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ORIGINAL RESEARCH

Long-Term Survival of Cancer Patients Following COVID-19 Infection: Prognostic Value of Inflammatory Indices and Vaccination Status

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ABSTRACT

The survival outcomes of cancer patients exposed to Coronavirus Disease 2019 (COVID-19), the duration required to resume oncological treatment, and the subsequent course of their malignancy remain areas with limited data. This retrospective study evaluated 128 cancer patients hospitalized for COVID-19 treatment between April 2020 and October 2023. Of the cohort, 39.8% were women and 60.2% were men. Findings revealed that patients with metastatic lung involvement faced a 3.34-fold increased risk of death during the acute infection. In the post-COVID survival cohort, multivariate analysis indicated that younger age, higher hemoglobin levels, higher systemic inflammatory index, lower pan-immune inflammation value, and absence of active cancer were associated with longer survival. Additionally, vaccine-related survival differences were observed; however, these findings should be interpreted cautiously as they likely reflect confounding factors such as prioritizing high-risk patients for certain vaccine types rather than a direct causal relationship. Notably, while treatment delays were common among patients with disease progression, these delays did not result in a statistically significant difference in overall survival during the long-term follow-up.

Keywords: COVID-19. Neoplasms. Messenger Ribonucleic Acid (mRNA). Inflammation. Time-to-treatment. Post-Acute COVID-19 Syndrome (Long COVID).

COVID-19 Enfeksiyonu Sonrası Kanser Hastalarında Uzun Süreli Sağkalım: İnflamatuar İndekslerin Ve Aşılama Durumunun Prognostik Değeri

ÖZET

Coronavirus Disease 2019 (COVID-19) enfeksiyonuna maruz kalan kanser hastalarının sağkalım sonuçları, enfeksiyon sonrası tedaviye yeniden başlama süresi ve malignitelerinin seyri hakkındaki veriler kısıtlıdır. Bu retrospektif çalışmada, Nisan 2020 ile Ekim 2023 tarihleri arasında merkezimizde COVID-19 nedeniyle yatarak tedavi gören 128 kanser hastası değerlendirilmiştir. Hastaların %39,8'i kadın, %60,2'si erkekti. Akut enfeksiyon sürecinde metastatik akciğer tutulumu olan hastaların, olmayanlara göre 3,34 kat daha yüksek ölüm riski taşıdığı saptanmıştır. Post-COVID sağkalım kohortunda yapılan çok değişkenli analizde; daha genç yaş, daha yüksek hemoglobin düzeyi, daha yüksek sistemik inflamatuvar indeks, daha düşük pan-immün inflamasyon değeri ve aktif kanser bulunmaması daha uzun sağkalım ile ilişkili bulunmuştur. Ayrıca aşı tipine bağlı sağkalım farklılıkları gözlenmiştir; ancak bu bulguların belirli aşı tiplerinin yüksek riskli hastalara öncelikli olarak uygulanması gibi karıştırıcı faktörleri yansıtma olasılığı nedeniyle doğrudan nedensel bir ilişkiyi göstermediği ve bu nedenle temkinli yorumlanması gerektiği düşünülmektedir. Çalışmanın ayırt edici özelliği olan uzun süreli takip sonucunda, progresyon gösteren hastalarda tedavi gecikmeleri yaygın görülse de bu gecikmelerin genel sağkalım üzerinde istatistiksel olarak anlamlı bir fark yaratmadığı belirlenmiştir.

Anahtar Kelimeler: COVID-19. Neoplaziler. Mesajcı Ribonükleik Asit (mRNA) Aşıları. İnflamasyon. Tedaviye kadar geçen süre. Post-Akut COVID-19 Sendromu (Uzamış COVID).

