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ORIGINAL ARTICLE

The impact of cancer on the severity of disease in patients affected with COVID-19: an umbrella review and meta-meta-analysis of systematic reviews and meta-analyses involving 1,064,476 participants

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Abstract

During the COVID-19 pandemic, cancer patients were among the most vulnerable patient groups to the SARS-CoV-2 infection effects. This paper aimed to conduct an umbrella review and meta-meta-analysis to determine the severity of disease in cancer patients affected by COVID-19. The umbrella review and meta-meta-analysis were undertaken according to the PRISMA and MOOSE guidelines. The PubMed/Medline, Web of Science, and Scopus databases were searched for published papers from the start of the pandemic through July 18, 2022. The pooled effect sizes (ES) and odds ratios (ORs) were calculated using a random effect model in the 95% confidence interval (CI) for ICU (Intensive Care Unit) admissions and mortality in cancer patients infected with SARS-CoV-2. Egger's linear regression test, schematic illustrations of funnel plots, and Begg and Mazumdar's rank correlation tests were used to quantify the possibility of publication bias. The pooled ES was calculated based on 1,031,783 participants, and mortality was significantly increased in cancer patients affected by COVID-19 (OR = 2.02, %95 CI: 1.74–2.35, $p < 0.001$). The pooled ES for ICU admission was also significantly increased in cancer patients infected with SARS-CoV-2 (OR = 1.84, %95 CI: 1.44–2.34, $p < 0.001$). As a result, this synthesis of systematic reviews and meta-analyses by the meta-meta-analysis method revealed that disease severity is higher in cancer patients affected by COVID-19. Since cancer patients are a more sensitive and specific patient group, they should be evaluated more carefully, especially during the COVID-19 pandemic and other pandemics that may occur in the future.

Keywords SARS-CoV-2 · COVID-19 · Cancer · ICU admission · Mortality

Introduction

The World Health Organization (WHO) reported the coronavirus disease 2019 (COVID-19) outbreak as a pandemic in early 2020, after a case was discovered in China on December 12, 2019 [1–6]. The virus that causes COVID-19 disease was called SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2). The COVID-19 pandemic has caused enormous morbidity and mortality all over the world [7]. WHO documented that COVID-19 worldwide mortality had reached 6.3 million by July 2022 [1].

Cancer, which includes several disorders such as abnormal cell development and an unregulated cell cycle, is still one of the leading causes of mortality globally [8]. During the pandemic, cancer patients were among the most vulnerable patient groups to the SARS-CoV-2 infection effects [2, 3, 5, 6, 9]. The vast majority of patients suffering from

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COVID-19 have experienced respiratory symptoms of varying severity. Furthermore, approximately 14% of COVID-19 patients experienced severe symptoms that could result in death [10–12]. In recent studies, the severity and prognosis of the disease are worse in COVID-19 patients with various comorbidities such as cancer, diabetes, and chronic heart diseases [12–15].

In meta-analyses with samples of various sizes published in the literature, it was reported that cancer increased susceptibility to SARS-CoV-2 infection and underlined that it is a risk factor for poor clinical outcomes in COVID-19 patients [16–25]. There has been a considerable increase in the number of meta-analyses reporting the severity of COVID-19 on cancer patients. Numerous meta-analyses have been published, reporting both death and ICU admission rates in cancer patients by COVID-19 [16–25]. Therefore, these meta-analyses need to be combined with an umbrella review and meta-meta-analysis method and re-evaluated with increased power. In this regard, we aimed to examine the severity of COVID-19 on cancer patients in a large sample size and comprehensively. This paper aimed to conduct an umbrella review and meta-meta-analysis to determine the severity of disease in cancer patients affected with COVID-19.

Materials and methods

Design, study selection and data extraction

Public health policies are formed by evaluating systematic reviews and meta-analyses, which are considered the highest levels of evidence. Therefore, we identified the most recent systematic reviews and meta-analyses evaluating the severe effects (fatal and/or ICU (Intensive Care Unit) admissions) of COVID-19 on cancer patients. The umbrella review and meta-meta-analysis were undertaken according to the "Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA)" [26] and "Meta-analysis of Observational Studies in Epidemiology (MOOSE)" [27] guidelines. The PRISMA checklist is included in Supplemental Table S3 [28].

