Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Is Cancer an Independent Risk Factor for Fatal Outcomes of Coronavirus Disease 2019 Patients?

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Background. Coronavirus disease 2019 (COVID-19), caused by a novel virus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has brought new challenges for global health systems.

Objective. The objective of this study was to investigate whether pre-diagnosed cancer was an independent risk factor for fatal outcomes of coronavirus disease 2019 (COVID-19) patients.

Method. A comprehensive search was conducted in major databases of PubMed, Web of Science, and EMBASE to identify all published full-text studies as of January 20, 2021. Inter-study heterogeneity was assessed using Cochran's Q-statistic and I^2 test. A meta-analysis of random- or fixed-effects model was used to estimate the effect size. Publication bias, sensitivity analysis and subgroup analysis were also carried out.

Results. The confounders-adjusted pooled effects (pooled odds ratio [OR] = 1.47, 95% confidence interval [CI]: 1.31–1.65; pooled hazard ratio [HR] = 1.37, 95% CI: 1.21–1.54) indicated that COVID-19 patients with pre-diagnosed cancer were more likely to progress to fatal outcomes based on 96 articles with 6,518,992 COVID-19 patients. Further subgroup analyses by age, sample size, the proportion of males, region, study design and quality rating exhibited consistent findings with the overall effect size.

Conclusion. Our analysis provides the objective findings based on the adjusted effect estimates that pre-diagnosed cancer is an independent risk factor for fatal outcome of COVID-19 patients. During the current COVID-19 pandemic, health workers should pay particular attention to cancer care for cancer patients and should prioritize cancer patients for vaccination.

Key Words: Coronavirus disease 2019, Cancer, Fatal outcome, Meta-analysis, Adjusted effect estimate.

Introduction

Coronavirus disease 2019 (COVID-19), caused by a novel virus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has brought new challenges for global health systems. Previous studies have demonstrated that COVID-19 patients with hypoimmunity have a higher risk of severe events (intensive care unit admission, need for mechanical ventilation, or death) than the general population, which needs to be considered (1–3). Cancer patients have lower immunity and are at higher risk of systemic immunosuppression caused by chemotherapy and radiation, leading them more susceptible to infection (4,5). Mounting studies indicated that cancer might impact the progression of COVID-19, but with little consistency (6–11). Although several studies have explored the relationship between tumor and prognosis in patients with COVID-19 (10–12), none of those studies was based

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on adjusted effects. It has been reported that several confounding factors (age, gender, and common comorbidities) had obvious influences on clinical outcomes of COVID-19 patients (13–18), which might modulate the relationship between pre-diagnosed cancer and fatal outcomes of COVID-19 patients. For instance, Zhang C, et al. noticed a significant association between cancer and fatal outcomes of COVID-19 patients in the univariate analysis (odds ratio [OR] = 7.3, 95% confidence interval [CI]: 1.5–35.2), but this association was not statistically significant in the multivariate analysis (OR = 3.7, 95% CI: 0.6–22.2) (19). The same findings also emerged in the Yehia BR, et al., and Trigo J, et al. study (20,21). Therefore, it is an urgent need to clarify the association of pre-diagnosed cancer with mortality of COVID-19 patients by a quantitative meta-analysis based on the adjusted effect estimates.

Method

Literature Search Strategy

A comprehensive literature search was performed in the major databases of PubMed, EMBASE, and Web of Science to identify all published full-text studies as of January 20, 2021, and our search met the PRISMA 2009 checklist criteria. The search terms were as follows: ("coronavirus disease 2019" OR "COVID-19" OR "2019-nCoV" OR "SARS-CoV-2") AND ("mortality" OR "fatality" OR "death" OR "non-survivor" OR "deceased") AND ("comorbidities" OR "clinical characteristics" OR "outcome" OR "cancer" OR "malignancy" OR "neoplasia" OR "tumor"). The language was limited to English. Additional records identified through relevant research were also considered.

Eligibility Criteria

Only studies that met all of the following criteria could be included: a) the included populations must be laboratory-confirmed patients with SARS-CoV-2 infection, b) the methods of statistical analysis must include confounders-adjusted multivariate analysis such as cox proportional hazard model, logistic regression analysis, and so on, c) exposure factors must include information about cancer and clinical subtypes, d) outcomes must include in-hospital mortality, death, deceased, non-survivor or fatality, e) original studies in English, f) all of our studies has passed peer review.

Studies were excluded when met one of the following criteria: a) meeting abstract, review, case report, duplicate, animal research, expert consensus, guideline, news, protocol, or comment, b) papers with insufficient data, unavailable full text, or overlapped sample.