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Coronavirus Disease 2019 (COVID-19), caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), has affected >770 million people and has led to >6 million deaths globally according to recent estimates[1]. In a study conducted in 2021, 57 patients with cancer who were infected with COVID-19 were compared with 203 patients without cancer. However, no significant difference in mortality was found. Moreover, it was noted that patients with cancer had higher rates of comorbidities, more frequent need for intubation, and experienced longer hospital stays[2]. Other studies have also reported that patients with active cancer experience a more fatal course of COVID-19[3]. The aim of the present study was to evaluate the clinical course of patients with cancer who underwent COVID-19 treatment in the pandemic clinic of our hospital, the time to resumption of cancer therapy after discharge, any delays in cancer treatment, and the survival outcomes of these patients.

Materials and Methods

The electronic records of patients with cancer who were hospitalized for COVID-19 treatment in the pandemic clinic between April 2020 and June 2022 were retrospectively reviewed. The study protocol was approved by the Local Ethics Committee. For these patients, we evaluated the course of the infection, cancer diagnosis, metastatic status, survival outcomes, and the subsequent course of the cancer after discharge. Patients received standard COVID-19 treatments (including antivirals, corticosteroids, and anticoagulants) in accordance with the updated national guidelines of the Turkish Ministry of Health applicable at the time of admission. Laboratory tests performed during hospitalization were evaluated as well as systemic inflammatory index (SII: neutrophils × platelets/lymphocytes), neutrophil-to-lymphocyte ratio, and pan-immune inflammation value (PIV: neutrophils × platelets × monocytes/lymphocytes) were calculated. Patients were followed-up until October 2023. Imaging assessments were performed using thoracic computed tomography to evaluate COVID-19 related pulmonary infection during the acute phase, and cancer status was subsequently monitored in COVID-19 survivors using tumor-specific standard imaging modalities, including computed tomography or positron emission tomography, according to routine clinical practice. Treatment delay was defined as any postponement or interruption of a patient's scheduled oncological treatment (chemotherapy, radiotherapy, or surgery) specifically resulting from a documented active COVID-19 infection. Following the clinical protocol, any deviation from the planned treatment date—regardless of the number of days—was recorded as a delay to capture the full impact of the infection on the treatment timeline. Overall survival (OS) was defined as the time from COVID-19 diagnosis to death from any cause or the date of last follow-up. To provide a more granular analysis, mortality was categorized into two distinct phases: acute COVID-19-related mortality (occurring during hospitalization for the infection) and long-term mortality among survivors, which primarily reflected cancer-specific outcomes or other complications during the follow-up period. Additionally, patients were classified as having active cancer (i.e., those in the neoadjuvant or metastatic phase) or as not having active cancer (i.e., those receiving adjuvant therapy or on follow-up). The post COVID-19 analyses were restricted to patients who survived the acute infection phase, as the primary objective of this study was to evaluate the long-term oncologic and clinical outcomes among COVID-19 survivors with cancer.

Statistical Analysis

The normality of data was assessed using the Shapiro–Wilk test. As variables were non-normally distributed, two independent groups were compared using the Mann–Whitney U test and results were presented as median (min–max). Categorical variables were analyzed using the Chi-square test and expressed as frequency and percentage. Survival analyses were performed using the Kaplan–Meier method with log-rank test comparisons. Variables significant in univariate survival analysis were entered into multivariate Cox regression, and Hazard Ratios were calculated. A significance level of $\alpha = 0.05$ was adopted; for multiple group comparisons, Bonferroni correction was applied ($\alpha = 0.017$ for three groups). All analyses were conducted using SPSS v25.

Results

A total of 128 patients with cancer who were under follow-up and treatment in the oncology outpatient clinics during the COVID-19 pandemic and were hospitalized for COVID-19 infection were evaluated. Of the patients, 51 (39.8%) were women and 77 (60.2%) were men. The median age at COVID-19 diagnosis was 64.05 years. Regarding cancer types, lung cancer was the most common diagnosis (25.8%), followed by gastrointestinal cancers (16.4%). The distribution of diagnoses is presented in Table I.

