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COVID-19 VACCINATION OUTCOMES IN PATIENTS WITH A SOLID MALIGNANCY: INSIGHTS FROM EXTENSIVE REAL-WORLD DATA AND PROPENSITY SCORE MATCHED ANALYSES

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Abstract

Objectives: This nationwide, multicentric, retrospective analysis of 1,126,946 COVID-19 cases (March 2020 to June 2022) aims to elucidate the impact of COVID-19 vaccination on mortality in patients with a sole solid malignancy.

Methods: Using data from the national digital medical record repository, outcomes were compared among fully vaccinated and non-vaccinated cohorts, factoring in gender, virus type, age, vaccination status, vaccine type, and cancer type. Logistic regression calculated odds ratios and their significance.

Results: Among 6,050 patients with both cancer and comorbidities, 1,797 had only solid malignancy. Vaccinated individuals in this group had reduced mortality rates, especially those >63 years [OR 0.169 (95%CI 0.090 to 0.317); P < 0.001]. Lower deaths were observed in non-ICU [OR 0.193 (95% CI 0.097 to 0.382); P < 0.001] and ICU cases [OR 0.224 (95% CI 0.077 to 0.646); P = 0.003], with both vaccine types. No statistically significant benefits were observed against delta and omicron variants. Intrathoracic malignancies [OR 0.376 (95%CI 0.146 to 0.971); P = 0.043] and palliative treatment [OR 0.384 (95%CI 0.192 to 0.766); P = 0.006] showed vaccination benefits. Logistic regression revealed a higher fatal risk in non-vaccinated males >63. Propensity score matching supported these outcomes.

Conclusion: Patients with sole solid malignancies face elevated COVID-19 mortality risk, particularly without active cytostatic therapy, with advanced disease on palliative treatment, or intrathoracic malignancies.

Keywords

COVID-19; Cancer; Chemotherapy; Mortality, Real-world data.

Introduction

Conflicting evidence exists regarding the relationship between cancer and COVID-19 outcomes. While it is generally understood that cancer patients are at higher risk, studies have reported varying mortality rates (1-3). The effects of specific cancer types and stages on COVID-19 outcomes are still debated and require further investigation (4-6). Numerous studies have supported the safety profile of vaccines in this population, emphasizing their role in preventing severe illness and mortality associated with COVID-19. Additionally, evidence suggests that vaccinated cancer patients may experience milder disease courses and reduced hospitalization rates compared to their unvaccinated counterparts (7, 8). However, factors such as study design, sample sizes, patient populations, and cancer types contribute to these discrepancies. Additionally, the impact of different cancer treatments on COVID-19 outcomes also shows conflicting evidence, with some studies suggesting increased risk and others finding no significant association (2, 9, 10). To gain insight into this matter, a nationwide, multicentric, retrospective analysis was carried out, specifically targeting patients who had a solid malignancy as their only chronic comorbidity. Such findings have the potential to inform clinical decision-making and public health strategies for COVID-19 management in this patient population.

Methods

Patient cohort criteria: This retrospective, multicenter real-world study involved an initial cohort of 1,126,946 individuals confirmed as COVID-19 patients between March 2020 and June 2022. These confirmations were made by medical professionals using polymerase chain reaction (n=612,378) or antigen testing (n=436,196) specifically within ambulatory and hospital settings, with home tests excluded. We obtained the necessary data through a formal request for access to the Bulgarian Ministry of Health's United Information Portal, serving as a comprehensive repository for information from all 28 provinces in Bulgaria. This government funded platform acts as a centralized digital medical record repository, housing all laboratory-verified COVID-19 cases and the associated patient records (11). The data utilized in this study categorized fatal cases into two groups: those deemed COVID-19 related and those classified as COVID-19 unrelated. For the purposes of this analysis, only patients with deaths attributed to COVID-19 were included.

