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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Epidemiological and clinical characteristics of cancer patients with COVID-19: A systematic review and meta-analysis of global data

Xiangyi Kong [a,1], Yihang Qi [a,1], Junjie Huang [b], Yang Zhao [c,d], Yongle Zhan [e], Xuzhen Qin [f], Zhihong Qi [f], Adejare (Jay) Atanda [g], Lei Zhang [h,i,j,k], Jing Wang [a,******], Yi Fang [a,*****], Peng Jia [l,m,****], Asieh Golozar [n,o,***], Lin Zhang [e,p,q,**], Yu Jiang [e,*]

[a] Department of Breast Surgical Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, 100021, China
[b] Jockey Club School of Public Health and Primary Care, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong
[c] The George Institute for Global Health at Peking University Health Science Center, Beijing, China
[d] WHO Collaborating Centre on Implementation Research for Prevention & Control of NCDs, The University of Melbourne, Victoria, 3010, Australia
[e] School of Population Medicine and Public Health, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, 100021, China
[f] Clinical Laboratory, Peking Union Medical College Hospital, Chinese Academy of Medical Science & Peking Union Medical College, Beijing, 100730, China
[g] School of Community Health and Policy, Morgan State University, Baltimore, MD, USA
[h] China-Australia Joint Research Center for Infectious Diseases, School of Public Health, Xi'an Jiaotong University Health Science Center, Xi'an, Shanxi, 710061, PR China
[i] Melbourne Sexual Health Centre, Alfred Health, Melbourne, Australia
[j] Central Clinical School, Faculty of Medicine, Monash University, Melbourne, Australia
[k] Department of Epidemiology and Biostatistics, College of Public Health, Zhengzhou University, Zhengzhou, 450001, Henan, China
[l] Department of Land Surveying and Geo-Informatics, The Hong Kong Polytechnic University, Hong Kong, China
[m] International Institute of Spatial Lifecourse Epidemiology (ISLE), Hong Kong, China
[n] Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA
[o] Regeneron Pharmaceuticals, New York, NY, USA
[p] Melbourne School of Population and Global Health, The University of Melbourne, Victoria, Australia
[q] Centre of Cancer Research, Victorian Comprehensive Cancer Centre, Melbourne, Victoria, Australia

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ABSTRACT

There are minimal data regarding the prevalence of cancer in patients with coronavirus disease 2019 (COVID-19), as well as the incidence of severe illness and rate of mortality in COVID-19 patients with cancer. PubMed, Embase, Cochrane Library, and Web of Science were systematically searched, from database inception to July 15, 2020, for studies of patients with COVID-19 that included information regarding comorbid cancer. In total, 109 eligible global studies were included in this systematic review. Ninety studies with 94,845 COVID-19 patients, among which 4106 exhibited comorbid cancer, were included in the meta-analysis regarding prevalence of comorbid cancer. Twenty-three studies with 71,969 COVID-19 patients, among which 4351 with comorbid cancer had severe illness or death, were included in the meta-analysis. The overall prevalence of cancer among COVID-19 patients was 0.07 (95% CI 0.05–0.09). The cancer prevalence in COVID-19 patients was higher in Europe (0.22, 95% CI 0.17–0.28) than in the Asia-Pacific region (0.04, 95% CI 0.03–0.06) or North America

* Corresponding authors. School of Population Medicine and Public Health, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, 100730, China.
** Corresponding authors. School of Population Medicine and Public Health, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, 100730, China.
*** Corresponding authors. The Johns Hopkins Bloomberg School of Public Health, Regeneron Pharmaceuticals, NY, USA.
**** Corresponding author. International Institute of Spatial Lifecourse Epidemiology (ISLE), China.
***** Corresponding author.
****** Corresponding author.
E-mail addresses: wangjing@cicams.ac.cn (J. Wang), fangyi@cicams.ac.cn (Y. Fang), jiapengff@hotmail.com (P. Jia), Asieh.golozar@gmail.com (A. Golozar), tony1982110@gmail.com (L. Zhang), jiangyu@pumc.edu.cn (Y. Jiang).
[1] These two authors contributed equally to this work.

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(0.05, 95% CI 0.04–0.06). The cancer prevalence in COVID-19 patients aged >60 years was 0.10 (95% CI 0.07–0.14), while the prevalence among patients aged ≤60 years was 0.05 (95% CI 0.03–0.06). The pooled prevalence of severe illness among COVID-19 patients with cancer was 0.34 (95% CI 0.26–0.42) and the pooled mortality rate of COVID-19 patients with cancer was 0.20 (95% CI 0.16–0.25). Pooled incidences of severe illness among COVID-19 patients with cancer from Asia Pacific, Europe, and North America were 0.38 (95% CI 0.24–0.52), 0.39 (95% CI 0.25–0.53), and 0.26 (95% CI 0.20–0.31), respectively; pooled mortality rates from the Asia-Pacific region, Europe, and North America were 0.17 (95% CI 0.10–0.24), 0.26 (95% CI 0.18–0.35), and 0.19 (95% CI 0.13–0.25), respectively.

1. Introduction

Globally, more than 18.5 million confirmed cases of coronavirus disease 2019 (COVID-19) have been reported (https://www.worldometers.info/coronavirus). As infection has become widespread, concern has grown regarding the influence of COVID-19 on patients with cancer. The results of previous studies suggest that patients with a history of active malignancy might have greater risks of COVID-19 onset, COVID-19-related complications, and worse prognosis [1,2]. These risks are partly related to the following factors [3]: *1)* a systemic immunosuppressive state caused by malignancy and anticancer treatments, such as chemotherapy, surgery, or immunomodulatory drugs (e.g., programmed death 1 [PD-1]/programmed death-ligand 1 [PD-L1] inhibitors) [4–6]; *2)* older ages and major comorbidities including cancer, which increase the risks of COVID-19-related morbidity and mortality [7]; and *3)* greater contact with the healthcare system through provider visits for anticancer therapy, monitoring, preventive care, and supportive care [3]. In February 2020, Liang et al. published a nationwide analysis of cancer patients with COVID-19 in China [8]. Eighteen (1%) of 1590 COVID-19 patients had a history of cancer, higher than the prevalence of cancer in the overall Chinese population (285.83 per 100000 people [0.29%], based on 2015 cancer epidemiology statistics [9]). There have been some clinical trials investigating the relationships between COVID-19 and cancers. Dai et al. performed a multicenter study including 105 patients with cancer and 536 age-matched noncancer patients confirmed with COVID-19, finding that patients with cancer appear more vulnerable to COVID-19 and COVID-19 patients with cancer had higher risks in all severe outcomes [2]. Further, patients with hematologic cancer, lung cancer, or with metastatic cancer (stage IV) had the highest frequency of severe events [2]. Patients with non-metastatic cancer experienced similar frequencies of severe conditions to those observed in patients without cancer [2]. In a multi-centre, two-arm, parallel-group, triple-blind, phase 2–3 randomised controlled trial, Allahyari et al. investigated the effect of hydroxychloroquine on the prevention of COVID-19 in cancer patients being treated [10]. The primary end point is to investigate the incidence of COVID-19 in patients being treated for their cancer over a 2-month period. The trial began on April 14, 2020 and recruitment is still ongoing [10].

