An approach to COVID-19 and oncology: From impact, staging and management to vaccine outcomes in cancer patients: A systematic review and meta-analysis

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Abstract. The COVID-19 pandemic has had a global impact, with >771 million confirmed cases and 6 million deaths reported by October 2023. Cancer patients, due to their immunosuppressed status, face an increased infection risk and higher COVID-19 complications. The present study aimed to assess clinical outcomes in COVID-19-infected cancer patients, focusing on mortality rates and other aspects, providing valuable insight for better protection and outcomes. This systematic review was conducted by searching the PubMed, Cochrane and Embase databases from August 2023 following the PRISMA guidelines. Studies from 2020 to 2023 pertaining to the impact of COVID-19 on patients previously diagnosed with malignancies were considered. Inclusion criteria entailed a pre-existing malignancy diagnosis, confirmed COVID-19 infection and an impact of COVID-19 on any aspect of the patient's cancer management. Studies written in English were exclusively reviewed. Post-COVID-19 malignancy diagnoses, case reports, review articles and data-insufficient studies were excluded. Screening and consensus on eligibility were carried out by a team of four authors, with disputes resolved by a non-screening author. Data extraction was performed by a five-author team, detailing study and population characteristics, as well as cancer patient outcomes related to COVID-19. Cross-checking was conducted by the same team, with conflicts resolved by a third author. The review of 27 studies explored COVID-19's impact on oncology, revealing diverse sample sizes (1,807,559 to 177 participants). Studies spanned various cancer types, including gastric adenocarcinoma, breast, lung, gynecologic, colorectal and non-melanoma skin cancer. Mortality rates were higher among cancer patients with COVID-19 compared to those without. Gastric adenocarcinoma exhibited a 5.9% mortality rate. Thoracic cancer patients faced elevated mortality and gastrectomies decreased. A meta-analysis (10 studies, 5,151 patients) showed a 19.1% mortality rate for COVID-19-infected cancer patients, contrasting with 1% for non-COVID-19 cancer patients (5 studies, 54,528 patients). The odds ratio for mortality in non-COVID-19 vs. COVID-19 cancer patients was 0.1036 (3 studies, 3,496 patients). Cancer patients consistently faced elevated mortality during the pandemic, with specific cancers showing unique impacts. Gastric adenocarcinoma exhibited a significant COVID-19 mortality rate. Patients with thoracic cancer faced increased risks, influencing surgical trends. Meta-analysis revealed an overall elevated mortality rate among COVID-19-infected cancer patients compared to non-COVID-19 counterparts.

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Introduction

The coronavirus disease 2019 (COVID-19) is a highly contagious viral illness, which has spread globally, affecting millions of individuals worldwide (1). According to the World

Health Organization, as of October 2023, there have been >771 million confirmed cases and >6 million deaths worldwide since the onset of the COVID-19 pandemic. To be specific, Saudi Arabia reported 841,469 confirmed cases in 2023, while the United States reported 103,436,829 cases by October 2023. These figures underscore the widespread impact of this disease (1).

Cancer patients, with their immunosuppressed status due to their condition or its treatment, are at an increased risk of infection in comparison to the general population. This immunosuppression can lead to serious complications, potentially resulting in delays of treatment and unnecessary hospitalizations, which may adversely affect the disease prognosis (2). The immunocompromised state of cancer patients may be attributed to antineoplastic therapies, supportive medications such as steroids or the immunosuppressive nature of cancer itself. In addition, immunomodulatory drugs, including programmed cell death 1 and programmed cell death ligand 1 inhibitors, can alter the immune responses to infections (3,4). Cancer patients, who are often at an advanced age (≥60 years) and have one or more significant comorbidities, are at an increased risk for COVID-19-related morbidity and mortality. These patients' frequent interactions with the healthcare system through anticancer therapies, monitoring and supportive care further elevate this risk (4). Treatment for cancer within 14 days of a COVID-19 diagnosis has been identified as a risk factor for developing severe complications, including acute respiratory distress syndrome (28.6%), septic shock (3.6%) and acute myocardial infarction (3.6%) (2). Among cancer patients diagnosed with COVID-19, a study showed that 21% succumbed to the disease as compared to 7.8% in non-cancer populations (5). Furthermore, research indicates that cancer patients diagnosed with COVID-19 are more likely to require hospitalization, intensive care unit (ICU) admission and mechanical ventilation, irrespective of the cancer type or treatment. These findings emphasize the importance of stringent infection control measures and the necessity of treating cancer patients in outpatient settings whenever feasible in order to decrease the risk (2). Given the global prevalence of cancer and the high transmissibility of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), understanding the disease course and the factors affecting clinical outcomes in cancer patients with COVID-19 is essential (4). However, most studies performed examining cancer patients with COVID-19 have been single-center investigations, with significant variability in both inclusion criteria and outcomes. A common limitation is that many of these research endeavours and studies are case series, making it challenging to generalize findings to broader populations (5). Cancer patients represent a diverse group and there is a need for a better understanding regarding which patients, and which tumor- or treatment-related factors, are associated with an increased risk of infection and related adverse outcomes. This knowledge is crucial in determining whether an elevated COVID-19 risk should influence cancer treatment approaches (5).

The present study aims to evaluate cancer patients in terms of clinical outcomes related to COVID-19 infection, with a focus on the type of malignancy, mortality rates and other clinical outcomes. The findings of this research could be instrumental in protecting at-risk populations from COVID-19 or similar viral infections, reducing disease progression, lowering mortality and morbidity rates and ensuring optimal outcomes for cancer patients.

Materials and methods

Literature search. A search was performed in the relevant databases, including PubMed (https://pubmed.ncbi.nlm.nih.gov), Cochrane (https://pubmed.ncbi.nlm.nih.gov) and Embase (https://www.elsevier.com/products/embase), starting from August 2023 in a systematic manner. The search terms and key words were 'cancer', 'COVID-19', 'mortality', 'oncology' and 'impact'.

In accordance with the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (6), the inclusion and exclusion criteria and main outcomes of the present study were clarified in a protocol, which was registered in International Prospective Register of Systematic Reviews (PROSPERO; https://www.crd.york.ac.uk/prospero/; no. CRD42023445522).

The collected studies were retrieved and downloaded from their databases, followed by arrangement on a Google Drive platform. The studies were arranged by folders denoting their year of publication for subsequent screening and data analysis. The focus was on studies relevant to the COVID-19 pandemic, so the years searched were from 2020 to 2023. The search and screening process of the studies is demonstrated in the flow chart (Fig. 1).

Eligibility criteria. The following criteria were required to be met for the studies to be included in the present review: i) Patients studied were diagnosed with any type of malignancy by any medically recognized diagnostic criteria before developing COVID-19; ii) patients were confirmed to have COVID-19 infection through any of clinical or laboratory method; iii) any aspect of the patient's malignancy was affected by COVID-19 infection, including their treatment, management, screening and vaccination outcomes; iv) the language of all included studies was confined to English.

The exclusion criteria were as follows: i) Patients who were diagnosed with any type of malignancy after a confirmed COVID-19 infection; ii) articles or studies categorized as case reports or review articles; iii) studies with insufficient or incomplete data to match any aspect of the inclusion criteria to obtain a complete data analysis. All of the studies eligible for the present review were evaluated by four authors (AhAA, TA, MeAA and MoAA) and any disagreements were resolved through consulting an author who was not part of the study's screening team (RA).