Table I. Distribution of patients according to cancer type

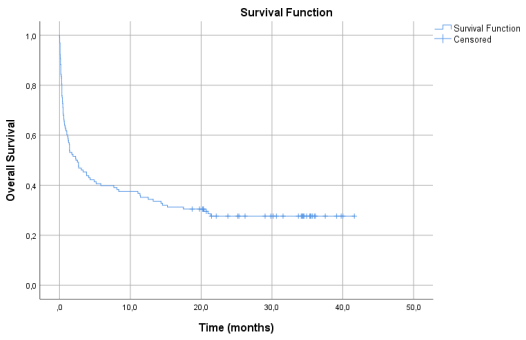
Diagnosis	Patients (n)	Percent (%)
Lung	33	25.8
GIS	21	16.4
GUS	20	15.6
Breast	19	14.8
Hepatobiliary & Pancreas	10	7.8
Sarcoma	6	4.7
Gynecological	6	4.7
Head-neck	5	3.9
CNS	2	1.6
Other	6	4.7
Total	128	100.0

CNS: Central Nervous System, GIS: Gastrointestinal System, GUS: Genitourinary System,

Among patients with metastatic disease, treatment delays were more frequent compared to those without metastasis. Specifically, among all 128 patients, 52 (40%) died due to COVID-19 infection. The COVID-19 related mortality rate was significantly higher in metastatic patients (48.7%, n=37) compared to non-metastatic patients (28.8%, n=15) (P=0.040).

The OS of the patients (n=128) was 13.91±1.57 months (Figure 1). A statistically significant difference in survival duration was observed between patients with and without metastasis. Patients with metastatic disease had a shorter survival period than those without metastasis (p<0.001), (Figure 2, Supplementary Table).

Mean survival time was 0.44 ± 0.06 months for patients who died due to COVID-19 infection and 23.12±2.07 months for those who survived COVID-19 infection (p<0.001). Considering the markedly short survival of patients who died during hospitalization from COVID-19 infection, the survival analysis categorized patients into two groups: those who died due to COVID-19 infection (Group 1: COVID-19 mortality group) and those who survived the COVID-19 infection (Group 2: COVID-19 survivor group).



Vertical tick marks indicate censored observations, representing patients who were alive at the last follow-up or lost to follow-up during the study period.

Figure 1.
Kaplan–Meier overall survival curve of the study population.

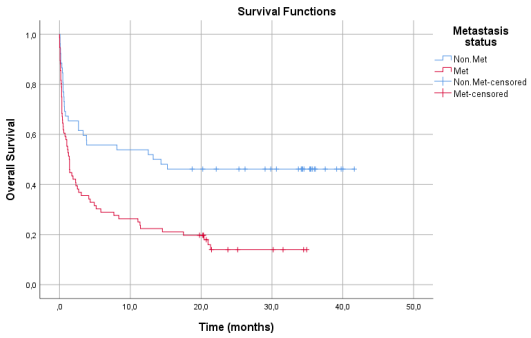


Figure 2.
Survival times according to metastasis status

When comparing the groups, the COVID-19 mortality group comprised 37/52 (71.2%) men and 15/52 (28.8%) women, whereas the COVID-19 survivor group included 40/76 (52.6%) were men and 36 (47.4%) women. There was a statistically significant difference in sex-based distribution between the two groups (p=0.036). A higher proportion of men were observed in the COVID-19 mortality group.

The age range in the COVID-19 mortality group was 33–84 years with a median of 65.3 years against 19–89 years with a median of 62.85 years in the COVID-19 survivor group. No statistically significant age difference was observed between the groups (p=0.150).

In both groups, no statistically significant differences in survival were found based on subcategories of variables like gender, age (using a 70-year threshold), fever, dyspnea, chronic conditions (e.g., hypertension, chronic obstructive pulmonary disease [COPD]), use of granulocyte colony-stimulating factor (G-CSF),

Table II. Multivariable Cox Regression Analysis of Survival Predictors in COVID-19 Mortality and Survivor Groups