The clinical and prognostic characteristics of cancer patients with COVID-19 have also been explored in recent studies. In March 2020, Zhang et al. carried out multivariate analyses on 28 cancer patients with COVID-19 from three hospitals in Wuhan, China; they showed that cancer patients exhibited deteriorating conditions and poor outcomes because of COVID-19 [11]. On behalf of the COVID-19 and Cancer Consortium, Kuderer et al. reported significant associations between 30-day all-cause mortality and multiple factors (older age, male sex, prior history of smoking, number of comorbidities, and receipt of azithromycin plus hydroxychloroquine) [3]. However, the previous studies have been restricted by small sample sizes, geographic regions, and a lack of generalisability to the overall population of COVID-19 patients with cancer. In addition, limited clinical information and considerable heterogeneity regarding the course of the disease lead to a lack of clarity concerning the epidemiological characteristics, clinical characteristics, and treatment principles of cancer patients with COVID-19. There is an urgent need to investigate the following points: *1)* the estimated prevalence of cancer among COVID-19 patients, as a function of various factors; *2)* whether cancer patients with COVID-19 have distinct clinical courses and worse outcomes, compared with COVID-19 patients without cancer; and *3)* whether there are geographic variations in the severe illness and mortality rate among cancer patients with COVID-19. Thus, we conducted a systematic review and meta-analysis of observational studies concerning cancer patients with COVID-19. Our findings will aid in the management of cancer patients with COVID-19.

2. Methods

This systematic review and meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [12]. Two reviewers (K.X. and Q.Y.) independently undertook the literature search, assessment for eligibility, data extraction, and qualitative assessment. Inconsistencies were reviewed by a third reviewer (L.Z.) and resolved by consensus. The research protocol was registered and approved in PROSPERO (registration #CRD42020196014).

2.1. Data sources and searches

A comprehensive literature search of bibliographic databases was conducted to identify all relevant articles. To identify studies regarding COVID-19 in cancer patients, PubMed, Embase, Cochrane Library, and Web of Science were searched from the inception of each database to July 15, 2020. Additionally, abstracts and presentations of all major conference proceedings were reviewed. Key/relevant MeSH terms and keywords used in this study were as follows: “2019-ncov,” “novel coronavirus,” “COVID-19,” “SARS-CoV-2,” “new coronavirus,” “coronavirus disease 2019,” “cancer,” “tumor,” “malignancy,” and “neoplasm.” The specific literature search strategies are shown in Table S1. Reference lists were also reviewed in a snowball sampling technique to identify additional studies. Two investigators (X.K. and Y.Q.) independently screened the titles and abstracts of identified articles. Major conflicts were resolved by a third researcher (L.Z.). The full texts of identified studies were further reviewed by two independent reviewers (J.W. and Y.F.). The search was again extended by review of references of articles included in the final selection.

2.2. Study selection and data extraction

Published studies containing epidemiological and clinical data of cancer patients with COVID-19 were identified without geographic restrictions. Eligibility criteria were as follows: *1)* studies reporting data regarding COVID-19 confirmed patients, survivors, and COVID-19-related death; *2)* studies containing epidemiological or clinicopathological data regarding cancer patients with COVID-19; and *3)* studies limited to humans. Exclusion criteria were as follows: *1)* letters, reviews, conference proceedings, commentaries, quality of life studies, cost-effectiveness analyses, and publications in which the cancer data or COVID-19 data could not be ascertained; and *2)* duplicate studies from the same population or database (only the most recent study was included in the analysis). Two investigators (K.X. and Q.Y.) independently reviewed the list of retrieved articles to choose potentially

relevant articles; disagreements were discussed and resolved by consensus with a third investigator (L.Z.). Both reviewers also independently extracted data from all studies; discrepancies were resolved by consensus with the third investigator (L.Z.). The following information was extracted from each publication: publication details, data collection period, sample size, sex, age, study design, data used for patient characterisation, clinical definition of COVID-19 used in the study, hospital where patients were treated, patients' basic vital signs, symptoms and signs, race, smoking status, obesity status, number of comorbidities, interval between cancer diagnosis and hospitalisation, cancer histotype, tumour stage, treatments used for both cancer and COVID-19, laboratory results, severity staging, and prognosis.

2.3. Endpoint setting and stratification strategy

The primary outcome was the prevalence of cancer among COVID-19 patients. This prevalence was defined as the number of COVID-19 patients with cancer divided by the total number of COVID-19 patients in the study. Secondary outcomes included the severe illness incidence and mortality rate among cancer patients with COVID-19. The stratification strategy for subgroup analysis of cancer prevalence in COVID-19 patients was as follows:

1) by continent: patient populations were stratified into three groups: Europe, the Asia-Pacific region, and North America.
2) by country: patient populations were stratified into two groups: China and other countries.
3) by age: patients were stratified into two groups: mean age >60 years and mean age ≤60 years.
4) by sample size: studies were stratified into two groups: sample size ≤100 and sample size >100.
5) by study design: studies were stratified into two groups: cohort studies and non-cohort studies (e.g., case-series, case-control, and cross-sectional studies).

To investigate severe illness incidence and mortality rate among COVID-19 patients with cancer, a subgroup analysis was also performed with stratification by continent.