Data extraction and risk of bias assessment. A team of five authors (AhAA, NA, TA, MeAA and MoAA) performed the task of data extraction. The extracted content was organized into the following categories: i) Study characteristics: First author, publication year, type of study, sample size, number of COVID-19 patients; ii) population characteristics: Average age and gender; iii) outcomes for cancer patients: Mortality in cancer patients without COVID-19, mortality in cancer patients with COVID-19, delay in treatment and complications. The data were cross-checked by the screening team consisting of four

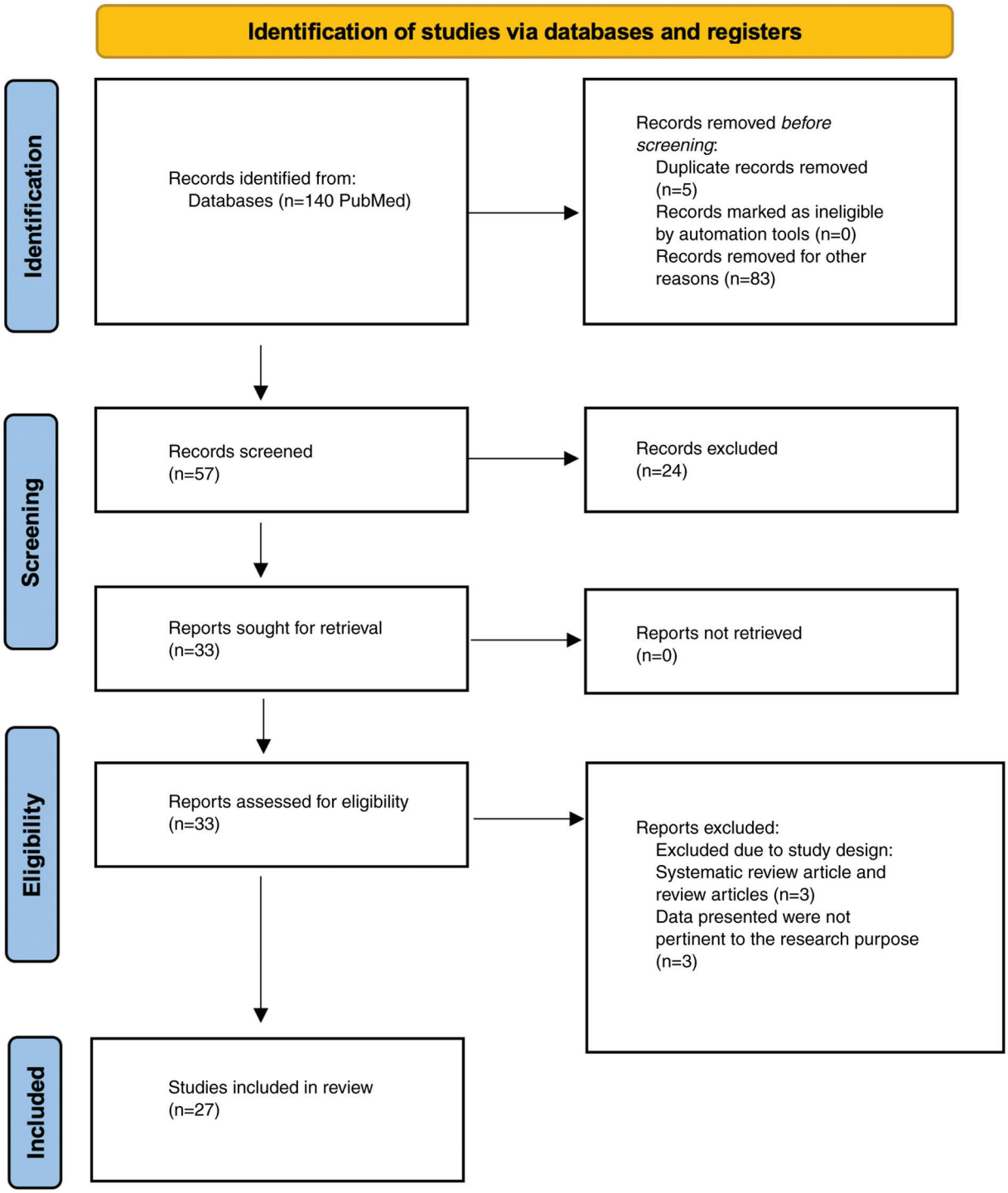

Figure 1. Flow chart of the search and screening process.

authors. At any point through the process, any disagreement between two authors was resolved or consulted by a third author (RA).

In further detail, 57 articles were transferred from Mendeley (https://www.mendeley.com/search/) to Rayyan (https://www.rayyan.ai) to undergo screening and duplicate identification. Subsequently, four authors (AhAA, TA, MeAA and MoAA) independently evaluated the articles based on their titles. The team identified and resolved five instances of duplication and addressed six disagreements through team discussions. Furthermore, three independent authors (AhAA, TA and MeAA) conducted full-text screening of the articles. Following the screening of articles, data extraction was performed within an Excel spreadsheet (Office 365; Version 16; Microsoft Corp.). Each author extracted several articles, focusing on authors' names, year of publication, country, sample size, number of COVID-19 patients, type of cancer, average age, sex, primary outcomes (e.g., mortality), secondary outcomes (e.g., complications and treatment obstacles) and concluding remarks. This process was thoroughly reviewed by an author (RA) to ensure accuracy and completeness.

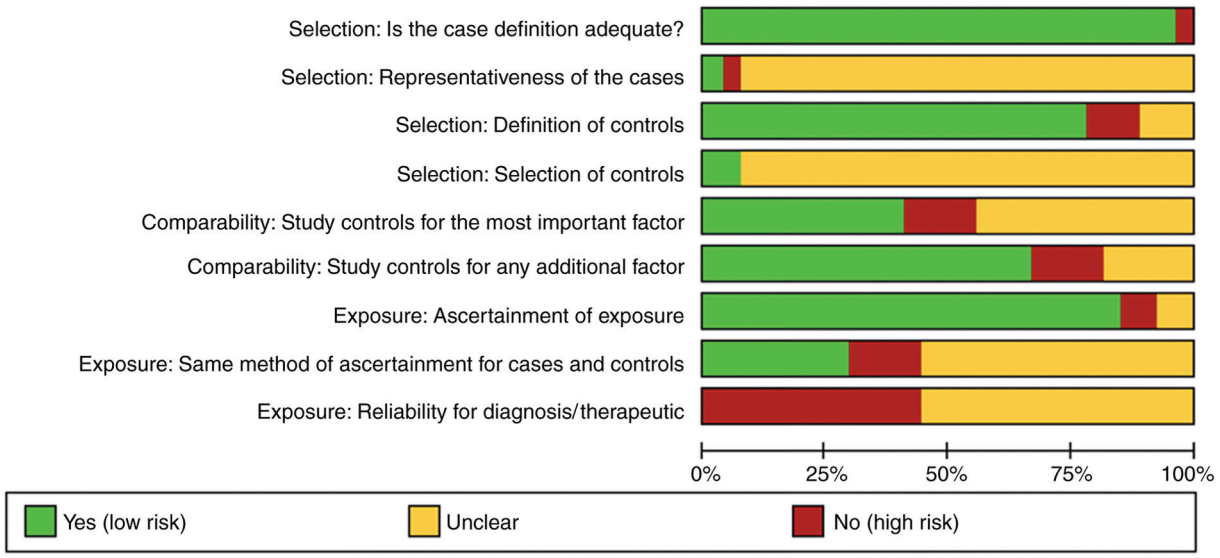

Figure 2. Risk of bias graph: Review authors' judgements about each risk of bias item presented as percentages across all included studies.