	COVID-19 mortality group				COVID-19 survivor group			
	p-value	Hazard Ratio (HR)	95.0% CI for HR		p-value	Hazard Ratio (HR)	95.0% CI for HR	
			Lower	Upper			Lower	Upper
Age	0.946	1.00	0.96	1.04	**.025**	1.06	1.01	1.11
Smoking:	0.583				.664			
Never*	0.466	0.62	0.17	2.24	.707	.83	.32	2.17
Quit Smoking	0.500	2.01	0.26	15.37	.426	3.82	.14	103.74
Metastasis status: (Non-met vs Met)	0.575	0.74	0.26	2.11	.581	.63	.12	3.31
CKD: No vs Yes	0.799	0.82	0.17	3.88	.054	4.56	.97	21.31
Diabetes: No vs Yes	0.641	1.29	0.44	3.76	.122	.46	.17	1.23
Vaccine status:	0.709				**.000**			
Inactive*	0.494	1.46	0.50	4.30	**.000**	33.57	5.74	196.24
mRNA or both					**.001**	20.82	3.57	121.37
No vaccine	0.937	0.94	0.21	4.17				
Lung involvement:	0.063				.989			
No metastasis*	**0.041**	3.34	1.05	10.66	.958	1.03	.30	3.60
Metastasis Primary lung	0.918	1.09	0.23	5.12	.881	1.10	.33	3.65
Hemoglobin	0.216	0.85	0.66	1.10	**.023**	.75	.58	.96
SII	0.708	1.00	1.00	1.00	**.013**	1.00	1.00	1.00
NLR	0.431	1.05	0.93	1.19	.063	1.14	.99	1.30
PIV	0.817	1.00	1.00	1.00	**.002**	1.00	1.00	1.00
CRP	0.518	1.00	1.00	1.01	.503	1.00	1.00	1.00
Active cancer: Yes vs No	-	-	-	-	**.008**	18.29	2.15	155.27

CKD: Chronic kidney disease, CRP: C-reactive protein, NLR: Neutrophil/Lymphocyte Ratio, PIV: Pan-immune inflammation value, SII: Systemic inflammation index,

Hazard ratios were estimated using Cox proportional hazards regression models. p-values for categorical variables represent overall Wald test results. Reference categories are marked with an asterisk (*). Continuous variables were entered into the model per unit increase.

active chemotherapy, history of lung surgery, vaccination status (vaccinated or not), COVID-19 computed tomography findings, cancer-related lymphatic spread, history of mediastinal radiotherapy, treatment regimen, or whether the treatment was primary (Supplementary Table II-III).

Table III. Comparison of treatment delay according to initial assessment after COVID-19

	Recurrence/Progression		p-value
	No (n=50)	Yes (n=26)	
Number of patients with delay in treatment (%)	21 (42.00)	25 (96.15)	**<0.001**

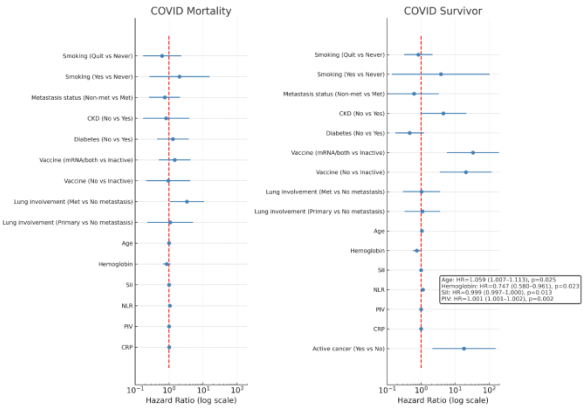
After the effects of the variables on survival duration (Supplementary Table II-III) were examined using univariate analysis in the COVID-19 mortality and survivor groups, the variables with a significant effect on survival were subsequently analyzed using Cox regression analysis to determine their impact on survival and to calculate the risk factors for death (Table II).

In the COVID-19 mortality group, using patients without metastatic lung involvement as the reference, those with metastasis had a 3.34-fold increased risk of death compared with those without metastasis. No statistically significant difference was found between patients without metastatic and those with primary lung cancer (Table II).