The study's objective was to contrast mortality rates among cohorts having a solitary solid malignancy as their sole chronic comorbidity. We performed stratified analyses based on sex and age at COVID-19 diagnosis, primary tumor localization, oncological treatment intent (categorized as either palliative for incurable disease or curative), vaccination status, the circulating viral variant, and recent active cancer treatment (within the last 30 days), as depicted in **Figure 1**. Patients were considered fully vaccinated if they had received either two doses of an mRNA-based vaccine (e.g., BNT162b2 or CX-024414), two doses of ChAdOx1-SARS-COV-2, or one dose of Ad26.COV2-S. Given that most patients included in this analysis received a single vaccine type, our study did not specifically investigate differences in vaccination regimens within the vaccinated cohort and excluded cases involving booster doses (**Supp. Table 1**).

The study adhered to ethical standards outlined in the Helsinki Declaration, the International Ethical Guidelines for Health-related Research Involving Humans (2016), and the Personal Data Protection Law № 25,326, as well as the resolution of the Ministry of Health of the Nation № 1480/11.

Statistical analysis: The statistical analysis was performed using SAS version 9.4 (SAS, Cary, North Carolina, USA). The associations between variables were assessed using the Pearson's Chi-Square test. The odds ratio (OR) was calculated to quantify the association between COVID-19 vaccination and mortality. A logistic regression model was employed to estimate odds ratios and their significance in this study. The probability of death served as the dependent variable, with gender, type of virus, grouped age, and vaccination status included as independent variables. Additionally, a similar model, excluding vaccination status, was utilized to calculate propensity scores.

Patient and public involvement: Patient involvement was not considered in formulating the research question or determining the outcome measures. Additionally, patients did not participate in the design or implementation of the study. There are no intentions to directly share the research results with the study participants or the relevant patient cohorts.

Results

Out of the total 1,126,946 confirmed COVID-19 patients, 0.53% (n=6,050) were diagnosed with both a solid malignancy and at least one additional comorbidity, encompassing cardiovascular, metabolic, chronic pulmonary, and immune-related disorders. The unadjusted univariate statistical analysis (**Table 1**) demonstrated a substantial reduction in mortality among COVID-19 vaccinated

patients (unvaccinated n = 1507/5020; vaccinated n = 71/1030) [OR 0.172 (95%CI 0.134 to 0.221); P < 0.001] (**Figure 2**).

Within this subset, 33.6% (n=1,797) had a solitary solid malignancy, with a median age of 63 years. Among these individuals, COVID-19 vaccinated patients with an isolated solid malignancy exhibited a significant reduction in mortality [OR 0.179 (95%CI 0.105 to 0.305); P < 0.001]. This reduction was most pronounced in the cohort aged over 63 years (unvaccinated n= 234/803; vaccinated n= 11/169) [OR 0.169 (95%CI 0.090 to 0.317); P < 0.001].

Both males (unvaccinated n = 167/647; vaccinated n = 8/149) [OR 0.163 (95%CI 0.078 to 0.3397); P < 0.001] and females (unvaccinated n = 148/827; vaccinated n = 7/174) [OR 0.192 (95%CI 0.088 to 0.418); P < 0.001] benefited equally from vaccination, demonstrating reduced mortality rates. Both the non-intensive care unit (unvaccinated n = 173/1279; vaccinated n = 9/307) [OR 0.193 (95%CI 0.097 to 0.382); P < 0.001] and ICU-related in-hospital deaths (unvaccinated n = 142/195; vaccinated n = 6/16) [OR 0.224 (95%CI 0.077 to 0.646); P = 0.003], demonstrated reduced mortality rates in the vaccinated cohorts.

When comparing the primary vaccine platforms in relation to mortality, both vector-based vaccines (unvaccinated n = 314/1451; vaccinated n = 5/78) [OR 0.248 (95%CI 0.099 to 0.619); P < 0.01] and mRNA-based vaccines (unvaccinated n = 313/1465; vaccinated n = 12/297) [OR 0.155 (95%CI 0.085 to 0.279); P < 0.001] demonstrated a reduction in fatal outcomes favoring the vaccinated cohorts, with a more pronounced benefit observed in the mRNA-based vaccine cohort.