2.4. Data synthesis and analysis

Statistical heterogeneity among studies was evaluated using Cochran's Q test and the I^2 statistic; I^2 (% residual variation due to heterogeneity) values of 25%, 50%, and 75% were considered to represent low, moderate, and high heterogeneity, respectively [13]. For I^2 values > 50%, a random-effects model was applied. For I^2 values < 50%, a fixed effects model was applied [14]. If substantial heterogeneity was detected, meta-regression analyses were performed to determine the proportion of between-study variance explained by participant characteristics and study characteristics. The pooled prevalence of cancer comorbidity among COVID-19 patients in different studies and corresponding 95% confidence intervals (CIs) were used to estimate cancer prevalence among COVID-19 patients, as well as the proportions of cancer patients with severe illness and death from COVID-19. Both Metan and Metaprop approaches were used to generate pooled prevalences. Metaprop built further on the Metan procedure, which allowed computation of 95% CIs using the score statistic and the exact binomial method; this approach incorporated the Freeman-Tukey double arcsine transformation of proportions [15]. Meta-analysis results using Metaprop are shown in the main text; results obtained using the Metan approach are shown in the supplementary material.

2.5. Assessment for study quality and risk of publication bias

Articles included in the single-arm prevalence meta-analysis were analysed for risk of bias by using guidelines from the Agency for Healthcare Research and Quality (AHRQ) (https://www.ncbi.nlm.nih.gov/books/NBK35156), which can be tailored for the assessment of cross-sectional studies [16]. This methodological quality assessment tool uses an 11-item checklist and is recommended for the assessment of cross-sectional studies. An item was scored "0" if the answer was "NO" or "UNCLEAR," and "1" if the answer was "YES." Article quality was assessed as follows: low quality = 0–3; moderate quality = 4–7; high quality = 8–11.

The Newcastle-Ottawa Scale (NOS) quality assessment tool was used to evaluate the quality of the selected comparative studies (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp). This tool measured the key aspects of the methodology in selected studies with regard to design quality and risk of bias estimates based on three design criteria: 1) selection of study participants; 2) comparability of study groups; 3) assessment of outcome and exposure with a star system (maximum of nine stars) [17]. Studies with a score of 7–9 stars were considered to have a low risk of bias, studies with a score of 4–6 stars were considered to have a medium risk of bias, and studies with a score of ≤3 were considered to have a high risk of bias.

Publication bias was estimated using Begg's funnel plot, in which the SE of the prevalence of each study was plotted against its prevalence; the corresponding Begg's test was performed to test for small-study effects [18]. All reported P-values are two-sided. A P-value <0.05 was considered to indicate statistical significance. All analyses were performed using Stata version 14.2 (StataCorp, College Station, TX, USA) [19,20].

2.6. Role of the funding sources

The funders have no conflicts of interest. The funders of the study had no roles in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding authors have full access to all data in this study and had final responsibility concerning the decision to submit for publication.

3. Results

3.1. Characteristics of the included studies

Fig. 1 shows the study selection flowchart. After screening and eligibility assessment, we included a total of 109 studies (79 retrospective cohort studies, 22 case-series studies, five case-control studies, and three cross-sectional studies) in the final quantitative and qualitative syntheses of evidence. Among the 109 studies, 90 reported the number of patients with comorbid cancer among COVID-19 patients. These studies were published between December 2019 and June 2020; they contained information regarding 94,845 COVID-19 patients, among which 4106 exhibited comorbid cancer (Table 1). Among the 109 studies, 23 included 71,969 COVID-19 patients, among which 4351 patients with comorbid cancer exhibited severe illness or death during the study period. These studies provided detailed clinical outcomes information concerning the COVID-19 patients with cancer, including severe illness incidence and mortality rate (Table 2).

3.2. Prevalence of cancer among COVID-19 patients

Pooled prevalence of cancer in different subgroups were shown in Fig. 2. The overall cancer prevalence among the entire COVID-19 patient cohort was 0.07 (95% CI 0.05–0.09, weights determined using random-effects analysis model, Fig. S1). For subgroup analysis, patient populations were from Europe (14 studies in total, including six from Italy, four from France, two from the United Kingdom (UK), one from Spain, and one from Norway), the Asia-Pacific region (72 studies in total, including 70 from China, one from Korea, and one from Australia), and North America (eight studies, all from the United States of America). There were 36 studies with patients aged >60 years; for the other 54