The PubMed/Medline, Web of Science, and Scopusdatabases were searched from the start of the pandemic through July 18, 2022, using the search terms"SARS-CoV-2," "COVID-19," "coronavirus," "severe acute respiratory syndrome coronavirus 2," "2019 ncov,""cancer," "tumor," "neoplasms," "malignancy," "ICU admission," "mortality," "death," and "meta-analysis." Medical Subject Headings (MeSH) and text terms were included in the search strategy using Boolean operators (AND/OR). The search strategies determined according to the relevant databases are presented in Supplemental Table S1. Systematic reviews and meta-analyses were required to report the serious effects of COVID-19 on cancer patients and to report at least one outcome related to ICU admission and/or mortality by the meta-analysis method. Systematic reviews without meta-analysis were not included in the study. Two independent researchers (MEA and HE) synthesized the results reported by each systematic review and meta-analysis and processed the data into a pre-defined and structured Microsoft Excel® spreadsheet.

Risk of bias and quality evaluation

The quality and risk of bias of the included systematic reviews and meta-analyses were assessed by two independent investigators using "The Newcastle–Ottawa Scale (NOS) for Assessing the Quality of Nonrandomized Studies in Meta-Analyses" [29]. After removing all the data from the included studies, the two researchers independently cross-checked all the data to reach consensus.

Outcomes

The primary outcome was the reporting of data on mortality in systematic reviews and meta-analyses. The secondary outcome was reporting data on ICU admissions. Reported outcomes should have been reported as odds ratios (ORs) or risk ratios (RRs).

PICOS:

1. *Population* "Patients with cancer and non-cancer affected with COVID-19"
2. *Intervention* "Cancer"
3. *Comparison* "Non-cancer"
4. *Outcomes* (i) "SARS-CoV-2 infection risk in cancer patients"; (ii) "COVID-19 severity risk, including: ICU admission / mortality risk."
5. *Study* "Systematic reviews and meta-analyses"

Statistical analysis

All statistical analyses in the meta-meta-analysis were carried out using ProMeta 3® [30] and R, version 4.0.4 (R Foundation for Statistical Computing), for MacOS. The pooled effect sizes (ES) and ORs were calculated in the 95% confidence interval (CI) for ICU admissions and mortality in cancer patients infected with SARS-CoV-2. Study heterogeneity was assessed using the I^2 statistics and Cochran's Q test and classified as follows: $I^2 \geq 50\%$ and $p < 0.10$ = significant heterogeneity [31]. If significant heterogeneity was detected in the meta-meta-analysis statistical analysis, the random effect model was used, and if there was no significant heterogeneity, the fixed effect model method was used.

In order to test the reliability of the study results, sensitivity analyses were performed in which all studies were excluded from the analysis separately. In addition, the research results were analyzed separately with a cumulative analysis. In the meta-meta-analysis, Egger's linear regression test, schematic illustrations of funnel plots, and Begg and Mazumdar's rank correlation tests, which report the z value for Kendall's tau, were used to quantify the possibility of publication bias. A two-sided $p < 0.05$ was used to determine statistical significance.

Results

Search results

We identified 570 papers (Web of Science: 172, PubMed/Medline: 181, Scopus: 217) from the initial search in related databases, of which 241 were excluded for duplicate records and title and abstract. Of the twenty-seven articles whose full texts were reviewed in detail, ten [16–25] of the studies that met the inclusion criteria, hospitalization in the ICU was reported. Relevant literature searches and the study selection process are illustrated in Fig. 1. The major outcomes and study characteristics of the included studies in the umbrella review and meta-meta-analysis are available in Table 1.