When assessing the impact of vaccination on mortality across various SARS-CoV-2 variants, despite observing numerical advantages, no benefits were detected. The logistic regression

analysis showed that non-vaccinated male patients aged over 63 face the highest risk of fatal COVID-19 (Supp. Table 2).

Propensity score matching (**Table 2**) supported the findings in the unadjusted statistical analyses (**Figure 3**).

Additional sub-grouping demonstrated statistically significant vaccination benefits in: patients with intrathoracic malignancies (unvaccinated n = 56/381; vaccinated n = 5/84) [OR 0.376 (95% CI 0.146 to 0.971); P = 0.043], individuals who had not received recent active treatment within the last 30 days (unvaccinated n = 127/1013; vaccinated n = 15/213) [OR 0.528 (95% CI 0.302 to 0.922); P = 0.024], and those on palliative treatment intent (unvaccinated n = 93/436; vaccinated n = 10/106) [OR 0.384 (95% CI 0.192 to 0.766); P = 0.006] (**Supp. Table 3**).

Discussion

To our knowledge, this study represents the first comprehensive real-world data report examining the outcomes of COVID-19 specifically in patients with a solid malignancy as their sole comorbidity. This study contributes to the existing body of literature by providing important insights into the impact of COVID-19 on patients with a solid malignancy. It is essential to acknowledge that conflicting evidence exists in this field, and our findings should be considered in the context of these discrepancies. While some studies have reported higher mortality rates in this population (12), others have found comparable or even lower mortality rates when compared to non-cancer COVID-19 patients (13). Moreover, individuals with cancer who contract COVID-19 might exhibit atypical symptoms and face an elevated risk of mortality. This heightened risk appears to be independent of demographic factors, comorbidities, and treatment modalities (14).

It is important to consider the variability in study design, sample sizes, patient populations, and cancer types when comparing our findings to conflicting evidence. The differences in methodologies and patient characteristics across studies may contribute to the discrepancies observed in the literature. Our study tried to mitigate this by examining the impact of COVID-19 only in patients with a solid malignancy as the sole comorbidity. Our findings of higher mortality rates in patients with a solid malignancy support the notion that this population faces an increased risk, especially in patients diagnosed with intrathoracic malignancies, which were associated with even higher mortality rates, aligning with published literature (15, 16).

Patients receiving palliative treatment for a non-curable solid malignancy exhibited higher mortality rates, suggesting the influence of underlying health status, disease stage and limited treatment options on COVID-19 outcomes (17). Furthermore, patients who had received chemotherapy within the last 30 days showed decrease mortality rates, emphasizing the potential impact of recent treatment on immune status and susceptibility to severe COVID-19 and the development of the often fatal immune phase of the disease in both vaccinated and unvaccinated patients (18, 19).

Our study reveals a numerical protective effect of vaccination against premature deaths in cases of infections caused by the delta and omicron variants of SARS-CoV-2. During the omicron variant's emergence, there was a notable reduction in viral pathogenicity, resulting in the wider confidence intervals compared to the delta variant (20). Additionally, during the periods dominated by the alpha and beta variants, the vaccinated cohort exhibited no recorded fatal cases, in contrast to the unvaccinated groups, making statistical analysis unnecessary. This can be attributed to the similarity between the viral spike protein mRNA sequence used in vaccine production and the one from the original Wuhan variant (21). This study demonstrated statistically significant reductions

in mortality rates for both vaccine platforms. Notably, the effectiveness of vaccines in preventing excess COVID-19-related mortality seemed to be more consistent in cases involving mRNA-based vaccines, which aligns with previously published data in non-cancer patient cohorts (22). Providing a "booster" dose may further mitigate these risks (23).

While our study has yielded valuable findings and insights, it is imperative to recognize and address several limitations that may influence the interpretation and generalizability of our results.

Firstly, our study adopted a retrospective design, which inherently entails limitations concerning data collection and the potential for biases. Relying on existing medical records and databases may have introduced selection biases, as the available data might not encompass all pertinent variables or outcomes. It's important to note that, unlike several published works, we did not conduct SARS-CoV-2 IgG testing or any other laboratory confirmatory tests in this study. This decision stems from existing literature demonstrating no significant difference in seroconversion rates between patients with solid malignancies and non-cancer patients (24, 25). Furthermore, we lacked access to demographic stratification data, limiting our ability to perform additional population subgrouping.