In the COVID-19 survivor group, vaccination status was significantly associated with OS. Compared to patients who received inactive vaccines, those who received messenger Ribonucleic Acid (mRNA) vaccines (or both) and those who remained unvaccinated showed a higher risk of mortality. Detailed Hazard Ratios and confidence intervals for these associations are presented in Table II.

Furthermore, in the COVID-19 survivor group, each 1-unit increase in hemoglobin was associated with a 0.74 decrease in the risk of death, each 1-unit increase in age corresponded to a 1.059-fold increase in the risk of death, each 1-unit increase in SII resulted in a 0.99 decrease in the risk of death, and each 1-unit increase in PIV led to a 1.001-fold increase in the risk of death. Additionally, having active cancer was associated with an 18.28-fold increased risk of death

(Table II). A summary of the multiple regression analysis evaluating predictors of COVID-19 mortality and survivor groups is presented in Figure 3.



* SII: Systemic inflammation index, NLR: Neutrophil/Lymphocyte Ratio, PIV: Pan-immune inflammation value, CRP: C-reactive protein, CKD: Chronic kidney disease

Figure 3.
Predictors of COVID-19 mortality and survivor groups

Treatment delays were significantly more frequent in patients who experienced disease recurrence or progression (96.15%) compared to those without progression (42%) ($p < 0.001$). (Table III). Although survival was shorter among patients with treatment delays, the difference was not statistically significant (Table IV, Figure 4).

Table IV. Delay in Treatment and Survival Status

Delay in treatment	Number of patients	Survival status Mean±SE	p-value
No	30	27.00±2.99	0.074
Yes	46	19.93±2.62	

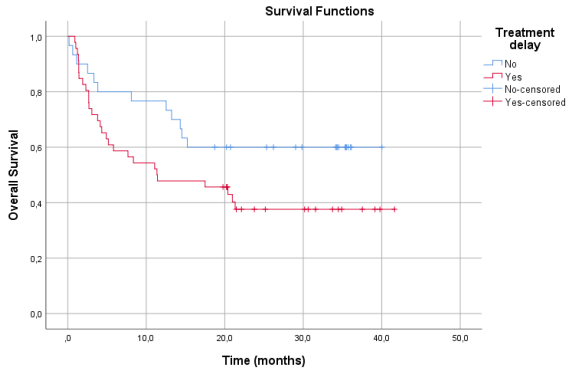


Figure 4.
Survival times according to treatment delay

Discussion and Conclusion

The primary aim of the present study was to evaluate the factors influencing the long-term prognosis of cancer patients who survived COVID-19 infection. To achieve this, we initially divided the patients into two groups: those who died due to COVID-19 infection and those who did not. When comparing these groups, no statistically significant difference was observed in terms of age. However, a higher proportion of men were observed among patients who died due to COVID-19 infection. This finding is consistent with a previous large-scale study demonstrating that male sex is associated with higher COVID-19 severity and mortality in cancer patients[3]. In contrast, a previous study by Ozer et al., which used similar groupings, did not find a significant sex-based difference. In the study by Ozer et al., the median ages of patients who died and those who survived COVID-19 infection were 77 and 67 years, respectively[4]. Similarly, multiple large-scale studies have consistently identified advanced age as a significant predictor of severe outcomes and mortality in patients with cancer and COVID-19[3,5].

In a comparative study involving 57 patients with cancer and 203 patients without cancer but with COVID-19 infection, the average age of the cancer patients was reported as 63.6±12.5 years, which was statistically higher than that of patients without cancer[2]. In the present study, the median age of the cohort was 64 years, and no comparison with patients without cancer was performed.

In the present study, 33 patients (25.8%) were followed-up for lung cancer, 21 patients (16.4%) for gastrointestinal cancers, 20 patients (16.4%) for genitourinary cancers, and 19 patients (14.8%) for breast cancer. In several large-scale studies evaluating cancer patients with COVID-19 infection, breast and prostate cancers were predominant[2,4,6,7]. However, similar to the present study, several studies reported that lung cancer patients constituted the majority of the cohort[8,9]. Because the present study exclusively included patients who received inpatient COVID-19 treatment, these proportions may differ from those seen in the general population, potentially reflecting a higher need for hospitalization among lung cancer patients.