Statistical analysis. Meta-analysis was conducted on the studies, which were extracted according to the guidelines from the PRISMA group (6). In the statistical analysis of events of mortality, the proportion (prevalence) of the total participants was used as the summary statistic. The proportion (prevalence) of mortality events among participants was used as the summary statistic in order to indicate how common the condition was in the study population. A random-effects model was used for meta-analysis and inter-study heterogeneity was assessed using χ^2 and I^2 statistics. The Q-test was used for heterogeneity. Higher values of I^2 and the χ^2 statistic signified increased levels of inconsistency inter-studies and $P<0.001$ was considered to provide evidence of significant heterogeneity. Sensitivity analysis was conducted by sequentially omitting one study at a time from the analysis to evaluate its impact on the overall results and statistical significance. This approach helped identify whether any single study disproportionately influences the findings and allows for detection of potential sources of heterogeneity across the included studies. The meta-regression model was also used to determine whether gender predominance was a source of heterogeneity. Statistical analysis was performed using the 'Meta' package of R-Studio.

Risk of bias/quality assessment. The methodological quality of the observational studies was assessed using the Newcastle-Ottawa scale (https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp) by three independent reviewers (AhAA, TA and MeAA), with conflict resolution achieved through mutual consensus or, if necessary, involvement of a third party (RA). The assessment comprised three sections, totaling nine components, examining study population selection, comparability of factors and exposure ascertainment. Each section featured 2 to 4 questions with ratings as high, low or unclear risk of bias. Discrepancies in ratings underwent resolution through discussion among reviewers (RA, AhAA and TA), with external mediation available if disagreements persisted. Figs. 2 and 3 provide a comprehensive risk of bias graph and summary, revealing generally low bias risk in study selection domains, such as adequate cases and control definition. However, other aspects demonstrated a higher average of risk of bias, such as the way complications or exposures to risk factors that were identified, measured or reported in the studies, as well as the reliability of diagnostic criteria used, underscoring the need for critical assessment in observational research.

Results

Sociodemographic characteristics. This review examines the findings of 27 studies (4,7-32), offering a detailed exploration of the interplay between COVID-19 and oncology. Initially, 140 studies were identified in accordance the objective for the review with 5 studies removed due to duplication, and 83 studies removed for additional reasons such as different language and non-eligible articles like case reports and brief reviews. Following the screening of 57 studies, 24 records were further excluded, as they did not meet the inclusion criteria. A total of 33 studies were further assessed for eligibility with 6 removed for reasons including the data not matching the study's purpose. Finally, 27 studies were included in the review, as they all met the eligibility criteria. The studies show diversity in sample sizes, with the study by Lee *et al* (7), a General Community Survey, presenting an extensive pool of 1,807,559 individuals, while a more focused cross-sectional survey by Košir *et al* (8) involved 177 participants. Examining the gender distribution within the COVID-19 patient cohorts revealed noteworthy patterns. In the randomized clinical trial (9), the BNT162b2 vaccine recipients showed a notable 63.9% female majority. Conversely, a retrospective cohort study by Solaini *et al* (10) displayed a balanced distribution among COVID-19 patients. With a focus on the impact of COVID-19 on cancer patients, Mathews *et al* (11) provided a detailed breakdown of 66 positive cases, demonstrating a nearly equal gender distribution among these vulnerable individuals. Meanwhile, Lee *et al* (7) reported 155 positive cases among 23,266 individuals with cancer, emphasizing the real-world implications of the virus in this specific population (Table I).

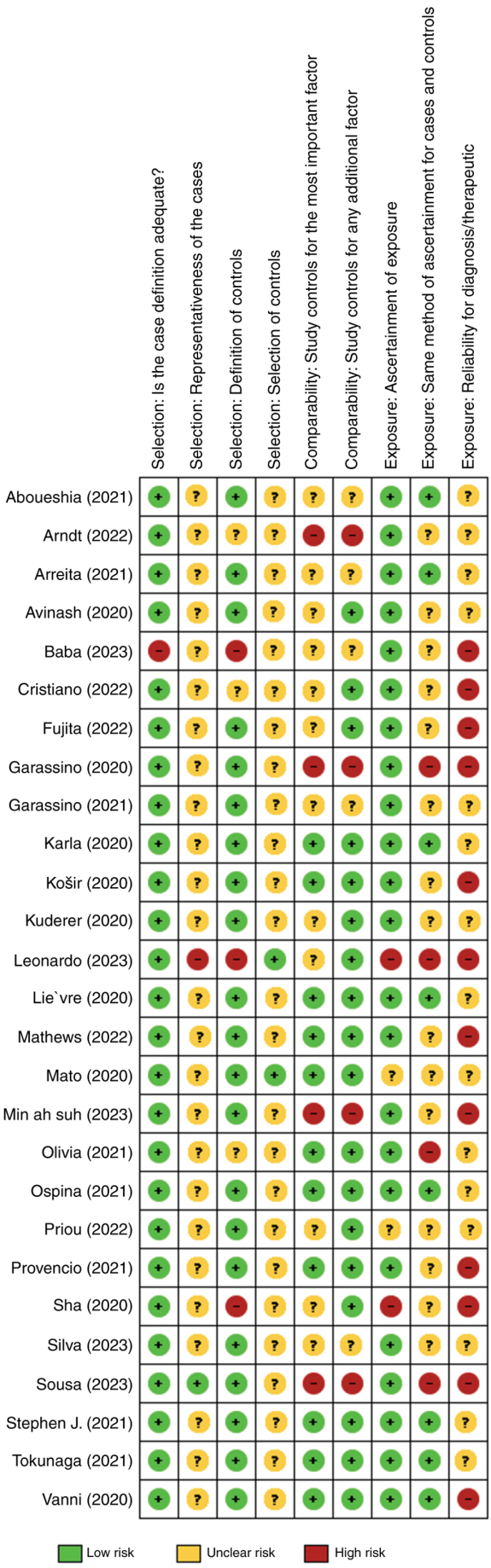

Figure 3. Risk of bias summary: Review authors' judgements about each risk of bias item for each included study.

Mortality and complications among cancer patients. This review study also encompassed various cancer types and their outcomes during the COVID-19 pandemic demonstrated in Table II, shedding light on mortality rates, treatment delays and complications. In gastric adenocarcinoma, Solaini *et al* (10) found a higher mortality rate in COVID-19 patients (5.9%) compared to pre-COVID cases (2.6%), with potential delays in diagnosis and treatment. Thomas *et al* (9) observed no mortality in patients with a history of malignancy, reporting a 94.4% vaccine efficacy but highlighting higher adverse events in vaccine recipients. Lee *et al* (7) identified a 60% increased risk of COVID-19 in cancer patients, with a twofold risk during chemotherapy/immunotherapy. Košir *et al* (8) reported a 45% impact on cancer treatment or care in adolescent and young adult patients. Decreases in cancer diagnoses and barriers to care were noted by Dinmohamed *et al* (12), while Mathews *et al* (11) reported a substantial increase in mortality for various cancers during COVID-19. Breast cancer outcomes varied, with Baba *et al* (14) finding no significant difference in critical events, while Resende *et al* (18) observed a lower prevalence of early-stage breast cancer and a higher prevalence of advanced-stage cases. In lung cancer, Sha *et al* (15) highlighted increased physical discomfort and psychological distress, and Abouesshia *et al* (16) reported higher mortality, longer hospital stays and more unplanned reintubations in COVID-19 patients. The study by Kuderer *et al* (4) on invasive or hematological malignancies indicated a mortality rate of 13%, with severe illness in 26% and ICU admissions of 14% of cancer patients with COVID-19. Vanni *et al* (21) warned of potential increases in invasive surgeries due to screening program suspensions. Patients with thoracic cancer, as per Garassino *et al* (22), faced high mortality and complications, while Tokunaga *et al* (23) noted a decrease in gastrectomies for gastric cancer due to restricted surgical spots in hospitals because of the pandemic. Lung cancer patients in the study by Priou *et al* (24) saw no significant impact of treatment delay on mortality (Study 2).

