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Research Article

Impact of COVID-19 Vaccination and Prior Infection on Survival Outcomes in Patients with Metastatic Solid Tumors

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Abstract

Objectives: To assess the effect of prior SARS-CoV-2 infection and COVID-19 vaccination on overall survival (OS) in patients with metastatic solid tumors and to examine potential variation in this association across major cancer subtypes.

Methods: This retrospective observational study included 62 patients with histologically confirmed metastatic solid tumors. Patients were categorized into four groups according to vaccination and infection status: vaccinated and previously infected, vaccinated only, infected only, and unvaccinated/uninfected controls.

Results: OS was longer in vaccinated or previously infected patients than in double-negative controls (51.4 months vs. 33.8 months) (p=0.324). Among patients in remission, survival was markedly longer in those with prior vaccination or COVID-19 infection than in individuals negative for both factors (90 vs. 36 months), although this difference did not reach statistical significance (p=0.302). The most pronounced benefit occurred within the breast cancer subgroup, where prior infection or vaccination was strongly associated with extended remission survival (106 months).

Conclusion: Prior COVID-19 infection and vaccination were associated with improved long-term survival in patients with metastatic solid tumors. These observations raise the possibility that immune activation triggered by viral exposure or vaccination may enhance tumor immunosurveillance and strengthen host resilience.

Keywords: COVID-19, Metastatic Cancer, Vaccination

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COVID-19 infection was first identified in December 2019 in Wuhan, China, as a novel infectious disease capable of causing severe acute respiratory syndrome. Within months, it evolved into a global pandemic with profound public health consequences. As of 26 October 2025, a total of 778,885,759 confirmed cases, 7,103,253 reported deaths, and more than 13.6 billion vaccine doses had been recorded worldwide.[1]

Early publications from the initial phase of the pandemic suggested that COVID-19 infection was more common and associated with higher mortality among patients with cancer, an observation widely attributed to cancer-related or treatment-induced immunosuppression.[2,3] However, as clinical experience expanded, it became evident that severe COVID-19 outcomes were largely driven by dysregulated hyperinflammatory responses rather than immunodefi-

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ciency alone.[4] This shift in understanding prompted subsequent studies reporting that the frequency and severity of COVID-19 infection in cancer patients were comparable to, rather than higher than, those in the general population.[5-7]

If clinical deterioration and mortality in COVID-19 result primarily from excessive immune activation, two key questions emerge:

1. Are COVID-19 infection rates and disease severity truly higher in patients with cancer compared with non-cancer controls?
2. Could the immunostimulatory effects of SARS-CoV-2 infection and vaccination influence long-term outcomes, particularly overall survival, in patients with metastatic cancer?

In the early post-pandemic period, we designed a two-stage retrospective observational study to address these questions. In the first stage, we determined that COVID-19 infection frequency and severity did not differ significantly between cancer patients and the control population.[8] Building on these findings, we proceeded to the second stage.

In this study, we evaluated overall survival (OS) and survivorship patterns among patients with histologically confirmed metastatic solid tumors, stratified by COVID-19 vaccination status (v+/v–) and prior infection history (COVID+/COVID–). We hypothesized that individuals who had received COVID-19 vaccination and/or had experienced SARS-CoV-2 infection may exhibit distinct—and potentially more favorable—survival outcomes compared with patients who had neither exposure.

Methods

Study Design and Population

This retrospective observational study included patients with histologically confirmed metastatic solid tumors who were managed in the Oncology Department of our institution between September 2021 and January 2022 and subsequently followed until August 2025. Eligible participants were required to have complete clinical documentation regarding COVID-19 vaccination status, history of SARS-CoV-2 infection, and overall survival (OS) outcomes. Patients with incomplete vaccination or infection records, as well as those lost to follow-up, were excluded from the analysis.

Grouping According to COVID-19 Vaccination and Infection Status

Patients were categorized into four subgroups based on vaccination and infection history:

1. v(+) COVID(+) – vaccinated and previously infected,
2. v(+) COVID(–) – vaccinated but never infected,
3. v(–) COVID(+) – unvaccinated but infected, and
4. v(–) COVID(–) – unvaccinated and uninfected controls.