In our cohort, 21% required mechanical ventilation, 18% ICU admission, and 40% died from COVID-19. Ozer et al. reported 27% ICU admission and 37% mortality[4], consistent with other studies showing high severity and mortality in cancer patients[2,3]. Another study reported 32% mortality[9]. Compared with pre-pandemic viral pneumonia cohorts, where 30-day mortality was 7.1% (up to 24.4% in cancer patients), COVID-19–related mortality in our cohort was markedly higher.[10]

In the present study, when assessing OS among patients who died due to COVID-19 infection, the presence of diabetes, metastasis to the lungs and active smoking were associated with poorer survival outcomes. In the multiple regression analysis, only patients with lung metastases demonstrated significantly shorter survival. In a study by Aboueshia et al. that compared mortality between patients with and without cancer, obesity, active smoking, diabetes, and age >65 years were shown to be associated with increased mortality[2]. Furthermore, another study revealed that only advanced age and the need for mechanical ventilation were independently associated with an increased risk of death, based on multivariate analyses[4]. In our COVID-19 mortality group, lung metastasis was identified as the sole independent predictor of death. This contrasts with previous literature where advanced age and performance status were the primary drivers of acute severity. Our findings suggest that for cancer patients who do not survive the acute infection, metastatic lung involvement carries a more critical prognostic weight than traditional risk factors like age[11].

Patients who survived COVID-19 infection were followed for a median of 12.8 months (range: 0.1–39 months). Among these patients, longer OS was observed in those with hemoglobin levels >12, who had not received an mRNA vaccine, without chronic kidney disease, without metastases, with cough during the COVID-19 infection, and patients without active cancer. In multivariate regression analyses, longer survival was significantly associated with younger age, absence of mRNA vaccination, lack of active disease, higher hemoglobin levels, higher SII, and lower PIV. To date, data regarding long-term outcomes of cancer patients after recovery from COVID-19 remain limited. Emerging evidence suggests that long COVID syndrome, characterized by persistent inflammation, endothelial dysfunction, fatigue, and organ impairment, may adversely affect long-term survival, particularly in vulnerable populations such as patients with cancer. These chronic sequelae may compromise physiological reserve, exacerbate comorbidities, and interfere with ongoing oncologic treatments, thereby contributing to the survival differences observed in long-term follow-up[12,13].

As expected, patients with metastatic disease exhibited shorter OS in the current study. However, in the multiple regression analysis, while the presence of active cancer emerged as a significant risk factor, presence of metastases did not reach statistical significance. This finding may be explained by the fact that most patients with active cancer were in the metastatic stage.

Additionally, low hemoglobin levels were identified as a poor prognostic factor. In a review by Knight et al., it was reported that approximately 30%–90% of patients with cancer experience anemia, which adversely affects prognosis. Anemia-induced tumor hypoxia diminishes the efficacy of radiotherapy and chemotherapy and promotes angiogenesis, rendering the tumor more aggressive[14]. Similarly, the present study also found that anemia adversely affected OS.

The impact of inflammation on cancer prognosis has been debated for years. In a meta-analysis on this topic, PIV was proposed as a potentially important biomarker for predicting cancer prognosis, with findings suggesting that patients exhibiting high PIV tend to have poorer outcomes[15]. It has been reported that platelets can support tumor growth and metastasis through various mechanisms. For instance, platelets are known to facilitate immune evasion by circulating tumor cells through thrombus formation and promote tumor invasion and progression by releasing growth factors[16]. In our study, we observed a divergence in the prognostic values of SII and PIV among COVID-19 survivors. While a higher SII was associated with longer survival, a higher PIV—which incorporates the monocyte count—emerged as a significant risk factor for mortality. This discrepancy likely underscores the distinct biological role of monocytes in both post-acute COVID-19 syndrome and malignancy. Monocytes are key drivers of the 'cytokine storm' during acute infection and can persist as pro-inflammatory non-classical monocytes in long COVID, contributing to chronic endothelial dysfunction and tissue damage. Within the tumor microenvironment, these cells often differentiate into tumor-associated macrophages (TAMs), which facilitate immune evasion, promote angiogenesis, and support metastatic spread[17,18]. Therefore, the inclusion of monocytes in the PIV formula may provide a more comprehensive reflection of the persistent, systemic inflammation that compromises the long-term physiological reserve of cancer patients following COVID-19.