Meta-analysis revealing overall mortality. The prevalence of mortality in COVID-19-infected individuals was assessed by 10 studies comprising 5,151 cancer patients (4,10,11,14,22,28-32). The pooled proportion, under a random-effects model, was 0.1913 (95% CI: 0.1109 to 0.2718; P<0.01), indicating a significant overall mortality rate of 19.1% among cancer patients infected with COVID-19 (Fig. 4). However, substantial heterogeneity was evident (I^2=98.7%), highlighting diverse outcomes across studies. The Q-test for heterogeneity was highly significant (P<0.0001). For non-COVID-19 cancer patients, reported in 5 studies including 54,528 cancer patients (4,9,10,14,25), the overall mortality rate was as low as 1% (95% CI: 0.00 to 0.02; P<0.01) under a random-effects model (Fig. 5). However, substantial heterogeneity was observed (I^2=97.1%, P<0.01).

Regarding the risk of mortality in non-COVID-19 vs. COVID-19 cancer patients, reported by 3 studies involving 3,496 cancer patients (4,10,14), the odds ratio (OR) for mortality was 0.1036 (95% CI: 0.0061 to 1.7614; P<0.01) under a random-effects model (Fig. 6). The overall estimate suggests a potentially decreased mortality risk for non-COVID-19 patients. However, substantial heterogeneity (I^2=82.1%; P<0.01) was observed, indicating variability among studies.

Table I. Study characteristics.

Author(s), year	Type of study	Sample size	Number of COVID-19 patients	Average age, years	Sex	(Refs.)
Solaini *et al*, 2023	Retrospective cohort study	632	205	71	Male before COVID-19, 254 (59.5%); Male after COVID-19, 124 (60.5%); Female before COVID-19, 173 (40.5%); Female after COVID-19, 81 (39.5%)	(10)
Thomas *et al*, 2022	Randomized, placebo-controlled, observer-blinded global phase 3 clinical trial	46,429	0	Participants received BNT162b2 vaccine: 64.0 (16-86)	Female received BNT162b2 vaccine, 1,215 (63.9%); Female received placebo, 1,198 (62.7%); Total, 21,627 (49.1%)	(9)
Lee *et al*, 2020	General community survey	1,807,559	I) Total Individuals: With cancer, 23,266; Without cancer, 1,784,293. II) Positive COVID-19 rest reports: Among those with cancer, 155 reports; Among those without cancer, 10,249 reports	Not provided	Male without cancer, 42.7%; Male with cancer, 55.2%; Male not on chemotherapy or immunotherapy, 42.9%; Male on chemotherapy or immunotherapy, 45.8%	(7)
Košir *et al*, 2020	Cross-sectional survey	177	0	29.33	Female, 154 (87%); Male, 20 (11%)	(8)
Dinmohamed *et al*, 2020	Nationwide Netherlands cancer registry-based study	Not Mentioned	Not Mentioned	Not mentioned	Not mentioned	(12)
Mathews *et al*, 2022	Observational study	631	PCR confirmed, 628; Clinical diagnosis, 3	Patients with cancer who tested positive for COVID-19, 66; Patients who tested positive for COVID-19, 62	Male patients with cancer who tested positive for COVID-19, 248; Female patients with cancer who tested positive for COVID-19, 261; Male patients who tested positive for COVID-19, 298; Female patients who tested positive for COVID-19, 333	(11)

Table I. Continued.

Author(s), year	Type of study	Sample size	Number of COVID-19 patients	Average age, years	Sex	(Refs.)
Mendonça *et al*, 2023	Retrospective study cohort	29,796	Not mentioned	The largest number of cases occurred in males aged 55-74 years and females aged 50-69 years	Male, 11,255; Female, 13,636	(13)
Baba *et al*, 2023	Retrospective	Two groups: 120 + 384=504	504	Pre-covid, 53; Pandemic, 54	All female (504)	(14)
Sha *et al*, 2020	Retrospective	161	161	57	Male, 94; Female, 67	(15)
Aboueshia *et al*, 2021	Retrospective	260	57	58.6	Female, 52.3 %	(16)
Rucinska and Nawrocki, 2022	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned	(17)
Resende *et al*, 2022	Retrospective	11,753	11,753	Not mentioned	Most patients were females	(18)
de Sousa *et al*, 2023	Observational cross-sectional	2019: 561,039 2020: 502,766 2021: 538,993	Not mentioned	Not mentioned	Not mentioned	(19)
Arndt *et al*, 2023	Prospective panel survey	Mentioned each month in 2020-2023	Not mentioned	Not mentioned	Not mentioned	(20)
Kuderer *et al*, 2020	Cohort study	928	928	66	Female, 459 (49%); Male, 468 (50%)	(4)
Vanni *et al*, 2020	Retrospective analysis	Not mentioned	Not mentioned	Not mentioned	Not mentioned	(21)
Garassino *et al*, 2020	Cross-sectional component and a longitudinal cohort component	Not mentioned	200	68	Male, 141; Female, 59	(22)
Tokunaga *et al*, 2022	Observational study based on survey	The total number of questionnaires sent was 744, but only 74% (551 out of 744) were answered and analyzed	Not mentioned	Not mentioned	Not mentioned	(23)

Table I. Continued.

Author(s), year	Type of study	Sample size	Number of COVID-19 patients	Average age, years	Sex	(Refs.)
Priou *et al*, 2022	Retrospective multicenter cohort study	6,240	Not mentioned	68	Female, 38%	(24)
Fujita *et al*, 2022	Retrospective cohort study	725	Not mentioned	73	Male before COVID-19, 298 (71.5%); Male after COVID-19, 209 (67.9%); Female before COVID-19, 119 (28.5%); Female after COVID-19, 99 (32.1%)	(25)
Suh *et al*, 2023	Retrospective nationwide population-based study	It was mentioned indirectly by the number of esophagogastroduodenoscopies on monthly bases in 2019, 2020 and 2021	Not Mentioned	Not mentioned	Not mentioned	(26)
Lara *et al*, 2021	Multi-institutional, retrospective, observational cohort study	193	193	65	Not mentioned	(27)
Arrieta *et al*, 2021	Prospective cohort study	548	66	Mean: 61.5±12.9	Female, 312; Male, 236	(28)
Provencio *et al*, 2021	Prospective observational study	447	447	Mean: 67.1±9	Male, 332; Female, 115	(29)
Mato *et al*, 2020	International cohort study, multicentric	198	198	Mean: 70.5 (38-98)	Male, 63%; Female, 37%	(30)
Ospina *et al*, 2021	Analytical cohort study	742	720	Not mentioned	Female, 403; Male, 339	(31)
Lièvre *et al*, 2020	Retro-prospective cohort study	1,289	1,289	Mean: 67 (19-100)	Female, 494; Male, 795	(32)

COVID-19, coronavirus disease 2019.

Table II. Outcomes for cancer patients.