A secondary binary grouping was also performed by combining all patients who were either vaccinated or previously infected (v(+) or COVID(+)) and comparing them with double-negative controls (v(–)/COVID(–)).

Clinical Data and Variables

Demographic variables (age, sex) and primary cancer type were recorded for all participants. Clinical follow-up data included overall survival (OS), defined as the time from diagnosis of metastatic disease to death or last follow-up, and disease status at last contact (alive with metastasis, alive in remission, or deceased). Survival times were expressed in months. COVID-19 infection was verified by positive RT-PCR testing or documented clinical diagnosis, whereas vaccination status was confirmed through national vaccination records or hospital charts. Subgroup analyses were conducted for major cancer types (breast, colorectal, and prostate cancer).

The study protocol was reviewed and approved by the Selcuk University Ethics Committee (Approval No: 2023/386; date: 04.10.2023). All procedures were conducted in accordance with the Declaration of Helsinki (2013 revision). Because of the retrospective design, informed consent was waived by the ethics committee.

Statistical Analysis

All statistical analyses were conducted using Wistats v3 (WisdomEra Corp., Istanbul, Türkiye), an AI-supported analytical platform based on Python statistical and machine-learning libraries (SciPy v1.2.3, scikit-learn v0.24, and statsmodels v0.9) (https://wistats.wisdomera.io/). Data distribution was assessed through skewness and kurtosis coefficients and validated using the Shapiro–Wilk test. The selection of parametric or non-parametric tests for comparative analyses was determined according to the results of the normality assessments. Comparisons of categorical variables were performed using the Chi-square or Fisher's exact test, whereas continuous and ordinal variables were analyzed with Kruskal–Wallis, one-way ANOVA, Student's t-test, or Mann–Whitney U tests, as appropriate. Pearson's or Spearman's correlation coefficients were employed to evaluate associations between continuous variables. A p-value <0.05 was considered statistically significant in all analyses.

Results

A total of 62 patients with metastatic cancer were included in the study. The mean age of the cohort was 59.3±10.8 years, and 61% were female. Patients were stratified according to COVID-19 vaccination status (v+/v–) and history of SARS-

Table 1. Characteristics and comparisons between covid-vaccine groups in study population

	Vaccine (+) Covid19(+)	Vaccine (+) Covid19(-)	Vaccine (-) Covid19(+)	Vaccine (-) Covid19(-)	p
Age (Mean±SD)	59.90±3.9	58.61±2.8	63.67±4.5	52.88±3.8	0.266
Gender, n (%)					
Female	11 (55.0)	17 (60.7)	4 (66.7)	6 (75.0)	0.791
Male	9 (45.0)	11 (39.3)	2 (33.3)	2 (25.0)	
Cancer disease, n (%)					
Bile ducts	0 (0.0)	2 (7.1)	0 (0.0)	1 (12.5)	
Breast	5 (25.0)	8 (28.6)	2 (33.3)	3 (37.5)	
Colorectum	6 (30.0)	4 (14.3)	2 (33.3)	2 (25.0)	
Endometrium	0 (0.0)	1 (3.6)	0 (0.0)	0 (0.0)	
Gastric	1 (5.0)	2 (7.1)	1 (16.7)	1 (12.5)	
Lung	4 (20.0)	2 (7.1)	0 (0.0)	1 (12.5)	
Mesothelioma	0 (0.0)	1 (3.6)	0 (0.0)	0 (0.0)	0.955
Neuroendocrine	0 (0.0)	3 (10.7)	0 (0.0)	0 (0.0)	
Ovarian	3 (15.0)	1 (3.6)	1 (16.7)	0 (0.0)	
Pancreas	0 (0.0)	1 (3.6)	0 (0.0)	0 (0.0)	
Prostate	1 (5.0)	2 (7.1)	0 (0.0)	0 (0.0)	
Renal cell carcinoma	0 (0.0)	1 (3.6)	0 (0.0)	0 (0.0)	
Total	20 (100)	28 (100)	6 (100)	8 (100)	
OS (months)	46.95	57.71	37.00	33.75	0.389
Survival, n (%)					
Alive	5 (25.0)	12 (42.9)	2 (33.3)	2 (25.0)	
Dead	15 (75.0)	16 (57.1)	4 (66.7)	6 (75.0)	0.574
Total	20 (100)	28 (100)	6 (100)	8 (100)	
Alive with metastatic disease (months)	80.00	81.82	72.50	52.00	0.745
Alive in remission (months)	74.00	106.00	0	36.00	**<0.001**

SD: Standard deviation; OS: Overall survival.