Data Extraction and Quality Assessment

Two investigators independently extracted the following information: the first author, source of data, country, date of data collection, study design, number of patients, mean/median age, the percent of males, the percent of COVID-19 patients with cancer, adjusted effect estimates and confounders. The disagreements were discussed until a consensus was reached. The quality of the included studies was evaluated by investigators according to the Newcastle-Ottawa Scale (NOS) or 11 item checklists recommended by the Agency for Healthcare Research and Quality (AHRQ). High-quality studies are considered studies with a score of 8 or above, medium-quality studies with a score of 4–7, and low-quality studies with a score of 3 or below.

Statistical Analysis

The pooled effects (OR hazard ratio [HR] and relative risk [RR]) and 95% CI were calculated to measure the risk of mortal outcomes in COVID-19 patients with a history of cancer. Heterogeneity was measured by Cochran's Q-statistic and I^2 test (12). If significant heterogeneity was observed (I^2 >50%, p <0.1), a random-effect model was adopted, if not, a fixed-effects model was adopted. Subgroup analyses were carried out to identify any redundant relationships. The robustness of the results was measured by sensitivity analysis. Begg's rank correlation test and Egger's linear regression test were conducted to measure the publication bias (22). If any publication bias was detected, the trim-and-fill analysis was applied to check whether the results are stable. All statistical analyses were conducted by Stata, version 12.0 and R, version 3.6.1.

Results

The flow diagram for study screening is shown in Figure 1. A total of 19,548 studies were identified through a comprehensive search, leaving 96 studies with 6,518,992 cases after excluding duplicates, screening records, and full-text article evaluation. Of those, OR was mentioned in 56 studies, HR was mentioned in 38 studies and RR was mentioned in the remaining 2 studies. The main distribution of these studies was as follows: Europe (41), Asia (27), North America (25), and the remaining 3 from 3 different regions (Supplementary Table 1). The sample size of the included studies ranged from 31–6,083,102. There were 21 studies rated high quality based on the NOS quality score (Supplementary Table 2). The main characteristics of all included studies are presented in Supplementary Table 1.

The overall results showed that COVID-19 patients with pre-diagnosed cancer had more likelihood to progress to fatal outcomes than non-cancer patients based on adjusted effect estimates (pooled OR = 1.47, 95% CI: 1.31–1.65; pooled HR = 1.37, 95% CI: 1.21–1.54; random-effects

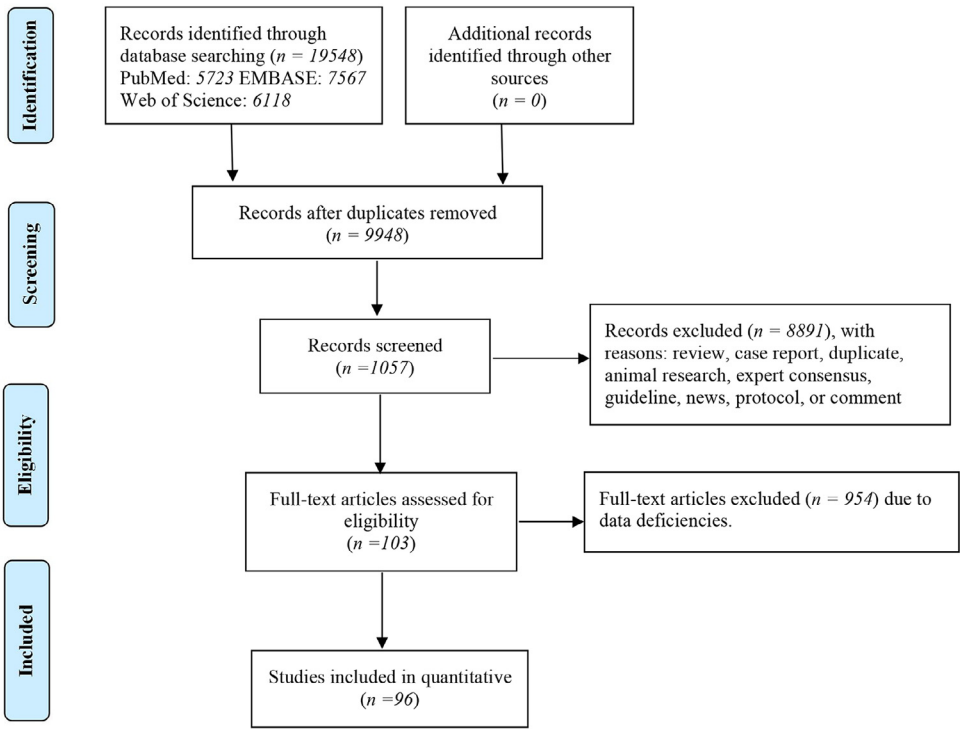

Figure 1. Flow diagram of the publication search and selection process.