Study author and year	Type of cancer	Mortality in cancer patients (without COVID-19)	Mortality in COVID cancer patients	Delay in treatment	Complications and conclusion	(Refs.)
Solaini *et al*, 2023	Gastric adenocarcinoma	Pre-COVID-19 pandemic: Mortality occurred in 10 cases (2.6%)	Mortality occurred in 9 cases (5.9%)	Potential delays in diagnosis and treatment	Longer median times from diagnosis to diagnostic work-up, chemotherapy and operation; Higher rate of conversion to open surgery	(10)
Thomas *et al*, 2022	History of past or active malignancy, including malignant tumors, benign tumors and other non-specific neoplasms.	0	0	Not mentioned	94.4% vaccine efficacy in participants with neoplasm history; 3 COVID-19 cases in participants with malignancy; Higher vaccine-related adverse events in BNT162b2 recipients	(9)
Lee *et al*, 2021	Not specific	Not mentioned	Not mentioned	Higher risk in older participants and males; Symptom-based prediction models indicating higher likelihood of predicted COVID-19	60% increased risk of testing positive for COVID-19 in cancer patients; Twofold increased risk with chemotherapy/ immunotherapy; Higher risk of hospitalization	(7)
Košir *et al*, 2020	Not specific	Not mentioned	Not mentioned	Postponed/canceled follow-up appointments, virtual appointments, postponed cancer treatment/ surgery, changes in treatment protocols	45% of adolescent and young adult patients reported an impact on cancer treatment or care	(8)
Dinmohamed *et al*, 2020	Statistics of head and neck cancers, gastrointestinal cancers, lung cancer, breast cancer, gynecologic cancers, urological cancers, hematological cancer and skin cancers	Not mentioned	Not mentioned	Not mentioned	Decrease in cancer diagnoses; Barriers to consultation, transition to telehealth, resource reallocation; Temporary halt of national screening programs	(12)

Table II. Continued.

Study author and year	Type of cancer	Mortality in cancer patients (without COVID-19)	Mortality in COVID cancer patients	Delay in treatment	Complications and conclusion	(Refs.)
Mathews *et al*, 2022	Breast, gastrointestinal, lung, lymphoma, genitourinary, gynecologic, leukemia, CNS and other (including thyroid cancer, skin cancer, liposarcoma, head and neck cancer, carcinoma of unknown primary origin).	17	49	Not mentioned	Not mentioned	(11)
Mendonça *et al*, 2023	Non-melanoma skin, breast, thyroid, prostate, melanoma skin, colorectal, lung, cervix uteri, kidney, stomach, oral cavity, oropharynx, larynx	Not mentioned	Not mentioned	Rapid screening and prevention measures necessary	Newly diagnosed cases declined; Changes in the stage of newly diagnosed cancers	(13)
Baba *et al*, 2023	Breast cancer	2	7	Not mentioned	No significant difference in the incidence of critical events	(14)
Sha *et al*, \2020	Lung cancer	Not mentioned	Not mentioned	Not mentioned	Cancer patients experienced increased physical discomfort and psychological distress due to the pandemic's impact on their treatment and overall well-being	(15)
Aboueshia *et al*, 2021	Not specific	Not mentioned	7	Higher frequency of unplanned reintubation and longer hospital stays in cancer patients with COVID-19	Obesity and active smoking associated with increased risk of mortality	(16)
Rucinska and Nawrocki, 2022	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned	(17)

Table II. Continued.

Study author and year	Type of cancer	Mortality in cancer patients (without COVID-19)	Mortality in COVID cancer patients	Delay in treatment	Complications and conclusion	(Refs.)
Resende *et al*, 2022	Breast cancer	Not mentioned	Not mentioned	Potential delay in diagnosis and treatment initiation	The study found a lower prevalence of early-stage breast cancer (stage I-II) and a higher prevalence of advanced-stage breast cancer (stage IV) during the COVID-19 pandemic compared to the pre-pandemic period	(18)
de Sousa *et al*, 2023	Not specific	Not mentioned	Not mentioned	Mortality may be more related to SARS-CoV-2 infection itself than to treatment delays	There was a significant stage shift towards more advanced stages (III and IV) in 2020 and 2021	(19)
Arndt *et al*, 2023	Not mentioned	Not mentioned	Not mentioned	Delay in diagnostic work-up	The provision of care was reduced by 21% in the area of aftercare, by 12% in psycho-oncological care and by 9% with respect to tumor surgery compared to the time before COVID-19	(20)
Kuderer *et al*, 2020	Invasive or hematological malignancy	0	121 (13%) patients had died, all within 30 days of COVID-19 diagnosis	116 (12%) required mechanical ventilation	242 (26%) patients met the composite severe illness endpoint and 132 (14%) patients were admitted to the ICU	(4)
Vanni *et al*, 2020	Breast cancer	Not mentioned	Not mentioned	Not mentioned	Due to suspension of screening programs, an increase in size and stage of breast cancer presentation was observed, which may have led to an increase in more invasive surgeries	(21)
Garassino *et al*, 2020	Any thoracic cancer (NSCLC, SCLC, mesothelioma, thymic epithelial tumors and other pulmonary neuro-	Not mentioned	66 (33%)	31 (53%) of 58 hospitalized patients with data on complete length of stay had a prolonged hospitalization, defined as longer than 8 days	High mortality and low admission to intensive care in patients with thoracic cancer. 13 (10%) of these patients were admitted to the ICU.	(22)

Table II. Continued.

Study author and year	Type of cancer	Mortality in cancer patients (without COVID-19)	Mortality in COVID cancer patients	Delay in treatment	Complications and conclusion	(Refs.)
	endocrine neoplasms)				Complications: Pneumonia or pneumonitis, 125/157 (80%); acute respiratory distress syndrome, 42/157 (27%); multi-organ failure, sepsis, coagulopathy, bacterial, infection, arrhythmia, heart failure	
Tokunaga *et al*, 2022	Gastric cancer	Not mentioned	Not mentioned	The number of gastrectomies during the study period was <80% that of the previous year	The number of gastrectomies was lower than that in the previous year	(23)
Priou *et al*, 2022	Lung cancer	Overall mortality during 2018-2019, 125 (2%)	Not mentioned	The mortality may have been more related to SARS-CoV-2 infection itself than to any treatment delays	The rates of non-metastatic lung cancer patients under going tumor resection, non-surgical multimodal treatment and best supportive care before vs. after the outbreak reached 42 vs. 42%, 49 vs. 50% and 9 vs. 8%, respectively.	(24)
Fujita *et al*, 2022	Gastric cancer	Not mentioned	Not mentioned	The median time to treatment was significantly shorter in patients during the COVID-19 pandemic (P<0.001)	In Japan, delays in diagnosing patients with gastric cancer, probably due to refraining from consultation, may have resulted in an increase in the diagnosis of advanced-stage cancer. Furthermore, an increasing proportion of patients required more invasive gastrectomy.	(25)
Suh *et al*, 2023	Gastric cancer	Not mentioned	Not mentioned	Not mentioned	The oncologic outcomes of gastric cancer during the COVID-19 pandemic may become worse, as many cases	(26)

Table II. Continued.