CoV-2 infection (COVID+/COVID–). No significant differences were observed among the four subgroups with respect to age (p=0.266) or gender distribution (p=0.791) (Table 1).

Overall survival (OS) differed numerically across groups: 46.9 months in v(+)/COVID(+) patients, 57.7 months in v(+)/COVID(–), 37.0 months in v(–)/COVID(+), and 33.8 months in v(–)/COVID(–). Although this variation did not reach statistical significance (p=0.389), vaccinated or previously infected patients demonstrated a clear trend toward longer survival (Fig. 1). Among patients who remained alive with metastatic disease, median follow-up durations were similar across groups (p=0.745). Tumor-type distribution was broadly comparable between subgroups, although isolated differences were observed for smaller categories (Table 1).

When all patients who were either vaccinated or had a history of COVID-19 infection (n=54) were compared with those negative for both (n=8), OS was longer in the v(+) or COVID-19(+) group (51.4 months vs. 33.8 months; p=0.324). Similarly, median duration of survival among patients living with metastatic disease was numerically greater (80.3 months vs. 52.0 months; p=0.399). Although these differences did not reach statistical significance, patients alive in remission again exhibited a favorable trend toward

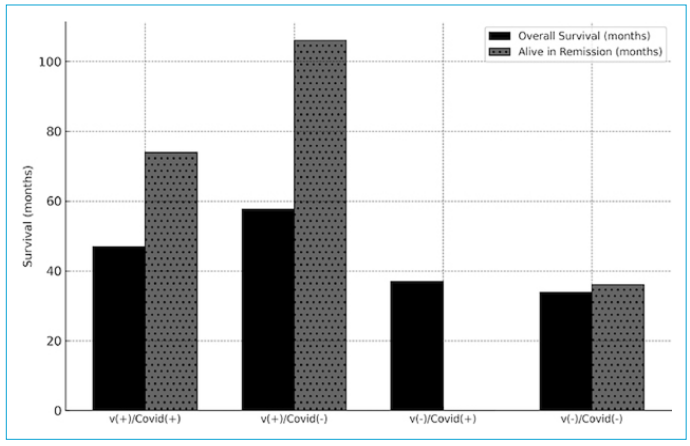

Figure 1. Comparison of overall survival and remission duration according to vaccination and COVID-19 status.

Table 2. Characteristics and comparisons between Covid and Vaccine Negative & Others in study population

	Vaccine (+) or Covid19 (+)	Vaccine (-) Covid19 (-)	p
N	54	8	
Age (Mean±SD)	59.65±2.1	52.88±3.5	0.092
Gender, n (%)			
Female	32 (59.3)	6 (75.0)	0.329
Male	22 (40.7)	2 (25.0)	
Cancer disease, n (%)			
Bile ducts	2 (3.7)	1 (12.5)	
Breast	15 (27.8)	3 (37.5)	
Colorectum	12 (22.2)	2 (25.0)	
Endometrium	1 (1.9)	0 (0.0)	
Gastric	4 (7.4)	1 (12.5)	
Lung	6 (11.1)	1 (12.5)	
Mesothelioma	1 (1.9)	0 (0.0)	0.975
Neuroendocrine	3 (5.6)	0 (0.0)	
Ovarian	5 (9.3)	0 (0.0)	
Pancreas	1 (1.9)	0 (0.0)	
Prostate	3 (5.6)	0 (0.0)	
Renal cell carcinoma	1 (1.9)	0 (0.0)	
Total	54 (100)	8 (100)	
OS (months)	51.43	33.75	0.324
Survival, n (%)			
Alive	19 (35.2)	2 (25.0)	
Dead	35 (64.8)	6 (75.0)	0.447
Total	54 (100)	8 (100)	
Alive with metastatic disease (months)	80.29	52.00	0.399
Alive in remission (months)	90.00	36.00	0.302

prolonged survival in the v(+) or COVID-19(+) group (90 months vs. 36 months; p=0.302) (Table 2).