The number of research and participants of the studies included in the meta-meta-analysis is as follows: a total of 58 studies and 709,908 participants were included in the meta-analysis performed by Arayici et al. [16], a total of 81 primary research and 61,532 individuals were included in the meta-analysis performed by Khoury et al. [17], a total of 35 studies and 142,355 participants were included in the meta-analysis performed by Di Felice et al. [18], a total of 57 papers and 63,413 participants were included in the meta-analysis performed by Han et al. [20], a total of 26 studies and 181,323 participants were included in the meta-analysis performed by Venkatesulu et al. [21], a total of 19 studies and 63,019 individuals were included in the meta-analysis performed by Yang et al. [22], a total of 13 papers and 3,775 participants were included in the meta-analysis performed by Salunke et al. [24], a total of 38 primary research and 7,094 participants were included in the meta-analysis performed by Tian et al. [23], a total of 32 research and 46,499 participants were included in the meta-analysis performed by Giannakoulis et al. [19], and a total of 14 papers and 29,900 participants were included in the meta-analysis performed by Parohan et al. [25].

Information on the quality risk assessments of the articles included in the meta-meta-analysis is presented in Supplemental Table S2. Fig. S5 and Fig. S6 also show a bubble chart illustrating the distribution of papers by year.

Outcomes

Mortality in patients with cancer affected by COVID-19

A total of 10 systematic reviews and meta-analyses [16–25] assessed the association between COVID-19 and mortality of cancer patients. The pooled ES was calculated based on 1,031,783 participants, and mortality was significantly increased in cancer patients affected by COVID-19 (OR = 2.02, %95 CI: 1.74–2.35, $p < 0.001$) (Fig. 2). Significant and moderate heterogeneity were detected in the analysis results (Q = 23.30, df = 9, $I^2 = 61.38\%$, $p < 0.001$). Therefore, the analysis was carried out using the random effect model. No significant publication bias was found according to Egger's linear regression test and Begg and Mazumdar's rank correlation test (Eggers's test: intercept = 0.88, t = 0.87, $p = 0.464$; Begg and Mazumdar' test: z value for Kendall's tau = 0.27, $p = 0.788$) (Supplemental Fig. S1). A sensitivity analysis was performed, excluding each study from the analysis. Sensitivity analysis confirmed the robustness of the test results (Fig. 3). A cumulative analysis was also performed according to the sample size and is presented visually in Supplemental Fig. S2.

ICU admission in patients with cancer affected by COVID-19

A total of five systematic reviews and meta-analyses [16, 18, 19, 21, 24] assessed the association between COVID-19 and ICU admission for cancer patients. The pooled ES which was calculated for ICU admission was significantly increased in cancer patients affected by COVID-19 (OR = 1.84, %95 CI: 1.44–2.34, $p < 0.001$) (Fig. 4). Significant and moderate heterogeneity was detected in the study results, and the analysis was performed using the random effects model (Q = 15.79, df = 4, $I^2 = 74.66\%$, $p = 0.003$). As shown in Supplemental Fig. S3, no significant publication bias was found according to Egger's linear regression test and Begg and Mazumdar's rank correlation test (Eggers's test: Intercept = 1.94, t = 1.34, $p = 0.273$; Begg and Mazumdar' test: z value for Kendall's tau = 0.98, $p = 0.327$). No significant change was observed in the sensitivity analysis visually presented in Fig. 5. The cumulative analysis results according to the effect sizes related to ICU admission are given in Supplemental Fig. S4.

Discussion

In this study, disease severity (mortality and ICU admission) was analyzed in patients with cancer affected by COVID-19. This is considered to be the first umbrella review to assess