To bolster the strength of evidence, the consideration of prospective studies with meticulously crafted protocols is essential, as they can provide more robust and reliable insights. However, it is crucial to acknowledge the dynamic and evolving nature of SARS-CoV-2 and the persistent challenges posed by the ongoing pandemic. The rapid viral evolution, emergence of new variants, and continually shifting epidemiological landscape create hurdles in conducting prospective studies in real time. These challenges underscore the need for ongoing research and adaptation to comprehensively investigate the impact of COVID-19 and its treatment on patients with cancer.

Secondly, our study did not stratify patients based on cancer stages or account for the specific types of chemotherapy administered for each tumor type. It is noteworthy that cancer staging and the precise chemotherapy regimens received by patients can exert a substantial impact on their overall health status and treatment outcomes. The omission of this stratification represents a limitation in our ability to offer a more nuanced analysis of the influence of these factors.

Conclusion

Individuals with a sole solid malignancy as their primary medical condition face a heightened risk of COVID-19-related mortality. This risk is particularly accentuated in individuals aged older than 63 years who are not undergoing active cytostatic therapy, patients on palliative treatment intent and those diagnosed with intrathoracic malignancies.

Ethics approval

Approval for this retrospective analysis was granted by the Bulgarian ministry of health - document number **94-4750** from **09.11.2022.**

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Conflict of interests

No conflict of interest to declare.

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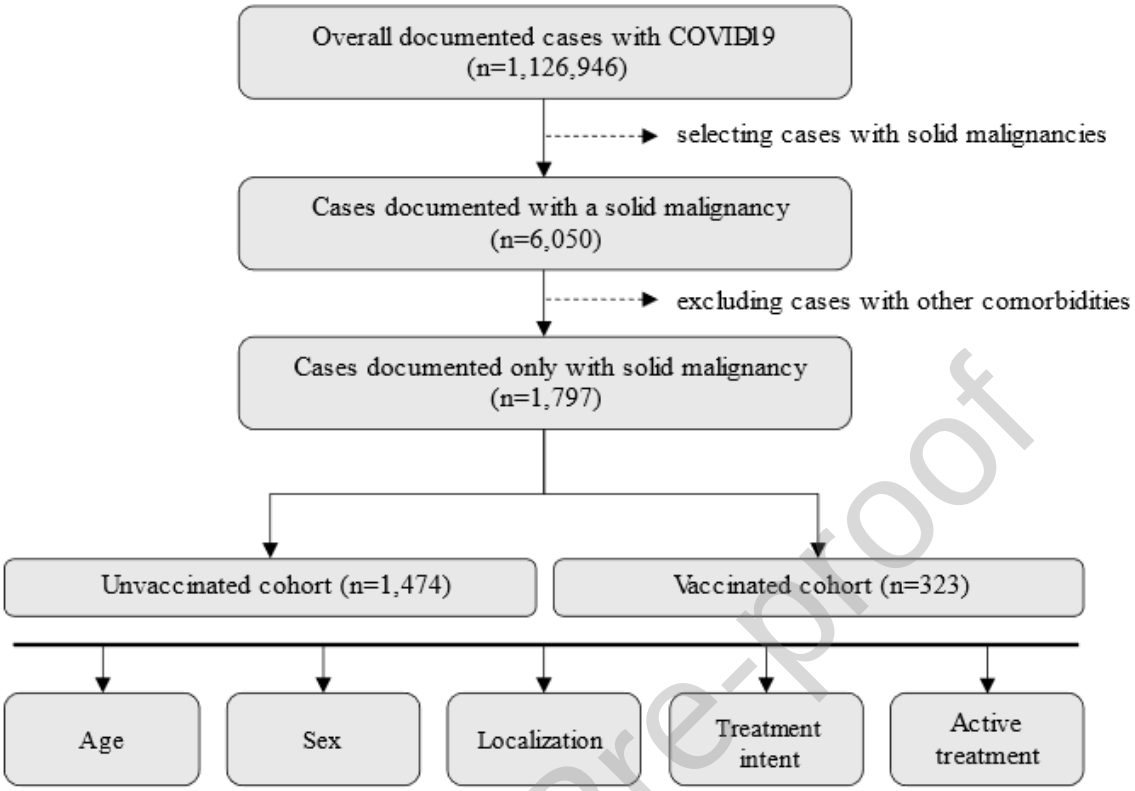