In the TREASURE study, wherein 368 patients who received COVID-19 vaccination were evaluated and 207 of whom were known to have received an mRNA vaccine, a transient inflammatory state that did not involve platelet activation was detected. It was proposed that minor changes in coagulation activation and endothelial function may explain the rare thromboembolic events observed following vaccination[19]. In another study investigating mRNA vaccine effects on endothelial dysfunction, a marked increase in inflammatory markers was observed after the second dose along with a transient deterioration in endothelial function during the first 24 hours, which returned to baseline within 48 hours[20]. Current evidence regarding the link between mRNA vaccines and inflammation remains inconclusive. In our study, patients vaccinated with mRNA technology showed

shorter OS compared to those who received inactivated vaccines or remained unvaccinated. The correlation between mRNA vaccination and lower survival requires a cautious approach. This finding is likely driven by confounding factors rather than causality. High-risk patients may have been prioritized for mRNA vaccines, and outcomes were further influenced by temporal shifts in pandemic protocols. Additionally, limiting the analysis to survivors with diverse cancer types may have introduced 'collider bias', making these results exploratory rather than definitive.

At the initial post-COVID-19 evaluation, treatment delays were identified in 96.15% of patients who demonstrated disease progression. Although patients with treatment delays exhibited shorter survival durations during the long-term follow-up, this difference did not reach statistical significance (p=0.074).

A major strength of the present study is its role as one of the few reports evaluating long-term outcomes in cancer patients after COVID-19 infection. However, several limitations must be acknowledged. The study's single-center, retrospective design and the marked heterogeneity in cancer diagnoses and stages may influence the generalizability of our findings to specific oncological populations. Due to this diversity, tumor burden was categorized broadly as metastatic versus non-metastatic, and COVID-19 severity was assessed through clinical symptoms, inflammatory markers, and intensive care requirements. Furthermore, the inclusion of various malignancies with distinct natural histories limits our ability to draw disease-specific conclusions, and these results should therefore be considered exploratory. A further limitation is the definition of treatment delay as any deviation from the planned treatment date, regardless of duration. Consequently, minor postponements with limited clinical relevance may have been included in this category.

This study provides a comprehensive long-term evaluation of cancer patients who survived COVID-19 and continued their oncological care. Our findings indicate that extended overall survival in this cohort is independently associated with younger age, higher hemoglobin levels, and absence of active malignancy. Regarding inflammatory markers, a higher SII correlated with better outcomes, whereas a higher PIV served as a predictor of poorer prognosis. Furthermore, although treatment delays were frequently observed—particularly in patients with disease progression—these interruptions did not lead to a statistically significant difference in long-term survival. Notably, the observed survival differences related to vaccination status should be interpreted with significant caution. These findings are exploratory and hypothesis-generating rather than indicative of a causal link, as they likely reflect complex confounding factors, such as the prioritization of high-risk patients for specific vaccine types and the inherent heterogeneity of cancer diagnoses. Future prospective trials with larger, disease-specific cohorts are necessary to further clarify these relationships.

Researcher Contribution Statement:
Idea and design: S.S., B.O., M.S., B.C., A.C., E.Ç., A.D., T.E. and E.Ç.; Data collection and processing: S.S., M.A.Ö., Ş.Ö., M.S., A.C., E.Ç., and S.O.O; Analysis and interpretation of data: S.S., A.B.Ş., B.C., S.O.O. and E.Ç.; Writing of significant parts of the article: S.S. and E.Ç.

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Conflict of Interest Statement:
The authors declare that they have no competing interests.

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