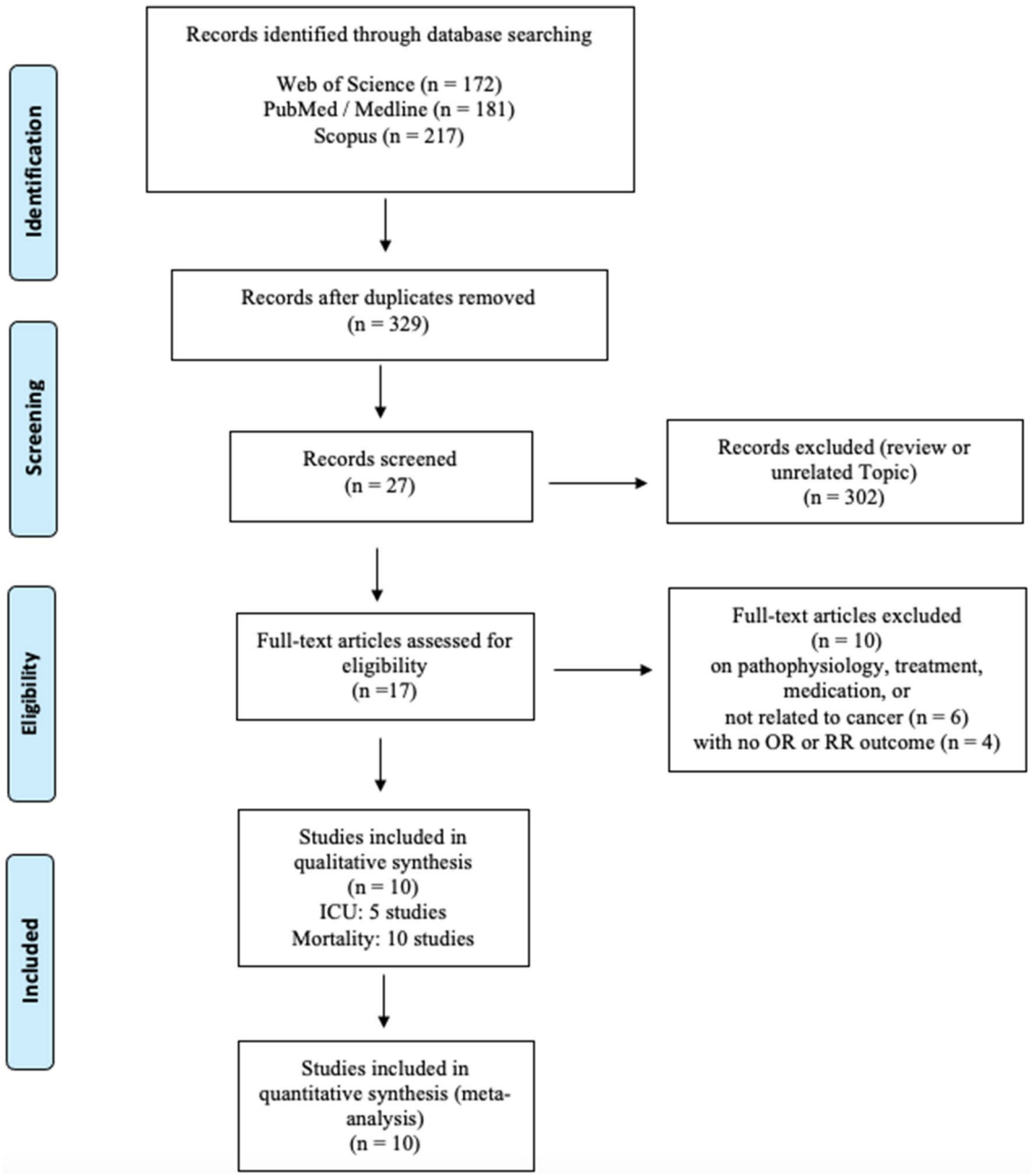

Fig. 1 The PRISMA flow diagram of the literature search and study collection process

this relationship by identifying the meta-analyses of previously published primary studies analyzed worldwide. The current meta-meta-analysis summarizes the information from over 300 primary studies and 10 meta-analyses (mortality) and adds to the strength of the findings of the separate studies. In addition, information about ICU admission was reported in five systematic reviews and meta-analyses.