Figure 1. The patient cohort selection process was standardized across both groups. The isolated patient groups were required to have only a solid malignancy as their documented pathology, and any duplicate cases were excluded from the study. These cohorts were further stratified based on criteria such as sex, age, primary tumor localization, treatment intent, and recent active treatment.

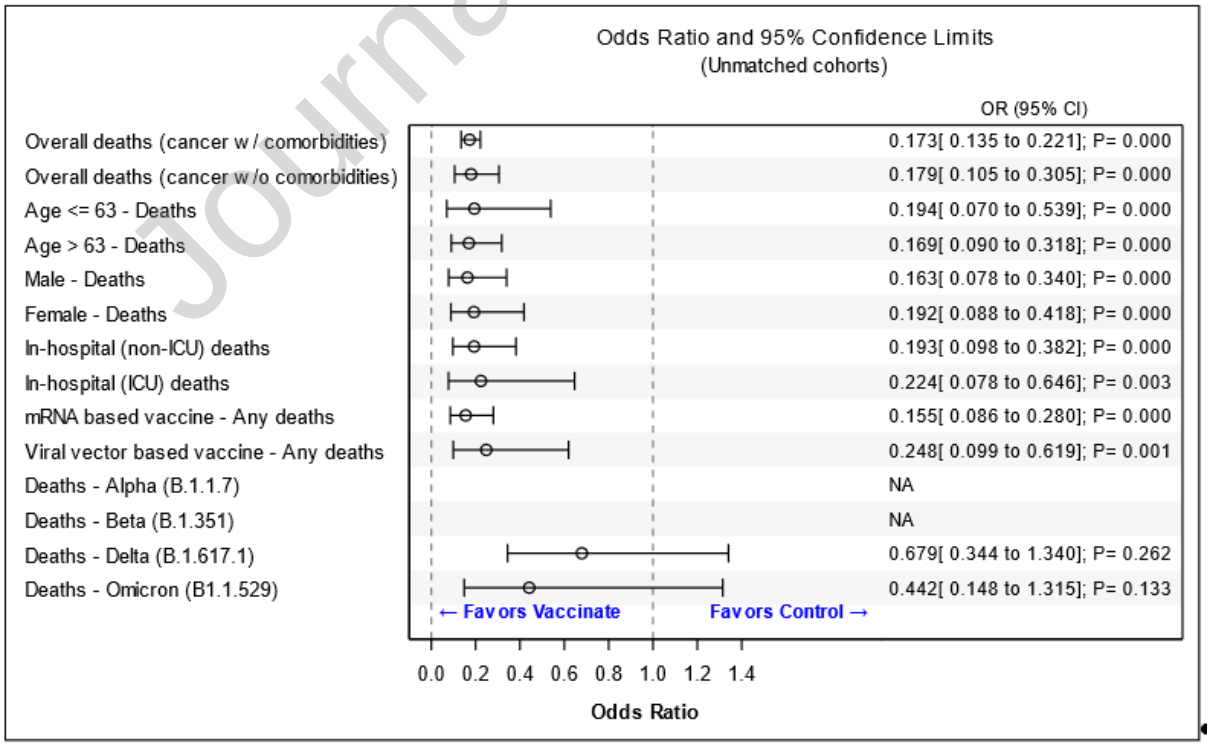

Figure 2. Forest plot of the unadjusted univariate statistical analyses.