In the subgroup of patients with metastatic breast cancer, mean OS was 77.5 months in those who were v(+) or COVID-19(+), compared with 45.0 months in double-negative patients (p=0.102). Among patients alive in remission, this difference was statistically significant (106 months vs. 36 months; p<0.001), suggesting a notable long-term benefit associated with vaccination or prior infection (Table 3). Among colorectal cancer patients, the mean OS was 42.9 months in v(+) or COVID-19(+) cases and 24.5 months in double-negative cases (p=0.370). The distribution of living versus deceased patients showed no significant difference (p=0.334) (Table 3). All three prostate cancer patients who had received vaccination or experienced COVID-19 infection were alive at last follow-up, with a mean survival of 74 months. No unvaccinated or COVID-negative cases were available for comparative analysis (Table 3, Fig. 2).

Table 3. Characteristics and comparisons between covid and vaccine negative & others in subgroup cancer patients

	Vaccine (+) or Covid19(+)	Vaccine (-) Covid19(-)	p
Breast cancer group			
n	15	3	
Age (Mean±SD)	53.2±1.2	47.2±1.8	0.157
OS (months)	77.53	45.00	0.102
Survival, n (%)			
Alive	9 (60.0)	2 (66.7)	0.674
Dead	6 (40.0)	1 (33.3)	
Total	15 (100)	3 (100)	
Alive with metastatic disease (months)	89.63	52.00	0.304
Alive in remission (months)	106.00	36.00	**<0.001**
Colorectal cancer group			
n	12	2	
Age (Mean±SD)	59.58±3.5	54.50±4.1	0.532
Gender, n (%)			
Female	4 (33.3)	1 (50.0)	
Male	8 (66.7)	1 (50.0)	0.604
Total	12 (100)	2 (100)	
OS (months)	42.92	24.50	0.370
Survival, n (%)			
Alive	4 (33.3)	0 (0.0)	
Dead	8 (66.7)	2 (100.0)	0.334
Total	12 (100)	2 (100)	
Alive with metastatic disease (months)	59.00	0	
Alive in remission (months)	74.00	0	
Prostate cancer group			
n	3	0	
Age (Mean±SD)	74.67±2.3	0	
Gender, n (%)			
Female	0 (0.0)	0 (0.0)	
Male	3 (100.0)	0 (0.0)	
Total	3 (100)	0 (100)	
OS (months)	74.00	0	
Survival, n (%)			
Alive	3 (100.0)	0 (0.0)	
Dead	0 (0.0)	0 (0.0)	
Total	3 (100)	0 (100)	
Alive with metastatic disease (months)	74.00	0	

Across the full cohort, patients who were vaccinated and/or previously infected with COVID-19 consistently exhibited longer survival durations, particularly among those in remission. Although statistical significance was limited by small subgroup sizes, the direction of effect was uniform, indicat-

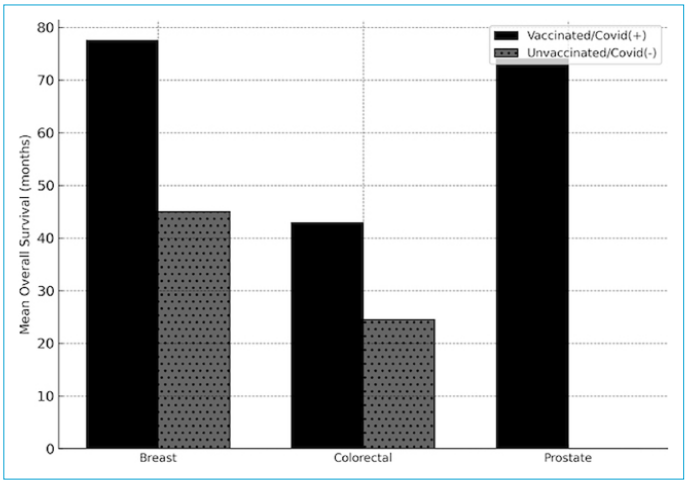

Figure 2. Subgroup survival comparison by tumor type.

ing a potential immunologic or host-response advantage linked to vaccination or viral exposure. The most pronounced difference was observed in the breast cancer subgroup, where remission survival was significantly extended among vaccinated or COVID-positive patients ($p<0.001$).