It is a well-known fact that the COVID-19 pandemic affects individuals with chronic diseases, especially cancer, more than other people. In a comprehensive review of COVID-19, it was underlined that elderly patients as well as individuals with various comorbidities, including arterial hypertension, obesity, diabetes mellitus, active malignancy, chronic obstructive pulmonary disease, chronic kidney disease, and cardiovascular disease, have worse clinical progression [32]. Clinical outcomes were much worse, particularly in patients with cancer affected by COVID-19. Numerous studies involving cancer patients with COVID-19 have revealed that SARS-CoV-2 is a serious risk factor that may cause adverse clinical outcomes for cancer patients

Table 1 Study characteristics and odds ratios (ORs) or risk ratios (RRs) of studies included in the umbrella review and meta-meta-analysis

First author / year	Number of studies (n)	Total sample size (n)	Outcome (s)	The number of studies included in mortality (n)	The number of studies included in ICU admission (n)	OR (95% CI) or RR (95% CI) for mortality	OR (95% CI) or RR (95% CI) for ICU admission
Arayici et al. [16]	58	709,908	Mortality, ICU	42	22	RR: 2.26 (1.94–2.62)	RR: 1.45 (1.28–1.64)
Khoury et al. [17]	81	61,532	Mortality	19	N/A	RR: 2.12 (1.71–2.62)	N/A
Di Felice et al. [18]	35	142,355	Mortality, ICU	24	5	OR: 2.32 (1.82–2.94)	OR: 2.39 (1.90–3.02)
Han et al. [20]	57	63,413	Mortality	7	N/A	RR: 1.41 (1.15–1.73)	N/A
Venkatesulu et al. [21]	26	181,323	Mortality, ICU	10	5	OR: 2.54 (1.47–4.42)	OR: 2.18 (0.78–6.04)
Yang et al. [22]	19	63,019	Mortality	10	N/A	RR: 1.80 (1.38–2.35)	N/A
Salunke et al. [24]	13	3,775	Mortality, ICU	5	4	OR: 2.25 (0.71–7.10)	OR: 2.88 (1.18–7.01)
Tian et al. [23]	38	7,094	Mortality	8	N/A	OR: 2.97 (1.48–5.96)	N/A
Giannakoulis et al. [19]	32	46,499	Mortality, ICU	8	26	RR: 1.66 (1.33–2.07)	RR: 1.66 (1.31–1.87)
Parohan et al. [25]	14	29,900	Mortality	7	N/A	OR: 3.04 (1.80–5.14)	N/A

OR Odds ratio, *RR* Risk ratio, *N/A* Not available

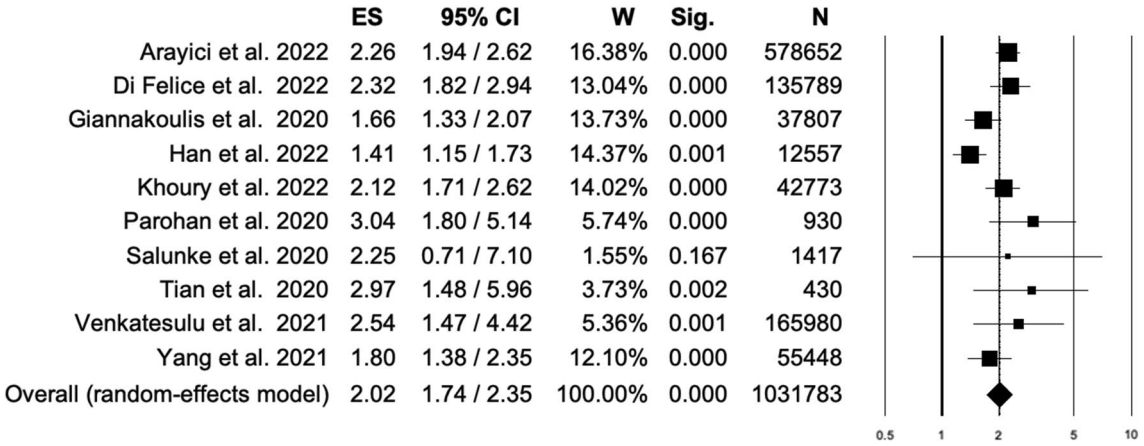

Fig. 2 The forest plot and pooled ES of mortality in cancer patients affected with COVID-19

[12–16, 33, 34]. Contrary to this, various studies published in the literature reported that there was no remarkable difference between cancer and non-cancerous groups in terms of COVID-19 mortality rates [35–37]. Similarly, in a study involving breast cancer patients in France, researchers revealed that serious events in breast cancer patients were almost as common as in the general population [38]. In addition, researchers highlighted that diagnostic studies of thyroid malignancies were affected as a result of the restrictions imposed on the cause of the pandemic [32]. In a study conducted in Italy, it was reported that there was a significant decrease in the number of thyroid fine-needle aspiration procedures during the pandemic [39].