Study author and year	Type of cancer	Mortality in cancer patients (without COVID-19)	Mortality in COVID cancer patients	Delay in treatment	Complications and conclusion	(Refs.)
					of esophagogastroduodenoscopy and gastric cancer management were suspended or delayed	
Lara *et al*, 2022	Gynecologic cancer (including endometrial, ovarian, cervical and vulvar cancer)	Not mentioned	34 (17.6%)	Not mentioned	The most common complications secondary to COVID-19 infection were pulmonary, cardio vascular and renal	(27)
Arrieta *et al*, 2021	Lung cancer, mesothelioma or thymomas	Not mentioned	61	The impact of COVID-19 on cancer care is evident in the observed delays and challenges	Patients with treatment adjustments during the studied period experienced a median PFS of 10.9 months, while those without modifications had an unreached median PFS	(28)
Provencio *et al*, 2021	NSCLC, SCLC, other lung cancers	Not mentioned	146 (32.7%)	350 (78.3%) patients were hospitalized, with a length of stay of 13.4±11.4 days	Nine of the 447 (2.0%) patients were admitted to the ICU	(29)
Mato *et al*, 2020	Chronic lymphocytic leukemia	Not mentioned	66 deaths were observed (33% case fatality rate) for this population identified with symptomatic COVID-19	Not mentioned	COVID-19-directed therapies were administered as part of a clinical trial or compassionate use protocol in 16 and 19% of patients, respectively. Antiviral ritonavir (17%) and remdesivir (7%)	(30)
Ospina *et al*, 2021	Types of malignancy: Breast, colorectal, prostate, head and neck, gastric, lung, cervix, sarcoma, renal, ovary, melanoma, nonmelanoma skin, neuroendocrine, anal vesicle, esophagus, osteosarcoma, thymus, gastrointestinal,	Not mentioned	96 (26.3%)	The frequency of mechanical ventilation was higher as the decade of age increased from 50 years, with a slight decrease after 70 years; a high frequency of invasive ventilatory support was found in the group aged 31-40 years	Secondary outcomes included the requirement for noninvasive mechanical ventilation and the requirement for invasive mechanical ventilation. A higher frequency of invasive ventilation was evidenced in men.	(31)

Table II. Continued.

Study author and year	Type of cancer	Mortality in cancer patients (without COVID-19)	Mortality in COVID cancer patients	Delay in treatment	Complications and conclusion	(Refs.)
	cholangiocarcinoma, penis, appendix, small intestine, mesothelioma, adrenal gland, giant cells, CNS, hepatocarcinoma, thyroid, bladder, uterus, germ, pancreas, and unknown primary					
Lièvre *et al*, 2020	Solid malignant tumor	Not mentioned	370 (29%)	412 (42%) patients required oxygen and 49 (5%) mechanical ventilation	Mortality and COVID-19 severity in cancer patients are high and are associated with general characteristics of patients	(32)

PFS, progression-free survival; ICU, intensive care unit; COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; CNS, central nervous system; NSCLC, non-small cell lung cancer.

Influential analysis (sensitivity analysis) was identified by Kuderer *et al* (4) as a potential source of heterogeneity, and its omission led to a lower pooled estimate (0.45, 95% CI: 0.20 to 0.99; P<0.01), implying a subgroup with lower mortality risk (Fig. 7).

Discussion

In this comprehensive review of the intersection of cancer and COVID-19, the findings revealed the complex dynamics influencing outcomes among cancer patients during the pandemic. The variation in sample sizes across studies, exemplified by the general community survey conducted with an extensive pool of 1,807,559 individuals and the more focused cross-sectional survey by Košir *et al* (8) involving 177 participants, underscores the diverse methodologies of different geographical samples and various health care systems employed in understanding this intersection. The randomized clinical trial reported by Thomas *et al* (9) revealed a significant 63.9% female majority among BNT162b2 vaccine recipients, while the retrospective cohort study conducted by Solaini *et al* (10) showcases a balanced distribution among COVID-19 patients. Shifting the focus to the impact of COVID-19 on cancer patients, Mathews *et al* (11) break down 66 positive cases, revealing a nearly equal gender distribution within this vulnerable group. Simultaneously, Lee *et al*'s (7) report on 155 positive cases among individuals with cancer accentuates the tangible real-world implications of the virus within this specific population. These findings collectively contribute to our understanding of the interplay between COVID-19 and oncology.

This study thoroughly investigated the variability in outcomes among different cancer types, particularly focusing on why certain cancers, such as gastric adenocarcinoma and thoracic cancers, may exhibit higher mortality rates in COVID-19 patients. It provided an analysis of the biological and clinical factors that could contribute to these disparities. For instance, the aggressive nature of these cancers, combined with the immunosuppressive effects of both the disease and its treatments, could exacerbate the severity of COVID-19. The manuscript explores how these patients' pre-existing conditions and the potential delay in diagnosis due to the pandemic may have contributed to their heightened vulnerability.

The present study also discusses the impact of COVID-19 on cancer management and treatment decisions. It shows how the pandemic has forced alterations in standard treatment protocols, including delays in surgery, modifications in chemotherapy regimens and the adoption of telemedicine for consultations. It also sheds light on the ethical dilemmas faced by oncologists in prioritizing treatment for patients with a higher chance of survival during resource-scarce periods. Furthermore, insights into how COVID-19 has affected surgical trends and the implementation of chemotherapy protocols are well-documented, emphasizing the need for adaptive strategies in oncological care during global health crises.

In gastric adenocarcinoma, Fox *et al* (2022) revealed a higher mortality rate in COVID-19 patients compared to the pre-COVID era, underscoring the challenges posed by potential delays in diagnosis and treatment (33). This aligns with earlier studies emphasizing the importance of timely intervention in

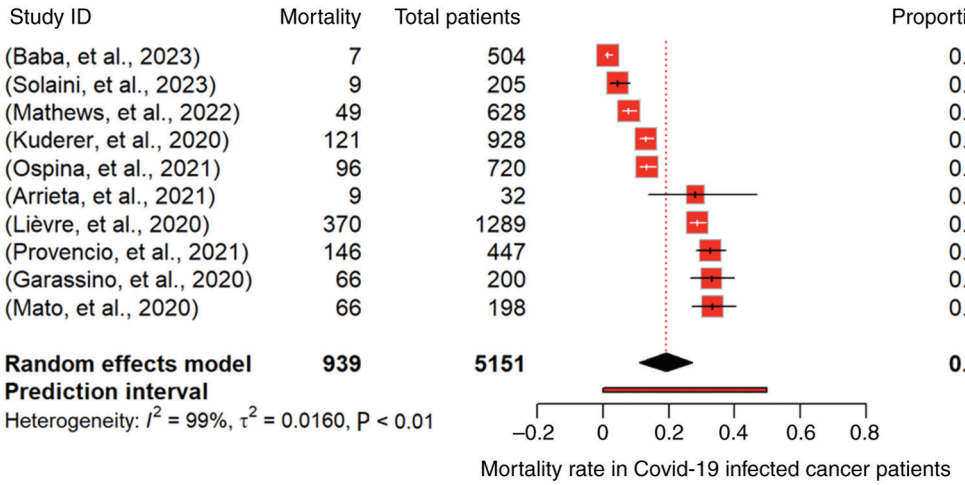

Figure 4. Forest plot showing the proportion of mortality among COVID-infected cancer patients. COVID-19, coronavirus disease 2019.