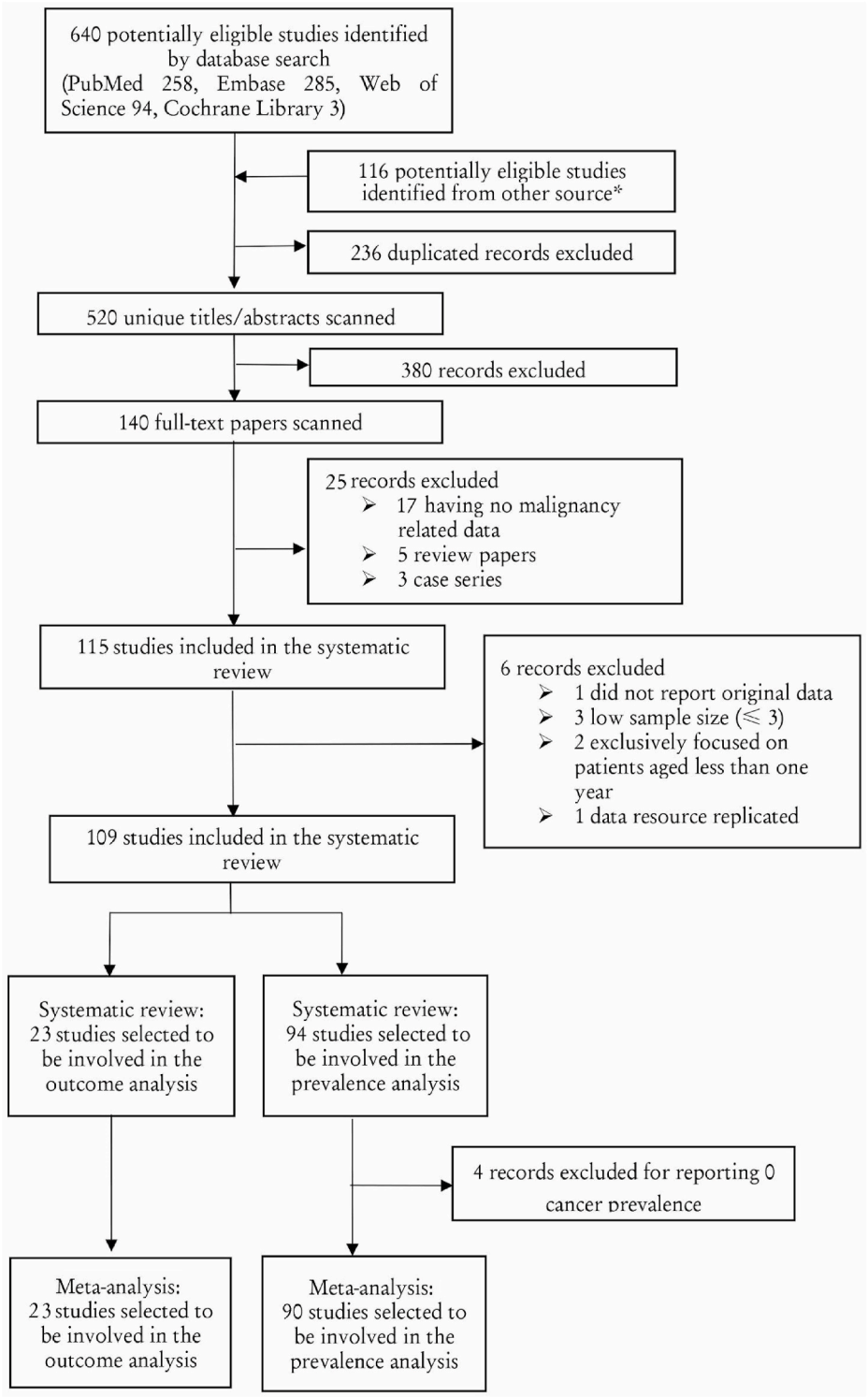

Fig. 1. Study Eligibility Flowchart. * Because many COVID-19 patients with comorbid cancer-related data were only reported in tables, we searched PubMed using a "COVID-19" search strategy, scanning and extracting studies with "data in tables."

studies, patients were aged ≤60 years. Subgroup analysis revealed that the prevalence of COVID-19 was higher among cancer patients in Europe (prevalence rate 0.22, 95% CI 0.17–0.28) than among cancer patients in the Asia-Pacific region (0.04, 95% CI 0.03–0.06) or North America (0.05, 95% CI 0.04–0.06) (Fig. S2). When stratified by country, the prevalence of COVID-19 among cancer patients was 0.04 (95% CI 0.03–0.06) in China; this rate was lower than in other countries (0.13, 95% CI 0.11–0.16) (Fig. S3). The prevalence of COVID-19 was higher among cancer patients aged >60 years (0.10, 95% CI 0.07–0.14) than among patients aged ≤60 years (0.05, 95% CI 0.03–0.06) (Fig. S4). The prevalence was slightly higher in studies with a sample size ≤100 (0.10, 95% CI 0.07–0.14) than in studies with a sample size >100 (0.05, 95% CI 0.04–0.07) (Fig. S5). As shown in Fig. S6, the pooled prevalence in cohort studies was estimated to be 0.07 (95% CI 0.05–0.09), similar to the estimated prevalence in non-cohort studies (0.07, 95% CI 0.05–0.09). The results obtained from the Metan method (Figs. S7A–F in

Table 1
Summary of characteristics of included studies of COVID-19 patients with comorbid cancer.

First author	Country	Continent	Study Design	Data Collection	Confirmation of COVID-19	COVID-19 Patients	Age (years)	Male Percentage	Cancer
Beyrouti R [26]	UK	Europe	Case Series	Medical Records	RT-PCR	6	61.0–85.0	0.83	2
Cai Q [27]	China	Asia Pacific	Retrospective Cohort	EHR	RT-PCR	298	47.5 ± 3.0–61.0	0.49	4
Chen J [28]	China	Asia Pacific	Retrospective Cohort	EHR	Laboratory confirmed	249	51.0 (36.0–64.0)	0.51	1
Chen L [29]	China	Asia Pacific	Retrospective Cohort	EHR	RT-PCR	29	56.0 (26.0–79.0)	0.72	1
Chen N [30]	China	Asia Pacific	Retrospective Cohort	Medical Records	RT-PCR	99	55.5 ± 13.1	0.68	1
Chen T [31]	China	Asia Pacific	Case Series	EHR	RT-PCR	274	62.0 (44.0–70.0)	0.62	7
Cheng Y [32]	China	Asia Pacific	Retrospective Cohort	Medical Records	RT-PCR	701	63.0 (50.0–71.0)	0.52	32
Conversano A [32]	Italy	Europe	Retrospective Cohort	Medical Records	RT-PCR	191	63.4 ± 14.9	0.69	29
Dai M [33]	China	Asia Pacific	Retrospective Cohort	EHR	WHO Guideline	641	64.0 ± 14.0	0.55	105
Deng G [34]	China	Asia Pacific	Retrospective Cohort	EHR	RT-PCR	44672	NA	0.51	107
Du RH [35]	China	Asia Pacific	Retrospective Cohort	EHR	RT-PCR	109	70.7 ± 10.9	0.68	8
Du Y [36]	China	Asia Pacific	Retrospective Cohort	EHR	PCR	85	65.8 ± 14.2	0.73	6
Duanmu Y [37]	USA	North America	Cross-Sectional Study	EHR	PCR	100	45.0 (32.0–65.0)	0.56	3
Feng Y [38]	China	Asia Pacific	Retrospective Cohort	Medical Records	RT-PCR	476	53.0 (40.0–64.0)	0.57	57
Fernández-Ruiz M [39]	Spain	Europe	Case Series	Medical Records	RT-PCR	18	71.0 ± 12.8	0.78	4
Grasselli G [40]	Italy	Europe	Case Series	EHR	RT-PCR	1591	63.0 (56.0–70.0)	0.82	81
Grillet F [41]	France	Europe	Retrospective Cohort	Medical Records	RT-PCR	100	66.0 ± 13.0	0.7	20
Guan WJ [42]	China	Asia Pacific	Retrospective Cohort	EHR	RT-PCR	1590	49.0 ± 16.0	0.57	130
Guan WJ [42]	China	Asia Pacific	Retrospective Cohort	EHR	RT-PCR	1099	47.0 (35.0–58.0)	0.58	10
Guo W [43]	China	Asia Pacific	Retrospective Cohort	EHR	RT-PCR	174	59 .0 (49.0–67.0)	0.44	21
He Y [32]	China	Asia Pacific	Retrospective Cohort	Medical Records	Not specified	65	51.0 (27.0–68.0)	0.48	1
Hou W [44]	China	Asia Pacific	Retrospective Cohort	EHR	PCR	101	50.9 ± 20.1	0.44	5
Hu L [45]	China	Asia Pacific	Retrospective Cohort	Medical Records	RT-PCR	323	61.0 (23.0–91.0)	0.51	5
Huang C [46]	China	Asia Pacific	Retrospective Cohort	EHR	RT-PCR	41	49.0 (41.0–58.0)	0.73	1
Ihle-Hansen H [47]	Norway	Europe	Retrospective Cohort	Medical Records	RT-PCR	43	67.8	0.67	5
Inciardi R M [48]	Italy	Europe	Retrospective Cohort	Medical Records	RT-PCR	99	68 .0 ± 12 .0	0.85	33
Ji M [49]	China	Asia Pacific	Retrospective Cohort	EHR	RT-PCR	101	51.0 (37.0–61.0)	0.48	12
Jin X [50]	China	Asia Pacific	Retrospective Cohort	Medical Records	RT-PCR	651	46.1 ± 14.2	NA	0
KCDC [51]	Korea	Asia Pacific	Cross-Sectional Study	Government reports	NA	54	75.5 (66.0–80.0)	0.61	13
Kalligeros M [52]	USA	North America	Retrospective Cohort	EHR	RT-PCR	103	60.0 (52.0–70.0)	0.61	9
Li J [53]	China	Asia Pacific	Case Series	Medical Records	RT-PCR	1178	55.5 (38.0–67.0)	0.46	32
Li K [32,54]	China	Asia Pacific	Retrospective Cohort	Medical Records	RT-PCR	78	44.6	0.49	9
Li X [55]	China	Asia Pacific	Retrospective Cohort	EHR	WHO Guideline	548	60.0 (48.0–69.0)	0.51	24
Liang W [5]	China	Asia Pacific	Retrospective Cohort	EHR	Laboratory confirmed	1590	NA	NA	18
Lin L [56]	China	Asia Pacific	Case-Control Study	Medical Records	RT-PCR	95	45.3	0.47	5
Liu K [57]	China	Asia Pacific	Retrospective Cohort	EHR	RT-PCR	137	57.0 (20.0–83.0)	0.45	2
Liu W [58]	China	Asia Pacific	Retrospective Cohort	Medical Records	RT-PCR	78	38.0 (33.0–57.0)	0.64	4