In a meta-analysis, which included a total of 81 studies (19 for mortality) and 61,532 participants, conducted by Khoury et al. [17], a significant increase in mortality was reported in patients with cancer affected by COVID-19 (RR = 2.12, 95% CI: 1.71–2.62, $p < 0.001$, $I^2 = 84.4\%$). They also reported an increased mortality in patients with hematological (RR = 1.42, 95% CI: 1.31–1.54, $p < 0.001$,

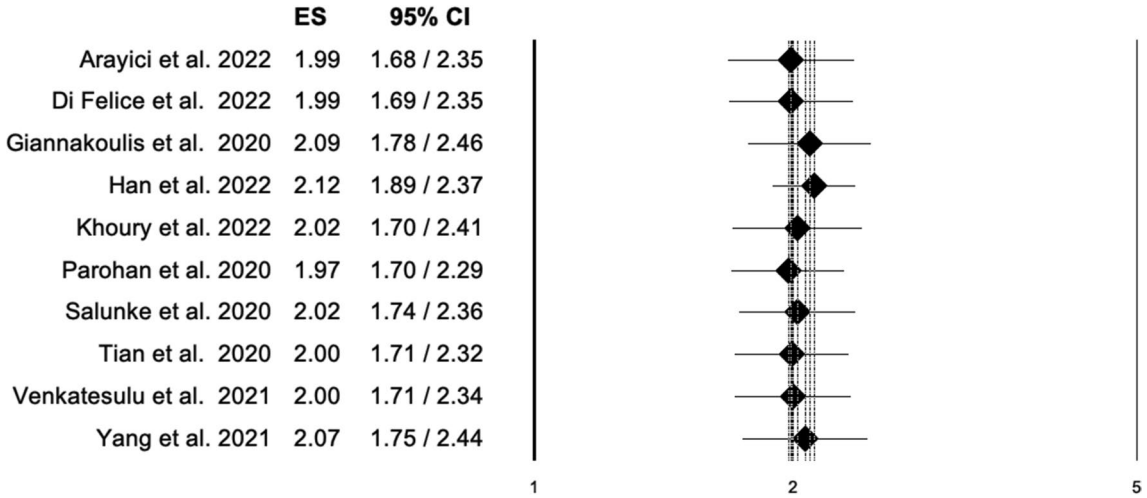

Fig. 3 Sensitivity analysis of mortality in cancer patients affected with COVID-19

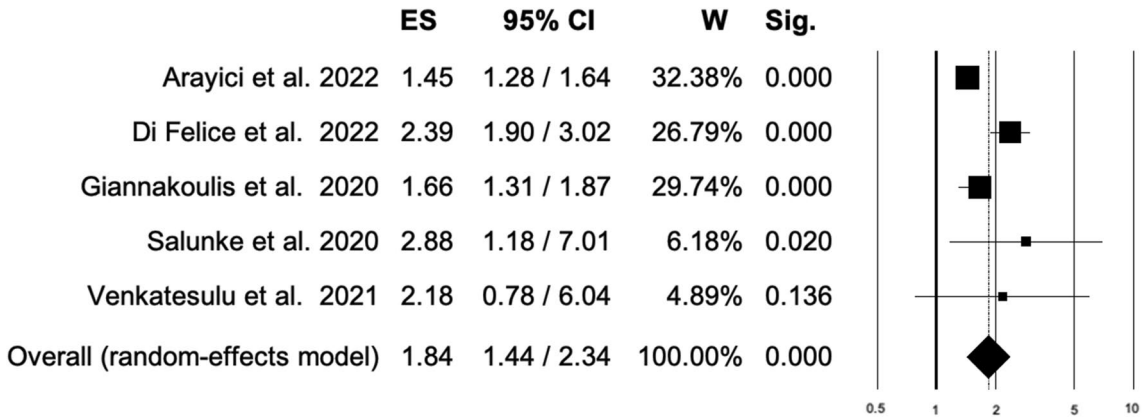

Fig. 4 The forest plot and pooled ES of ICU admission in cancer patients affected with COVID-19