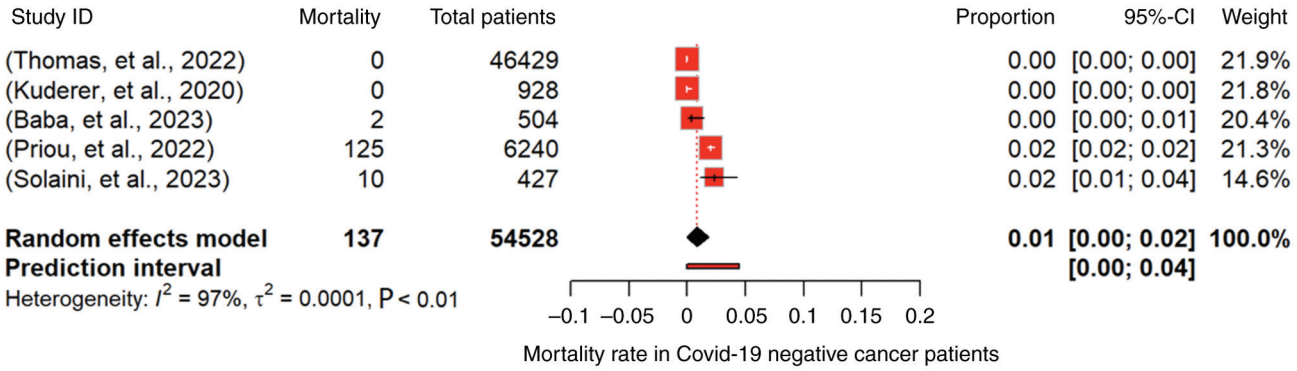

Figure 5. Forest plot showing the proportion of mortality among non-COVID-19 cancer patients. COVID-19, coronavirus disease 2019.

gastric cancers to improve survival rates (34,35). The observation of Thomas *et al* (9) of no mortality in individuals with a history of malignancy, coupled with high vaccine efficacy, corroborates with previous research on the potential protective effects of vaccinations in cancer patients (36).

The increased risk of COVID-19 in cancer patients, as reported by Lee *et al* (7), echoes concerns raised in earlier studies about the vulnerability of cancer patients to infectious diseases (37,38). Košir *et al*'s (8) identification of a substantial impact on adolescent and young adult cancer patients aligns with broader discussions on the unique challenges faced by this demographic group during the pandemic (39,40). The decrease in cancer diagnoses and barriers to care highlighted by Dinmohamed *et al* (12) resonates with concerns raised in the early stages of the pandemic regarding disruptions to routine healthcare services and the downstream effects on cancer outcomes (41,42).

Breast cancer outcomes, as reported by Baba *et al* (14) and Resende *et al* (18), showcase the variability in responses to the pandemic. While the former found no significant difference in critical events, the latter identified a stage shift towards more advanced cases. These findings contribute to the ongoing discourse on the multifaceted impacts of COVID-19 on breast cancer patients, necessitating tailored approaches to care (43,44).

In lung cancer, the increased physical discomfort and psychological distress reported by Sha *et al* (15) highlight the broader mental health implications of the pandemic on cancer patients, an aspect that has gained prominence in recent literature (45). Aboueshia *et al* (16) findings of higher mortality, longer hospital stays and increased unplanned reintubations in COVID-19 patients with lung cancer emphasize the need for targeted interventions in this vulnerable population, aligning with prior research on the intersection of respiratory diseases and COVID-19 outcomes (46,47).

The study by Kuderer *et al* (4) on invasive or hematological malignancies signifies the severity of COVID-19 in this patient group. The observed mortality, severe illness and ICU admissions are consistent with earlier reports on the heightened risks faced by individuals with hematological malignancies during the pandemic (48). Vanni *et al* (21) caution about potential increases in invasive surgeries due to screening program suspensions, which echoes broader concerns about the collateral damage on cancer care caused by pandemic-related disruptions (49).

The association between hemogram parameters and COVID-19 infection has been examined in various studies (50), and parameters including the platelet-to-lymphocyte ratio (51) were found to be related to the infection. Furthermore, the red cell distribution width, a marker of anisocytosis in the

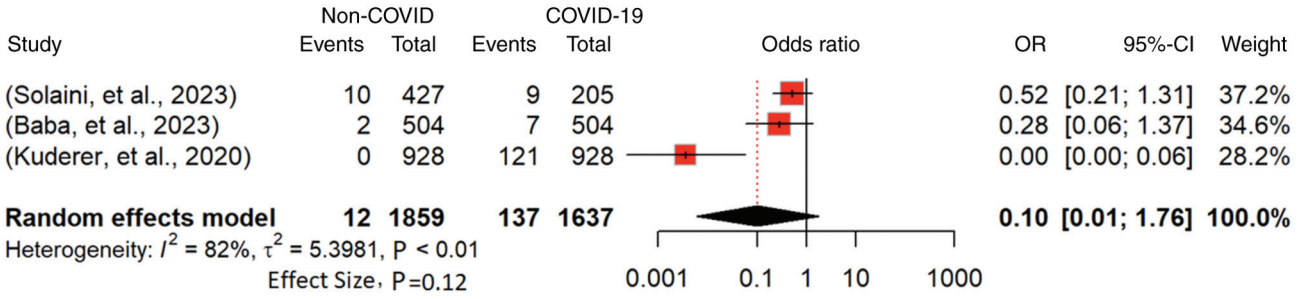

Figure 6. Forest plot showing the OR of mortality between non-COVID-19 vs. COVID-19 cancer patients (events=deaths). OR, odds ratio; COVID-19, coronavirus disease 2019.

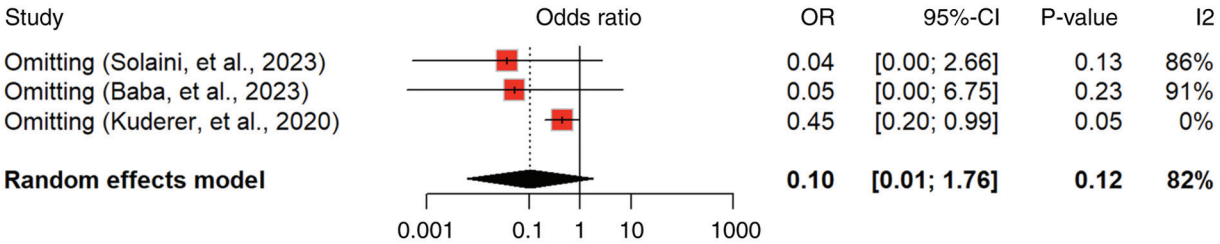

Figure 7. Forest plot showing sensitivity analysis to find sources of heterogeneity. OR, odds ratio.

hemogram, has been associated with recurrent hospitalizations of patients with COVID-19 (52). Other inflammatory markers were introduced as predictors of frailty in diabetics during COVID-19 (53). In addition, the role of inflammation in cancer has been reported in various studies (54,55). Furthermore, mortality is increased when markers of inflammation are elevated (56).

The high mortality and complications faced by patients with thoracic cancer, as highlighted by Passaro *et al* (57), underscore the critical need for specialized care in this population. Previous studies reinforce the consistent challenges faced by patients with thoracic cancer (3), emphasizing the importance of maintaining continuity in care during pandemics (58). Tokunaga *et al*'s (23) finding of a decrease in gastrectomies for gastric cancer aligns with concerns about reduced access to surgical interventions during the pandemic, potentially impacting long-term outcomes (59,60).

Mullangi *et al*'s (61) study on patients with lung cancer presents a unique perspective, suggesting that mortality may be more related to SARS-CoV-2 infection itself rather than to treatment delays. This observation prompts further investigation into the specific factors contributing to mortality in patients with lung cancer during the pandemic, providing a basis for tailored interventions (62).

The present meta-analysis accounts for various potential confounding factors, including age, comorbidities and cancer stage, when comparing mortality rates between COVID-19-infected cancer patients and their non-COVID counterparts. The study used multivariate analysis to determine the impact of COVID-19 on cancer outcomes, ensuring that the differences observed are not merely due to these confounders. This methodological approach enhances the reliability of the findings, providing a clearer understanding of how COVID-19 specifically affects cancer mortality rates.