(*continued on next page*)

Table 1 (*continued*)

First author	Country	Continent	Study Design	Data Collection	Confirmation of COVID-19	COVID-19 Patients	Age (years)	Male Percentage	Cancer
Liu Y [59]	China	Asia Pacific	Case Series	Medical Records	Laboratory confirmed	12	NA	0.66	0
Lovell N [60]	UK	Europe	Case Series	Medical Records	Not specified	101	82.0 (72.0–89.0)	NA	25
Luong-Nguyen M [61]	France	Europe	Retrospective Cohort	Medical Records	Not specified	15	62.0 (35.0–68.0)	0.6	8
Malard F [62]	France	Europe	Retrospective Cohort	Medical Records	PCR	25	72	0.68	20
Mancia G [63]	Italy	Europe	Case-Control Study	Medical Records	RT-PCR	6272	68.0 ± 13.0	0.63	1091
Mao L [64]	China	Asia Pacific	Case Series	EHR	RT-PCR	214	52.7 ± 15.5	0.41	13
Meng Y [65]	China	Asia Pacific	Retrospective Cohort	Medical Records	Not specified	168	67.0 ± 15.0	0.52	1
Million M [66]	France	Europe	Retrospective Cohort	EHR	RT-PCR	1061	43.6	0.46	161
Miyashita H [1]	USA	North America	Retrospective Cohort	EHR	RT-PCR	5688	NA	NA	334
Molina JM [67]	France	Europe	Retrospective Cohort	Medical Records	PCR	11	58.7	0.64	5
Montopoli M [68]	Italy	Europe	Case-Control Study	EHR	WHO Guideline	9280	NA	0.49	786
Myers LC [69]	USA	North America	Retrospective Cohort	Medical Records	PCR	377	61.0 (50.0–73.0)	0.56	18
Nair V [70]	USA	North America	Case Series	EHR	RT-PCR	10	57.0 (47.0–67.0)	0.6	0
O'Reilly GM [71]	Australia	Asia Pacific	Retrospective Cohort	EHR	RT-PCR	240	60.0 ± 21.0	0.55	1
Pan L [72]	China	Asia Pacific	Cross-Sectional Study	EHR	RT-PCR	204	52.9 ± 16.0	0.55	13
Pereira MR [73]	USA	North America	Case Series	Medical Records	RT-PCR	90	57.0 (46.0–68.0)	0.59	3
Qi X [74]	China	Asia Pacific	Retrospective Cohort	Medical Records	Not specified	70	41.0 (27.5–50.0);	0.72	2
Qin C [75]	China	Asia Pacific	Retrospective Cohort	EHR	WHO Guideline	452	58.0 (22.0–95.0)	0.52	54
Safiya Richardson [76]	USA	North America	Case Series	EHR	PCR	5700	63.0 (52.0–75.0)	0.6	320
Shi H [77]	China	Asia Pacific	Retrospective Cohort	EHR	RT-PCR	81	49.5 ± 11.0	0.52	4
Shi S [78]	China	Asia Pacific	Retrospective Cohort	Medical Records	WHO Guideline	416	64.0 (21.0–95.0)	0.49	9
Shi Y [79]	China	Asia Pacific	Retrospective Cohort	EHR	WHO Guideline	487	46.0 ± 19.0	0.53	5
Stroppa EM [80]	Italy	Europe	Retrospective Cohort	EHR	RT-PCR	56	71.64 (50–84)	0.8	25
Sun B [81]	China	Asia Pacific	Retrospective Cohort	Medical Records	Not specified	38	58.0 (49.0–69.5)	91	4
Sun H [82]	USA	North America	Case Series	EHR	PCR	30	84.5 (71.0–97.0)	0.47	7
Sun Y [83]	Singapore	Singapore	Case-Control Study	EHR	PCR	788	34	0.49	94
Wan S [84]	China	Asia Pacific	Case Series	EHR	RT-PCR	135	47.0 (36.0–5.0)	0.53	4
Wang B [85]	China	Asia Pacific	Case Series	Medical Records	RT-PCR	26	5.0–72.0	0.42	1
Wang D [86]	China	Asia Pacific	Case Series	EHR	RT-PCR	138	56.0 (42.0–68.0)	0.54	10
Wang K [87]	China	Asia Pacific	Case Series	Medical Records	RT-PCR	144	53	0.51	1
Wang L [88]	China	Asia Pacific	Case Series	EHR	PCR	26	42.0 (33.5–53.3)	0.42	1
Wang L [89]	China	Asia Pacific	Retrospective Cohort	Medical Records	RT-PCR	116	54.0 (38.0–69.0)	0.58	12
Wang L [90]	China	Asia Pacific	Retrospective Cohort	EHR	Laboratory confirmed	339	71.0 ± 8.0	NA	15
Wang Y [91]	China	Asia Pacific	Retrospective Cohort	Medical Records	WHO Guideline	46	NA	0.57	2
Wang Z [92]	China	Asia Pacific	Case Series	EHR	RT-PCR	69	42.0 (35.0–62.0)	0.46	4
Wang, K. [93]	China	Asia Pacific	Retrospective Cohort	EHR	Not specified	114	53.0 (23.0–78.0)	0.51	1
Wu C [94]	China	Asia Pacific	Retrospective Cohort	EHR	RT-PCR	201	51.0 (43.0–60.0)	0.64	1
Wu J [95]	China	Asia Pacific	Retrospective Cohort	EHR	WHO Guideline	280	43.1 ± 19.0	0.54	33
Xie J [96]	China	Asia Pacific	Retrospective Cohort	Medical Records	RT-PCR	140	60.0 (47.0–68.0)	0.51	5