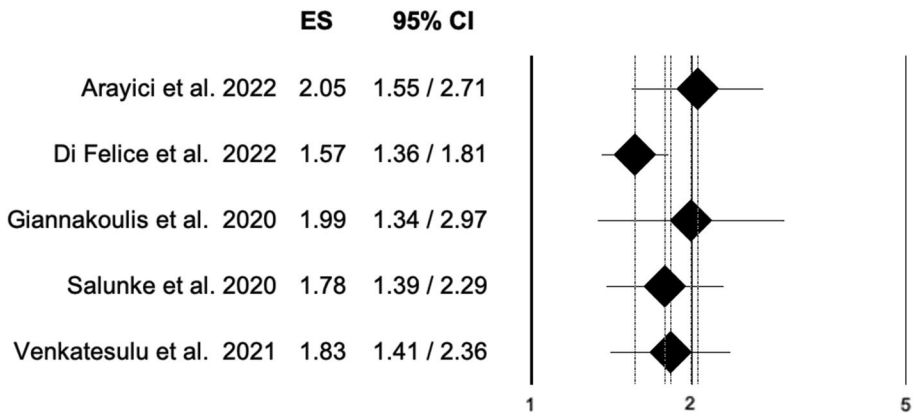

Fig. 5 Sensitivity analysis of ICU admission in cancer patients affected with COVID-19

$I^2 = 6.8\%$) and lung cancers (RR = 1.68, 95% CI: 1.45–1.94, $p < 0.001$, $I^2 = 32.9\%$) compared to patients with other cancers. In the systematic review and meta-analysis conducted by Arayici et al. [16], which included 709,908 participants and 58 primary studies, it was revealed that both mortality (RR = 2.26, 95% CI: 1.94–2.62, $p < 0.001$, $I^2 = 96.0\%$) and ICU admission (RR = 1.45, 95% CI: 1.28–1.64, $p < 0.001$, $I^2 = 87.0\%$) considerably increased in SARS-CoV-2 infected

cancer patients. They also reported that the incidence of cancer (%8, 95% CI: 8–9%) is higher than the worldwide incidence of cancer (approximately 0.2%) [16, 40]. Similarly, in another meta-analysis including 22,166 cancer groups and 143,814 control groups, it was reported that mortality increased 2.54 (95% CI: 1.47–4.42, $p < 0.001$) times and ICU admission increased 2.18 (95% CI: 0.78–6.04, $p < 0.001$) times in cancer patients suffering from COVID-19 [21]. In other systematic reviews and meta-analyses reporting mortality and/or ICU-related risks in SARS-CoV-2 infected cancer patients, increased mortality and intensive care admissions were reported in cancer patients compared to the control group [18–20, 22–25]. All meta-analyses included in the current umbrella review had an increased mortality rate and ICU admission in cancer patients infected with SARS-CoV-2. It has been clearly observed that there is a body of literature on this subject.

Data from ten studies [16–25] for mortality and five eligible studies for ICU admission [16, 18, 19, 21, 24] were evaluated by the meta-meta-analysis method in this investigation. The current umbrella review and meta-meta-analysis concluded that disease severity is worse in patients with cancer affected by COVID-19. In the analyses, it was determined that mortality (OR = 2.02, %95 CI: 1.74–2.35, $p < 0.001$) (Fig. 2) and ICU admission (OR = 1.84, %95 CI: 1.44–2.34, $p < 0.001$) (Fig. 4) significantly increased in cancer patients suffering from COVID-19. Sensitivity analyses—each study is excluded from the analysis separately—were performed to confirm the robustness of the analysis results. No significant changes were observed in the sensitivity analyses. Egger's linear regression test, schematic illustrations of funnel plots, and Begg and Mazumdar's rank correlation test were applied to evaluate publication bias. No significant publication bias was found in the test results and funnel plots (Supplemental Fig. S1 and Supplemental Fig. S3) (Mortality: Eggers's test: intercept = 0.88, t = 0.87, $p = 0.464$; Begg test = 0.27, $p = 0.788$, ICU: Eggers's test: Intercept = 1.94, t = 1.34, $p = 0.273$; Begg test = 0.98, $p = 0.327$).