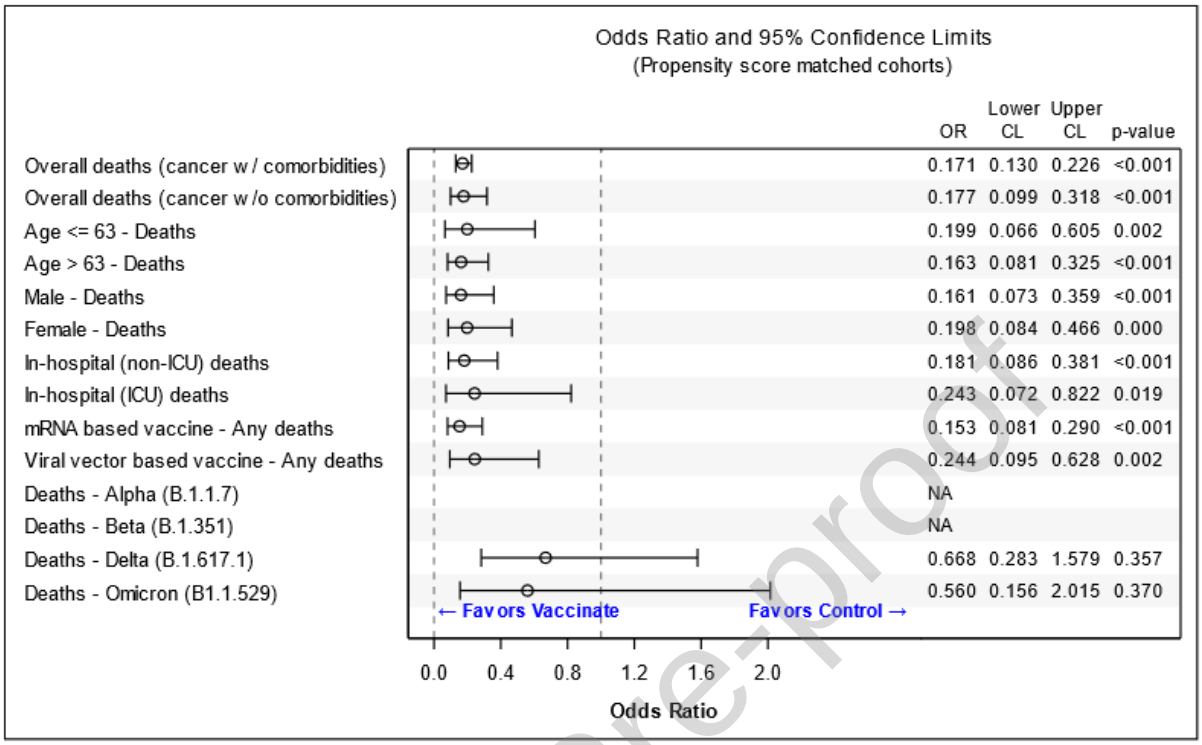

Figure 3. Forest plot of the propensity score matched univariate statistical analyses

Table 1. Confirmed COVID-19 cases and unadjusted statistical analysis in cancer patients by vaccination status and deaths indexed between March 2020 and June 2022. NA = Not Applicable

CRITERIA	TOTAL DEATHS (N=1578)	UNVACCINATED CASES (N=5020)	VACCINATED CASES (N=1030)	OR (95% CI)
Overall deaths (cancer w/ comorbidities)	n=1578	1507/5020(30.0%)	71/1030(6.9%)	0.172 [0.134 to 0.221]; P<0.001
Overall deaths (cancer w/o comorbidities)	n=330	315/1474(21.4%)	15/323(4.6%)	0.179 [0.105 to 0.305]; P<0.001
Age ≤ 63 - Deaths	n=85	81/671(12.1%)	4/154(2.6%)	0.194 [0.070 to 0.538]; P<0.001