Table 1. Subgroup analysis and meta-regression

Variables	No. of studies	Meta-regression			Subgroup analysis		Heterogeneity		
		Tau^2	*t*	*p*	Pooled ES (95% CI)	*p*	I^2	χ^2	*p*
Sample size		0	–21.24	<0.001					
≥1000	47	-	-	-	1.36 (1.23–1.51)	<0.001	75.2%	185.59	<0.001
<1000	49	-	-	-	1.55 (1.35–1.77)	<0.001	50.4%	96.80	<0.001
Age (years)		0		<0.001					
≥60	57	-	–23.33	<0.001	1.34 (1.22–1.48)	<0.001	62.3%	148.55	<0.01
<60	32	-	-	-	1.67 (1.40–2.00)	<0.001	76.0%	129.11	<0.01
NR	7	-	–11.87	<0.001	1.48 (1.27–1.72)	<0.001	0.0%	2.90	<0.01
Male (%)		0		<0.001					
≥60	37	-	–24.50	<0.001	1.41 (1.24–1.61)	<0.001	65.6%	104.50	<0.001
<60	56	-	-	-	1.46 (1.30–1.64)	<0.001	70.0%	183.38	<0.001
NR	3	-	–7.03	<0.001	1.40 (1.07–1.85)	0.015	0.0%	0.80	0.671
Region		0		*<0.001*					
Asia	27	-	–17.01	<0.001	2.03 (1.59–2.59)	<0.001	71.9%	92.48	<0.001
Americas	25	-	-	-	1.15 (1.03–1.30)	0.016	67.2%	73.07	<0.001
Europe	41	-	–22.48	<0.001	1.43 (1.28–1.60)	<0.001	49.3%	78.82	<0.001
Others	3	-	–7.26	<0.001	1.43 (1.10–1.86)	0.008	0.0%	0.22	0.897
Study design		0		<0.001					
Retrospective/case series	22	-	–11.46	<0.001	2.03 (1.34–3.07)	0.001	70.8%	34.23	<0.001
Prospective/RCT	6	-	–24.12	<0.001	1.51 (1.34–1.71)	<0.001	61.1%	149.05	<0.001
Others	3	-	-	-	1.25 (1.12–1.40)	<0.001	70.2%	83.94	<0.001
Effect		0		<0.001					
OR	56		–25.03	<0.001	1.47 (1.31–1.65)	<0.001	68.4%	174.08	<0.001
HR	38		-	-	1.37 (1.21–1.54)	<0.001	65.3%	106.77	<0.001
RR	2		–1.93	<0.001	7.16 (0.21–248.04)	0.276	82.6%	5.75	0.017
Quality score		0	–22.69	<0.001					
High	21	-	-	-	1.35 (1.15–1.57)	<0.001	69.4%	65.39	<0.001
Moderate/Low	75	-	-	-	1.47 (1.33–1.62)	<0.001	67.0%	223.99	<0.001

RCT, randomized controlled trial; ES, effect sizes; CI, confidence interval.