Limitations and strengths

The strengths of the current umbrella review and meta-meta-analysis include the inclusion of multiple systematic reviews and meta-analyses; a reassessment of analyses with increased strength; and, importantly, raising the level of evidence. In addition, since it gathers meta-analyses with a high level of evidence under one umbrella, it will make it easier for researchers working on the severity of COVID-19 on cancer patients to review these studies. As known, public health policies are formed by evaluating systematic reviews and meta-analyses, which are considered the highest levels of evidence. Therefore, we identified the most recent systematic reviews and meta-analyses evaluating the severe effects (fatal and/or ICU (Intensive Care Unit) admissions) of COVID-19 on cancer patients. We reassessed these meta-analyses with increased power, along with an umbrella review. Therefore, it has been clearly demonstrated that cancer patients should be evaluated more sensitively in the current pandemic and any other pandemic that may occur. The limitations include: primary studies included in meta-analyses may have differences in patient selection and treatment regimens; there may be a potential bias in the selection of non-hospitalized patients, particularly for mortality; the effect of treatments received by cancer patients could not be evaluated; the COVID-19 pandemic has been managed differently in each country, which may lead to a variation in the results of primary studies, particularly for susceptibility to COVID-19. In addition, the primary studies of the meta-analyses included in our study involved patients from a wide variety of countries and geographies. Therefore, healthcare, lifestyles, ethnic differences, and treatment processes may have increased or decreased susceptibility to cancer or COVID-19. This situation was not evaluated in our study. Finally, differences in death and ICU admission rates between cancer types were not evaluated in this paper. In addition to all these, the same samples and studies may have been included in some meta-analyses. However, since primary studies were combined into different studies and a new result was reported, each meta-analysis was considered as a new study.

Conclusions

Cancer, which includes various disorders such as abnormal cell development and an irregular cell cycle, is still one of the leading causes of death globally. COVID-19 has more severely affected patients with cancer. As a result, this synthesis of systematic reviews and meta-analyses with the meta-meta-analysis method revealed that disease severity is higher in cancer patients affected by COVID-19. Both mortality and ICU admission were significantly increased in cancer patients infected with SARS-CoV-2. In conclusion, it is recommended to examine in more detail the increase in both mortality and ICU admission rates in cancer patients affected by the COVID-19 pandemic. Planning well-designed clinical trials in which both cancer types and cancer patients can be evaluated with more precision and individually is of critical importance. In these studies, it is recommended to report the causes of the increased mortality and ICU admission rates, especially in cancer patients infected with SARS-CoV-2. In addition, it is recommended to define clearer rules regarding the diagnosis and treatment processes of cancer patients during a pandemic, in case such a pandemic may occur again in the future. Errors and/or deficiencies experienced in this

pandemic should be well identified and necessary precautions should be taken to ensure that they do not recur. In this respect, it is essential that cancer patients should not be ignored while creating public health policies regarding the pandemic. Importantly, since cancer patients are a more sensitive and specific patient group, they should be evaluated more carefully, especially during the COVID-19 pandemic.

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Author's contribution MEA contributed to conceptualization, methodology, software, writing—original draft preparation, writing—reviewing and editing, and critical review. YB contributed to visualization, investigation, validation, writing—original draft preparation, and critical review. HE contributed to conceptualization, methodology, software, writing—original draft preparation, writing—reviewing and editing, and critical review. The final manuscript was reviewed and approved by all authors.

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Data availability The datasets used and/or analyzed in this study are available upon reasonable request from the corresponding author.

Declarations

Conflict of interest As all authors, we declare that we have no conflicts of interest to be disclosed.

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