Discussion

This retrospective analysis demonstrated that metastatic cancer patients who had been vaccinated against SARS-CoV-2 and/or experienced prior COVID-19 infection exhibited consistently longer survival compared with double-negative controls. Although statistical significance was limited in some comparisons, the directionality of the findings suggests that systemic immune activation—whether induced by vaccination or infection—may influence host–tumor dynamics and long-term oncologic outcomes.

The potential association between immune activation and improved cancer outcomes has long been recognized. Tumor immunology research has shown that transient immune stimulation can enhance antigen presentation, cytotoxic T-cell priming, and interferon-mediated tumor surveillance.[9] COVID-19 vaccination engages innate and adaptive immune pathways, including pattern-recognition receptor–mediated activation of antigen-presenting cells and the induction of strong TH1-biased $CD4^+$ and $CD8^+$ effector T-cell responses.[10] These effects might augment existing anti-tumor immunity or synergize with checkpoint-mediated immune reactivation.

Recent clinical observations lend support to this hypothesis. In patients with advanced melanoma or lung cancer treated with immune checkpoint inhibitors (ICIs), concurrent or recent COVID-19 vaccination was associated with longer progression-free and overall survival.[11] Another cohort demonstrated that mRNA vaccination enhances peripheral $CD8^+$ T-cell activation and cytokine responses, potentially amplifying anti-tumor immune control.[12] A similar pattern was observed in metastatic colorectal cancer: SARS-CoV-2 mRNA-BNT162b2 vaccination independently predicted longer PFS and OS in patients receiving bevacizumab-based therapy.[13] In one case series, 14 cases associated with COVID-19 infection and 2 cases of spontaneous cancer regression resulting from vaccination were reported.[14] In contrast, studies have reported that the COVID-19 vaccine did not increase the incidence of immune-related adverse events (irAEs) or affect disease-free survival (PFS) in lung cancer patients receiving immune checkpoint inhibitor (ICI) therapy. However, in this study, the inactive vaccination rate was very high (85%), and the mRNA vaccination rate was only 15%. These characteristics of the study may explain its differing results.[15]

Interestingly, the most significant benefit in our dataset was observed in breast cancer patients. This observation may be due to the fact that these patients' treatments often involve hormonal therapy. The range of chemotherapy and high-dose steroid use may be lower compared with other cancer types. Conversely, the smaller difference in colorectal cancer may be due to the higher range of chemotherapy and high-dose steroid treatment use compared with breast cancer. In prostate cancer, although limited by sample size, it was observed that all vaccinated patients survived during follow-up. This may be due to their treatment. They all received antiandrogen therapy, not chemotherapy or high-dose steroid therapy. Vaccine-induced immune responses can be affected by different cancer treatments; patients receiving immunotherapy or targeted therapy are more likely to achieve seropositive status than those receiving cytotoxic chemotherapy.[16-18]

The retrospective nature of this study and the modest sample size in certain tumor subgroups limit causal inference. Unmeasured confounders, such as treatment intensity, socioeconomic factors, and comorbidities, may have influenced outcomes. Additionally, our data did not differentiate between vaccine types or infection severity, which may variably affect immune modulation.

Conclusion

COVID-19 vaccination and prior infection were associated with improved survival among patients with metastatic solid tumors. These findings support the hypothesis that transient immune activation—whether through vaccination or infection—may reinforce tumor immunosurveillance mechanisms. While causality cannot be established, the consistent trends observed across tumor types underscore the potential role of systemic immune conditioning in metastatic cancer outcomes. Validation in larger, prospective cohorts and mechanistic studies is warranted to determine whether this association represents a modifiable therapeutic target.

Disclosures

Ethics Committee Approval: Because of the retrospective design, informed consent was waived by the ethics committee.

Informed Consent: Due to the retrospective design utilizing archival pathology specimens, the ethics committee waived the necessity for individual informed consent.

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