The pooled analysis of 10 studies involving 5,151 cancer patients infected with COVID-19 reveals a significant overall mortality rate of 19.1%. This finding is consistent with emerging evidence highlighting the high vulnerability of cancer patients to severe outcomes of COVID-19 (63). However, the substantial heterogeneity (I^2=98.7%) suggests diverse outcomes across these studies, emphasizing the need for nuanced interpretations. The observed variability may be attributed to differences in patient populations, cancer types, treatment modalities and healthcare infrastructure among the included studies. The low P-value for the Q-test for heterogeneity further underscores the significance of this observed heterogeneity (P<0.0001). This variability underscores the complexity of the interaction between COVID-19 and cancer, necessitating tailored approaches to patient care (64).

By contrast, the overall mortality rate among non-COVID cancer patients, as reported by 5 studies comprising 54,528 individuals (4,9,10,14,24), was considerably lower at 0.01 (1%). This finding aligns with prior research suggesting that cancer patients not infected with COVID-19 experience relatively lower mortality rates (65). However, similar to the COVID-19-infected group, substantial heterogeneity is observed (I^2=97.1%, P<0.0001). The wide range of mortality rates among non-COVID cancer patients could be attributed to variations in cancer types, stages and treatment responses.

Regarding the risk of mortality, the OR for non-COVID vs. COVID cancer patients was 0.1036 (95%CI: 0.0061 to 1.7614) based on 3 studies involving 3,496 cancer patients. The overall estimate suggests a potential decrease in mortality risk for non-COVID patients, indicating that cancer patients not infected with COVID-19 may have a comparatively lower risk of mortality (66). However, the substantial heterogeneity (I^2=82.1%) signals variability among studies. Sensitivity analysis identified the study by Kuderer *et al* (4) as a potential

source of heterogeneity. Its omission led to a lower pooled estimate (0.4473, 95% CI: 0.2026 to 0.9878), implying a subgroup with a lower mortality risk among non-COVID cancer patients. This underscores the importance of considering the characteristics of individual studies and potential sources of heterogeneity in meta-analyses to derive more accurate and clinically relevant conclusions. The identification of a subgroup with a lower mortality risk could guide further research into factors influencing outcomes in cancer patients not infected with COVID-19.

This study clarifies that while COVID-19 may worsen the prognosis for cancer patients, the mechanisms by which it does so differ significantly from other chronic diseases. For instance, the immune dysregulation caused by cancer and its treatment can create a unique vulnerability to COVID-19 that is not present in other conditions. It integrates these distinctions into its broader analysis, providing an understanding of the intersection between cancer and COVID-19.

This study carries significant implications for both clinical practice and public health. The observed high vulnerability of cancer patients to severe outcomes underscores the need for tailored interventions and prioritized care. Clinicians should be mindful of potential delays in diagnosis and treatment, particularly in gastric adenocarcinoma, and consider personalized strategies for diverse patient cohorts, as exemplified by the variability in breast cancer responses. Furthermore, the study highlights the broader mental health implications of the pandemic on lung cancer patients, emphasizing the importance of holistic care approaches. These implications necessitate ongoing efforts to integrate pandemic-specific considerations into cancer care protocols and public health strategies. The manuscript suggests that guidelines are updated to reflect the challenges posed by COVID-19, such as ensuring timely treatment while minimizing infection risks. Recommendations for improving patient outcomes may include vaccination strategies tailored to cancer patients (10,14,18,21,23,25,26).

Future research should explore specific factors influencing mortality in patients with lung cancer during the pandemic, building on the unique perspective presented by Priou *et al* (24). Additionally, there is a critical need for comprehensive studies investigating the long-term mental health impacts on lung cancer patients, informed by Sha *et al*'s (15) findings. Exploring the collateral damage on cancer care, as raised by Vanni *et al* (21), requires in-depth investigations into the consequences of disruptions in cancer screening programs. Not all of the studies included in the present analysis adequately controlled for key confounding factors, which could have led to the introduction of bias into the pooled estimates. This variability in controlling for confounders, such as patient demographics, disease severity, cancer stage, comorbidities and treatment history, may impact the comparability of the study's outcomes and the overall robustness of the study's findings. In order to improve the reliability and accuracy of future research, the usage of more rigorous and multivariate models may be recommended, which can better adjust for these critical confounders, as it will ensure that the observed associations more accurately reflect true causal relationships. In addition, further research should focus on understanding the characteristics of the subgroup with a lower mortality risk among non-COVID cancer patients, providing insights for targeted interventions. Long-term outcomes in patients with thoracic cancer, as emphasized by Garassino *et al* (22), warrant dedicated research efforts to ensure continuous and specialized care during pandemics and other healthcare disruptions.

Despite the comprehensive nature of the systematic review and meta-analysis, several limitations need to be acknowledged. The inherent heterogeneity across the included studies highlights the diverse patient populations, cancer types and treatment modalities considered. This heterogeneity underscores the challenge of synthesizing data from studies with varying methodologies and emphasizes the need for cautious interpretation. The reliance on published literature may introduce publication bias, as studies with positive or statistically significant results are more likely to be published. This potential bias may affect the generalizability of findings and should be considered when extrapolating conclusions to the broader population. The dynamic nature of the COVID-19 pandemic may introduce temporal biases, with outcomes influenced by evolving healthcare practices, treatments and vaccination strategies. Furthermore, the limitations of the individual studies, such as varying sample sizes and methodologies, could impact the overall robustness of the meta-analysis. In addition, the COVID-19 pandemic has had significant effects on the various aspects of oncological care, which include chemotherapy protocols and surgical trends. For instance, surgical delays or changes and modifications in chemotherapy administration schedules have been widely reported as adaptations in order to mitigate the risk of infection and to manage healthcare resource limitations. However, due to the constraints of the included studies in the current study, which often lacked detailed information on these particular treatment adjustments, the present analysis was unable to comprehensively evaluate the extent of these pandemic-related impacts. Despite these limitations, the present study provides valuable insights into the intersection of COVID-19 and oncology, offering a foundation for future research and clinical considerations.

In conclusion, the present review signifies the high vulnerability of cancer patients to severe outcomes from COVID-19, emphasizing the need for tailored interventions and prioritized care. The variability in outcomes across different cancer types and patient cohorts highlights the nuanced nature of this intersection. Noteworthy patterns emerge, such as the differential mortality rates in gastric adenocarcinoma patients during the pandemic and the varied outcomes for vaccine recipients with a history of malignancy. The increased risk of COVID-19 among cancer patients, particularly during chemotherapy/immunotherapy, highlights the vulnerability of this population. This study not only informs immediate clinical considerations but also sets the stage for future research, aimed at refining the current understanding of the interaction between COVID-19 and oncology, ultimately improving outcomes for this vulnerable population.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

RAA: Protocol preparation and submission, manuscript writing, proofreading, reviewing, editing, finalization of the study. AhAA: Screening, data extraction, reviewing collected data, manuscript writing. NIA: Data extraction, reviewing collected data, manuscript writing. TAA, MeAA and MoAA: Screening, data extraction, reviewing collected data, manuscript writing. MMMA, AbAA and LA: Data extraction, reviewing collected data, manuscript writing. NAA: Proofreading the manuscript, reviewing data, finalization of the study. All authors have read and approved the final version of the study. RAA and AhAA confirm the authenticity of the raw data.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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