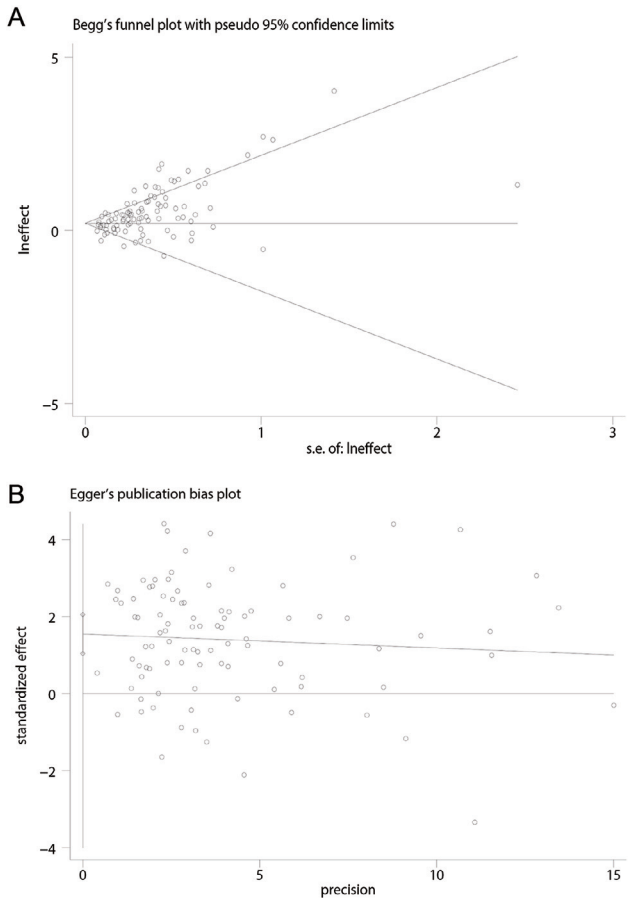

Figure 2. Funnel plot for publication bias. A. Begg's test and B. Egger's test, respectively.

model; Supplementary Figure 2, Table 1). Subgroup analysis stratified by confounders such as age, the proportion of males, sample size, study design, region and quality rating also consisted with the above result (Table 1, Supplementary Figure 3–8). The leave-one-out sensitivity analysis revealed that our results were robust (Supplementary Figure 1). Although publication bias was detected in both Begg' s test ($p = 0.00$, Figure 2A) and Egger's test ($p = 0.00$, Figure 2B), the result of trim-and-fill analysis showed the above results still hold after added 30 studies (pooled effect = 1.187, 95% CI: 1.086–1.297; $n = 30$; random-effects model).

Discussion

There is evidence that elderly and hypertensive patients are at increased risk for adverse outcomes due to higher ACE-2 expression (ACE-2 tends to increase with age and use of the anti-hypertensive drugs) and more comorbidities (23–26). However, advanced age, hypertension, dementia, and many other factors are also contributing to the poor prognosis in patients with cancer (27–29). Therefore, it is necessary to adjust those confounders while exploring the exact links between pre-diagnosed cancer and fatal outcomes of COVID-19 patients. In this meta-analysis, we summarized all available studies on multivariate analyses of the relationship between pre-diagnosed cancer and fatal outcomes in COVID-19 patients. Our results based on adjusted effect estimates demonstrated that the presence of pre-diagnosed cancer did increase the likelihood of fatal outcomes in COVID-19 patients based on 96 eligible articles with 6,518,992 cases, which meant that pre-existing cancer might be an independent risk factor for fatal outcomes of COVID-19 patients.

Cancer patients tended to be more prone to hypoproteinemia, anemia, and immune dysfunction that may have negative effects, making them more susceptible to respiratory pathogens than the general population (13,30). Despite mild coronavirus infection could self-heal through classic regulatory inflammatory and adaptive immune responses (10,31,32), but lymphopenia was common in cancer patients, as well as in those on active treatment, so the immune regulation required by the patient was impaired (33). The sustained release of cytokines might cause "cytokine storm" and lead to severe lung injury (23). Additionally, IL-6 (overexpressed in almost all types of cancer) (34), as a pro-inflammatory factor, could increase blood vessel permeability and cause large amounts of fluid and blood cells to enter the alveoli, leading to breathing difficulty and even respiratory failure (35). The above evidence might explain why COVID-19 patients with pre-diagnosed cancer were more likely to progress to fatal outcomes than patients without cancer. Therefore, during the current COVID-19 pandemic, health workers should pay particular attention to cancer care for cancer patients and should prioritize cancer patients for vaccination.

There are still some limitations. Firstly, although we try our best to avoid the inclusion of duplicate data, some of the included studies are based on the database and did not specify the data source, so the overlapped sample might be included. Secondly, data on medication and supportive care in the selected studies are not yet available, and therefore the effect of treatment on the association between cancer and fatal outcomes in COVID-19 patients cannot be assessed. Thirdly, there are too few studies on the correlation between cancer type, tumor stage, survival status, prior cancer treatment, COVID-19 infection status, and prognosis in patients with COVID-19, which cannot be further explored and needed be supplemented by follow-up studies.

In summary, our meta-analysis provides the first objective findings based on the adjusted effect estimates that pre-existing cancers is an independent risk factor for fatal outcomes in patients with COVID-19. Despite so many confounders related cancer patients with worst outcome of COVID-19, special measurement and target medical interventions are needed to protect patients with cancer from SARS-CoV-2 infection and further disease

progression. Meanwhile, vulnerable groups such as cancer patients should be given priority for vaccination.

Declarations

Not applicable.

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Data Availability Statement

All data relevant to the study are included in the article or uploaded as supplementary information.

Patient and Public Involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Conflicts of Interest

All authors report that they have no potential conflicts of interest.

Supplementary Materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.arcmed.2021.05.003.

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