Age > 63 - Deaths	n=245	234/803(29.1%)	11/169(6.5%)	0.169 [0.090 to 0.317]; P<0.001
Male - Deaths	n=175	167/647(25.8%)	8/149(5.4%)	0.163 [0.078 to 0.339]; P<0.001
Female - Deaths	n=155	148/827(17.9%)	7/174(4.0%)	0.192 [0.088 to 0.418]; P<0.001
In-hospital (non-ICU) deaths	n=182	173/1279(13.5%)	9/307(2.9%)	0.193 [0.097 to 0.382]; P<0.001
In-hospital (ICU) deaths	n=148	142/195(72.8%)	6/16(37.5%)	0.224 [0.077 to 0.646]; P=0.003
mRNA based vaccine - Any deaths	n=325	313/1465(21.4%)	12/297(4.0%)	0.155 [0.085 to 0.279]; P<0.001
Viral vector based vaccine - Any deaths	n=319	314/1451(21.6%)	5/78(6.4%)	0.248 [0.099 to 0.619]; P<0.01
Deaths - Alpha (B.1.1.7)	n=74	74/350(21.1%)	0/132(0.0%)	NA
Deaths - Beta (B.1.351)	n=104	104/452(23.0%)	0/73(0.0%)	NA
Deaths - Delta (B.1.617.1)	n=116	105/481(21.8%)	11/69(15.9%)	0.679 [0.344 to 1.340]; P=0.262
Deaths - Omicron (B1.1.529)	n=36	32/191(16.8%)	4/49(8.2%)	0.441 [0.148 to 1.314]; P=0.133

Table 2. Propensity score matching in cancer patients by vaccination status and deaths indexed between March 2020 and June 2022. NA = Not Applicable

CRITERIA	TOTAL DEATHS (N=382)	UNVACCINATED CASES (N=1030)	VACCINATED CASES (N=1030)	OR (95% CI)

Overall deaths (cancer w/ comorbidities)	n=382	311/1030(30.2%)	71/1030(6.9%)	0.171 [0.130 to 0.225]; P<0.001
Overall deaths (cancer w/o comorbidities)	n=84	69/319(21.5%)	15/323(4.6%)	0.177 [0.099 to 0.317]; P<0.001
Age <= 63 - Deaths	n=22	18/148(11.8%)	4/154(2.6%)	0.199 [0.065 to 0.604]; P<0.001
Age > 63 - Deaths	n=62	51/171(30.0%)	11/169(6.5%)	0.162 [0.081 to 0.325]; P<0.001
Male - Deaths	n=48	40/153(26.0%)	8/149(5.4%)	0.161 [0.072 to 0.358]; P<0.001
Female - Deaths	n=36	29/167(17.4%)	7/174(4.0%)	0.198 [0.084 to 0.466]; P<0.001
In-hospital (non-ICU) deaths	n=49	40/279(14.3%)	9/307(2.9%)	0.181 [0.086 to 0.380]; P<0.001
In-hospital (ICU) deaths	n=35	29/41(71.2%)	6/16(37.5%)	0.243 [0.071 to 0.821]; P<0.05
mRNA based vaccine - Any deaths	n=81	69/318(21.6%)	12/297(4.0%)	0.153 [0.081 to 0.289]; P<0.001
Viral vector based vaccine - Any deaths	n=74	69/313(21.9%)	5/78(6.4%)	0.244 [0.094 to 0.627]; P<0.01
Deaths - Alpha (B.1.1.7)	n=23	23/110(21.2%)	0/132(0.0%)	NA
Deaths - Beta (B.1.351)	n=23	23/86(26.6%)	0/73(0.0%)	NA
Deaths - Delta (B.1.617.1)	n=26	15/69(22.1%)	11/69(15.9%)	0.668 [0.283 to 1.579]; P=0.356
Deaths - Omicron (B1.1.529)	n=12	8/55(13.7%)	4/49(8.2%)	0.560 [0.155 to 2.014]; P=0.369

CRediT authorship contribution statement

Both authors, GD and TV, made equal contributions to the study design and manuscript preparation. KK performed the statistical analyses and propensity score matching.

HIGHLIGHTS

- Vaccinated isolated solid malignancy patients had significantly reduced mortality notably for those aged older than 63 years.
- Statistically significant mortality reductions in non-ICU and ICU cases with both mRNA and vector-based vaccines.
- No significant vaccination benefits seen with variants.
- Intrathoracic malignancies and palliative treatment demonstrated significant vaccination benefits.
- Propensity score matching supported findings.