(*continued on next page*)

Table 1 (*continued*)

First author	Country	Continent	Study Design	Data Collection	Confirmation of COVID-19	COVID-19 Patients	Age (years)	Male Percentage	Cancer
Xu X [97]	China	Asia Pacific	Case Series	EHR	RT-PCR	90	50.0 (18.0–86.0)	0.43	2
Yang F [98]	China	Asia Pacific	Retrospective Cohort	Medical Records	RT-PCR	92	69.8 (30.0–97.0)	0.58	4
Yang F [99]	China	Asia Pacific	Retrospective Cohort	EHR	RT-PCR	1575	63 (34–98)	0.54	52
Yang X [100]	China	Asia Pacific	Retrospective Cohort	EHR	Laboratory confirmed	52	59.7 (13.3)	0.67	2
Yao Q [101]	China	Asia Pacific	Retrospective Cohort	Medical Records	Not specified	108	52.0 (37.0–58.0)	0.4	2
Yasukawa K [102]	USA	North America	Retrospective Cohort	Medical Records	Not specified	50	62.0 (22.0–78.0)	0.58	4
Yin L [103]	China	Asia Pacific	Case-Control Study	EHR	RT-PCR	45	52.4	0.56	3
Yu Q [104]	China	Asia Pacific	Retrospective Cohort	Medical Records	Laboratory confirmed	625	46.9 ± 15.4	0.53	6
Yuan M [105]	China	Asia Pacific	Retrospective Cohort	Medical Records	RT-PCR	27	60.0 (47.0–69.0)	0.44	1
Zhang J [106]	China	Asia Pacific	Retrospective Cohort	Medical Records	RT-PCR	290	NA	0.53	35
Zhang J [107]	China	Asia Pacific	Retrospective Cohort	Medical Records	Laboratory confirmed	111	38.0 (32.0–57.0)	0.41	8
Zhang L [108]	China	Asia Pacific	Retrospective Cohort	EHR	Laboratory confirmed	343	62.0 (48.0–69.0)	0.5	41
Zhang R [109]	China	Asia Pacific	Case Series	EHR	RT-PCR	120	45.4 ± 15.6	0.36	7
Zhang X [110]	China	Asia Pacific	Retrospective Cohort	EHR	WHO Guideline	645	46.7 ± 13.8	51.50%	0
Zhou F [111]	China	Asia Pacific	Retrospective Cohort	EHR	RT-PCR	191	56.0 (18.0–87.0)	0.62	2
Zhou Z [112]	China	Asia Pacific	Retrospective Cohort	EHR	WHO Guideline	254	50.6 (5.0–87.0)	0.45	30
Zhu W [113]	China	Asia Pacific	Retrospective Cohort	EHR	PCR	32	46.0 (35.0–52.0)	0.47	2
Ziehr DR [114]	USA	North America	Retrospective Cohort	EHR	Not specified	66	58.0 (23.0–87.0)	0.65	5

Note: COVID-19: Defined in accordance with WHO Guidelines [118]; Age (years): Mean ± SD or Median (range).

supplementary material) were similar to results obtained from the Metaprop method.

3.3. Severe illness incidence and mortality rate in COVID-19 patients with cancer

Based on the included 18 studies with available data, the pooled incidence of severe illness in COVID-19 patients with cancer was 0.34 (95% CI 0.26–0.42; Fig. 3A); based on four studies with available data, the pooled incidence of severe illness in COVID-19 patients without cancer was 0.14 (95% CI 0.08–0.20; Fig. S8A). Seventeen studies reported mortality data for COVID-19 patients with cancer. Their mortalities were synthesised using a random-effects model; the pooled mortality rate was 0.20 (95% CI 0.16–0.25; Fig. 4A). Based on the six included studies with available mortality data concerning COVID-19 patients without cancer, the pooled mortality rate was estimated to be 0.05 (95% CI 0.03–0.08; Fig. S8B).

Subgroup analysis by continent, on the basis of the 10 studies with available data, the pooled incidence of severe illness in COVID-19 patients with cancer from the Asia-Pacific region was 0.38 (95% CI 0.24–0.52); this was similar to the pooled incidence in patients from Europe, based on three studies (0.39, 95% CI 0.25–0.53; Fig. 3B), but was higher than the pooled incidence in patients from North America, based on three studies (0.26, 95% CI 0.20–0.31). Fig. 4B shows that the pooled mortality rates of COVID-19 patients with cancer were 0.17 in the Asia-Pacific region (95% CI 0.10–0.24; 10 studies), 0.26 in Europe (95% CI 0.18–0.35; four studies), and 0.19 in North America (95% CI 0.13–0.25; five studies).

3.4. Heterogeneity and meta-regression

Forest plots of cancer prevalence among COVID-19 patients (Figs. S1–S6) reveal high heterogeneity, with an overall I^2 of 98.68% ($P < 0.001$). Table 3 shows the results of meta-regression for the included 90 studies regarding cancer prevalence in COVID-19 patients. The between-study variance could be explained by the estimated differences with continent as a statistically significant variable ($I^2 = 62.37\%$, $\tau^2 = 0.0015$, and $P = 0.04$), and with country as a statistically significant variable ($I^2 = 46.74\%$, $\tau^2 = 0.0011$, and $P < 0.001$). Age group ($I^2 = 70.49\%$, $\tau^2 = 0.0016$, and $P = 0.20$), study design ($I^2 = 57.22\%$, $\tau^2 = 0.0015$, and $P = 0.35$), and sample size ($I^2 = 70.17\%$, $\tau^2 = 0.0015$, and $P = 0.075$) could not explain the heterogeneity.

