Table 3.

Discussion

This retrospective study aimed to evaluate the outcomes of COVID-19 infected cancer patients who were hospitalized in the intensive care unit. Our results revealed that mortality was significantly higher in COVID-19 patients with cancer who were admitted to the intensive care unit. Cancer patients are a particularly vulnerable group due to the impact of the tumor as well as the weakened immune system caused by anti-cancer treatments (8). These patients often require frequent hospital visits for treatment or due to additional complications, placing them at greater risk of exposure to viral factors such as COVID-19, which can be transmitted through the respiratory tract. Moreover, previous studies have demonstrated that patients with a history of cancer experience more severe symptoms than those without cancer (13).

In a meta-analysis conducted in China, which included 575 hospitals and 1590 COVID-19 patients, 18 patients were found to have cancer. Although the number of cancer patients was small, the incidence of cancer was higher than that of the general Chinese population, and these patients had higher rates of acute complications compared to COVID-19 patients without cancer. Age was found to be an important risk factor in this study, which is contrary to our findings. Similar to our study, it was reported that cancer patients had a higher risk of needing invasive mechanical ventilation or dying compared to patients without cancer (14). Zhang et al. reported that the most common symptoms in cancer patients with COVID-19 were fever, dry cough, and fatigue, with symptoms such as fatigue and shortness of breath ranking second in prevalence (15). Similarly to the study by Erdal et al., the most common finding in our patients was dyspnea (16). However, this difference may be due to the fact that dyspnea is more prominent in patients hospitalized in the intensive care unit.

A study found that COVID-19 patients typically have lymphopenia and high CRP levels, as well as low hemoglobin and albumin levels due to malnutrition, which can negatively impact the immune system and worsen outcomes for cancer patients (15). Our study also showed similar results, with the cancer group having significantly lower albumin and hemoglobin levels and higher CRP levels than the group without cancer, which we believe is a risk factor for increased mortality. However, contrary to our findings, it has been suggested that lymphopenia may be associated with the severity of infection in both COVID-19 and cancer patients, possibly due to its increased frequency in both groups. Thrombocytopenia may also be related to immune system dysfunction in cancer patients (17,18). In our study, platelet count was significantly lower in the cancer group compared to all COVID-19 patients, which may be related to the hematological effects of existing cancers. In another study by Erdal et al., anemia was found in 70.4% of patients, neutropenia in 15.5%, and lymphopenia in 52.1%, with mortality being significantly higher in patients with lymphopenia. The study also showed that high D-dimer, procalcitonin, CRP, and troponin levels correlated with mortality upon hospitalization (16). Although our study found high CRP levels, we did not find a significant difference in procalcitonin levels. Procalcitonin is a more sensitive marker than CRP in bacterial infections, but the increase in acute phase reactant CRP resulting from cancer-related inflammation seems to be an expected outcome. In terms of D-dimer and troponin levels, there was no difference between the groups in our study.

It is well-established that COVID-19 patients with cancer are at a high risk of mortality and morbidity, and patients with hematologic, lung, or metastatic cancer (stage IV) are particularly susceptible to serious events. This is not surprising, as respiratory infections such as COVID-19 pose a significant risk to patients with lung cancer who already have insufficient lung capacity. Yang et al. reported that mortality was higher in COVID-19 patients with cancer, particularly in those with hematologic malignancies (19,20).

Unfortunately, delays in cancer screening during the pandemic have led to delayed diagnoses, increased rates of patients diagnosed in the emergency department, more advanced-stage cancer with higher tumor burden, and delayed effective treatment for newly diagnosed malignancies (21,22). The type of cancer, cancer treatments, and cancer stage are also important risk factors for COVID-19 in cancer patients (19). Additionally, cancer patients are more vulnerable during the pandemic because not only does the disease itself cause immunodeficiency, but life-saving treatments such as stem cell or blood donation also have an impact on their health (23).

Cancer patients represent a diverse population, and

various risk factors are linked to poor outcomes. The COVID-19 and Cancer Consortium (CCC19) is an international group that collects data on cancer and COVID-19 patients. Findings from their studies suggest that older age, male gender, smoking, comorbidities, hematological malignancies, and active cancer increase the risk of severe COVID-19 outcomes. Our study had similar results, although there was no difference in age or gender (24). In cancer patients, obesity, active smoking, diabetes, and a high Rapid Ranked Organ Failure Assessment (qSOFA) score have been associated with intensive care unit (ICU) admission. However, in our study, more detailed SOFA and APACHE 2 scores did not differ between the groups. In contrast to our findings, other studies have reported no significant differences in terms of ICU admission, complication rates, or mortality between patients with and without cancer (25). These results are consistent with Mehta et al.'s work. However, the risk of intubation was significantly higher in cancer patients aged 66-80 years, and the 30-day all-cause mortality rate was higher in this group (26-28). Although there is limited literature and conflicting results, the overall data suggests higher mortality in COVID-19 patients with cancer. Many questions remain about the coexistence of COVID-19 and cancer that need to be clarified.

In conclusion, cancer patients are highly susceptible to infectious diseases like COVID-19, both as a result of the disease itself and due to treatment-related immunosuppression. Given their vulnerability, it is essential to prepare for unforeseen events such as pandemics and take necessary precautions to protect cancer patients.

Conflict of Interest Statement
The authors have no conflicts of interest to declare.

Ethical Approval
Our study was approved by the Clinical Research Ethics Committee of Süleyman Demirel University (19.04.2022 – 9/131).

Consent to Participate and Publish
Informed consent was not obtained from the patients because it was a retrospective study.

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Availability of Data and Materials
Data available on request from the authors.

Authors Contributions
PK: Data curation; Validation;
Resources; Visualization; Writing-original draft.

AB: Data curation; Formal analysis; Investigation; Validation; Writing-review & editing.

ESÖ: Data curation; Formal analysis;
Investigation; Validation.

MSÖ: Data curation; Formal analysis;
Investigation; Validation.

HÖO: Conceptualization;
Formal analysis; Visualization.

PK: Data curation; Formal analysis;
Supervision; Writing-review & editing.

Editorial
Although Kırdemir P., one of the authors of the article, is editorial board member of the journal, she has not taken part in any stage of the publication processes of this article.

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