3.5. Qualitative assessment and publication bias

Selected single-arm studies were evaluated for quality in accordance with AHRQ guidelines. As indicated in Table S2, of the 94 studies, 48 (score 4–7; 51.06%) showed a moderate risk of bias and 46 (score 0–3; 48.94%) showed a low risk of bias. The NOS tool was used to conduct a qualitative assessment of the selected studies to review their quality and detect possible bias. As shown in Table S3, of the 23 studies, one exhibited a low risk of bias (7–9 stars; 4.35%), 19 studies exhibited a moderate risk of bias (4–6 stars; 78.26%), one exhibited a high risk of bias (≤3 stars; 4.35%), and two could not be assessed because they were case series studies. No significant publication bias was observed in this meta-analysis ($P = 0.224$; funnel plot shown in Fig. 5).

4. Discussion

This systematic review and meta-analysis of 109 global studies is the

Table 2
Summary of characteristics of included studies of COVID-19 patients with cancer and clinical outcomes.

First author	Country	Study Design	Data Collection	COVID-19 Confirmation	COVID-19 Patients	Age (year)	Male Percentage	Cancer Patients	Severe illness with cancer	Severe illness without cancer	Death with cancer	Death without cancer
Dai M [33]	China	Retrospective Cohort	EHR	WHO guideline	641	64	0.55	105	35	75	12	27
Guan WJ [42]	China	Retrospective Cohort	EHR	RT-PCR	1590	49	0.57	130	9	245	3	47
He W [115]	China	Retrospective Cohort	EHR	CT scan	13	35	0.54	13	4	NA	8	NA
Liang W [8]	China	Retrospective Cohort	EHR	Laboratory confirmed	1590	63.1	NA	18	7	124	NA	NA
Luo J [116]	USA	Retrospective Cohort	EHR	RT-PCR	69	69 (31–91)	0.48	69	24	NA	16	NA
Ma J [117]	China	Retrospective Cohort	EHR	RT-PCR	37	62	0.541	37	20	NA	5	NA
Martín-MoroF [118]	Spain	Retrospective Cohort	EHR	RT-PCR	34	72.5 (35–94)	0.56	34	NA	NA	11	NA
Mehta V [119]	USA	Retrospective Cohort	EHR	RT-PCR	218	69(10–92)	NA	218	45	NA	61	NA
Miyashita H [120]	USA	Retrospective Cohort	EHR	RT-PCR	5688	NA	NA	334	NA	NA	37	518
Montopoli M [68]	Italy	Case-Control Study	EHR	WHO guideline	4532	NA	0.49	430	121	NA	75	312
Nicole M Kuderer [121]	USA, Canada and Spain	Retrospective Cohort	EHR	Laboratory confirmed	928	66 (57–76)	0.5	928	242	NA	121	NA
Rafi Kabarriti NPB [122]	USA	Retrospective Cohort	EHR	RT-PCR	107	70 (30–95)	0.5	107	NA	NA	24	NA
Stroppa EM [80]	Italy	Retrospective Cohort	EHR	RT-PCR	56	71 (50–84).	0.8	25	12	NA	9	NA
T de Rojas [123]	Spain	Case Series	EHR	PCR	15	11(1–19)	0.93	15	NA	NA	NA	NA
Wei X [124]	China	Retrospective Cohort	EHR	RT-PCR	252	64.8 ± 13.3	0.52	252	121	NA	NA	NA
Yang F [99]	China	Retrospective Cohort	EHR	RT-PCR	1575	63 (34–98)	0.54	52	19	NA	11	NA
Yang KY [125]	China	Retrospective Cohort	EHR	RT-PCR	8161	63 (14–96)	0.47	205	52	NA	40	NA
Yu J [126]	China	Case Series	EHR	WHO guideline	12	66	0.83	12	3	NA	3	NA
Zhang L [11]	China	Retrospective Cohort	EHR	RT-PCR	28	65	0.61	28	15	NA	8	NA
Lee LY [127]	UK	Retrospective Cohort	EHR	RT-PCR	800	69 (59–76)	0.56	800	360	NA	226	NA
Garassino MC [128]	Italy/Spain/France/ Switzerland/Netherlands/ USA/UK/China	Retrospective Cohort	EHR	RT-PCR; Symptom or radiologically suspected COVID-19.	200	68.0 (61.8–75.0)	0.70	200	13	NA	66	NA

Note: COVID-19: Defined in accordance with WHO Guidelines [118]; Age (years): Mean ± SD or Median (range).

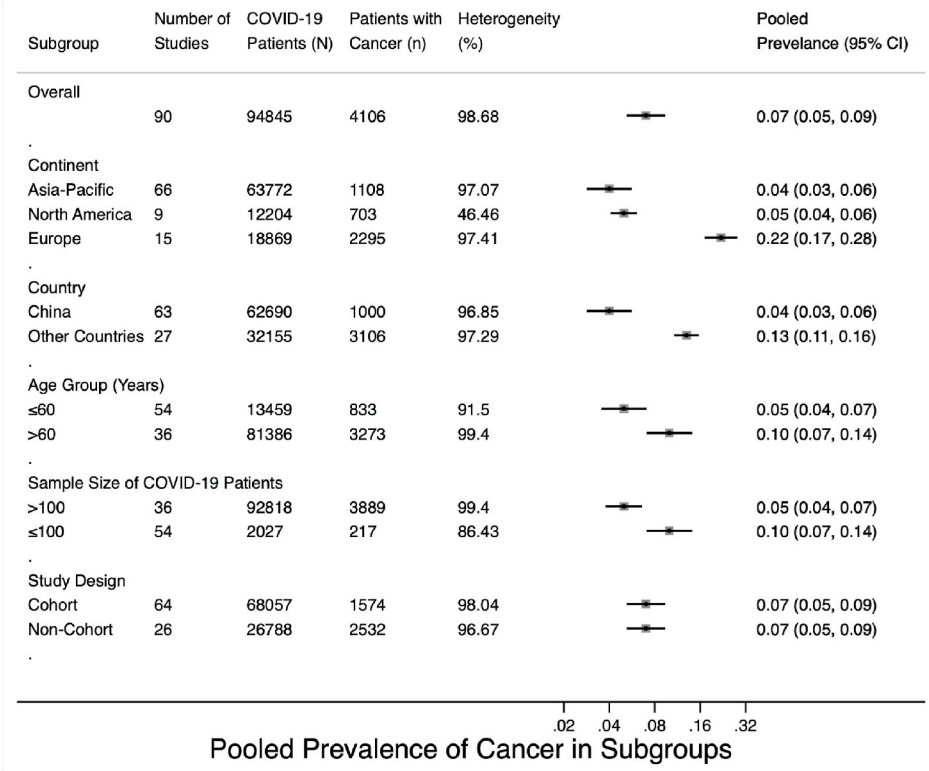

Fig. 2. Pooled prevalence of cancer in subgroups.

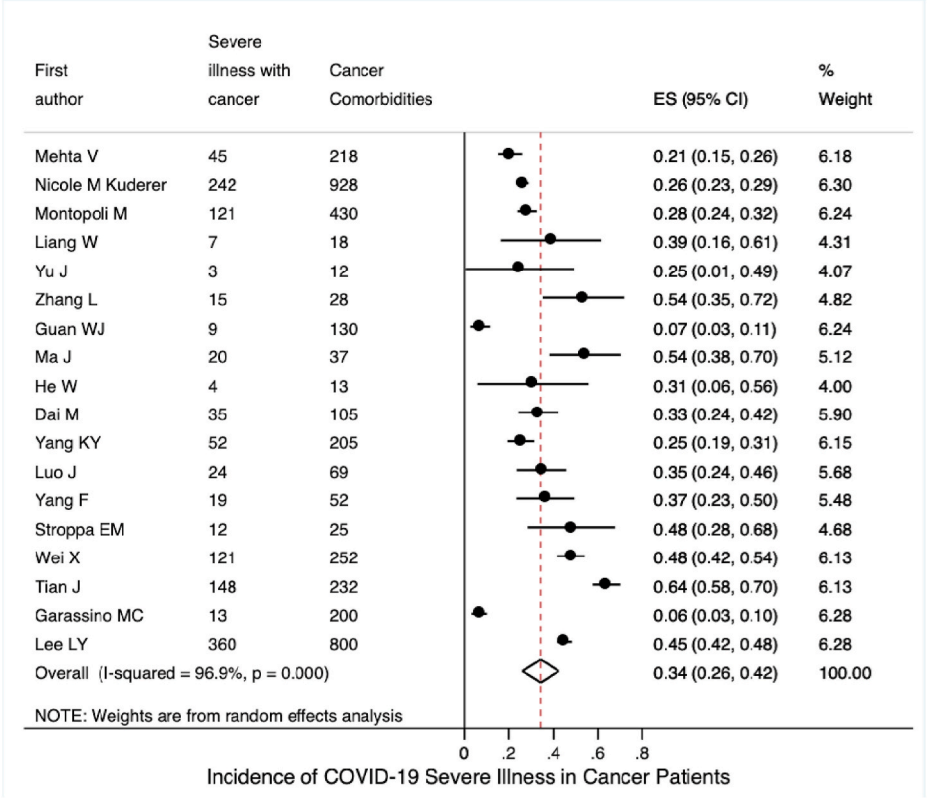

Fig. 3(A). Incidence of severe illness among COVID-19 patients with cancer.

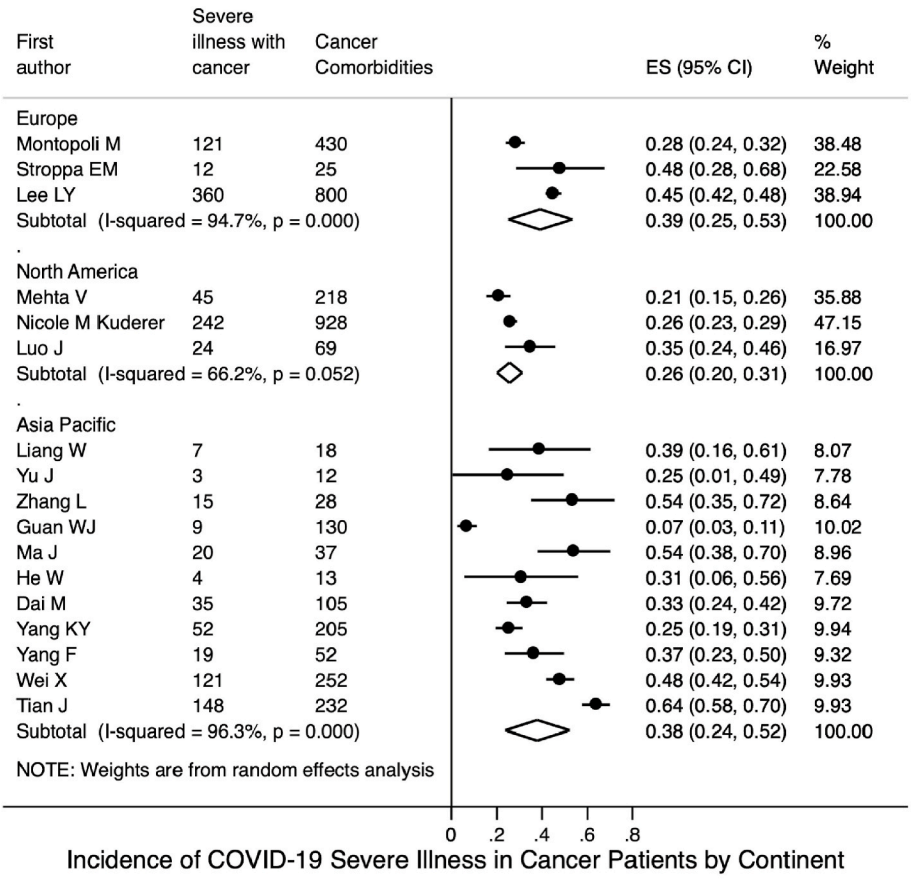

Fig. 3(B). Incidence of severe illness among COVID-19 patients with cancer stratified by continent.

most comprehensive meta-analysis to pool formally published studies concerning the prevalence of cancer in patients with COVID-19, as well as the incidence of severe illness and rate of mortality in cancer patients with COVID-19. Our findings revealed that the overall pooled prevalence of cancer in patients with COVID-19 in these studies was 0.07, higher than the prevalence of 0.02 (95% CI, 0.02–0.03) published by Aakash et al. in April 2020 [21]. In the Asia-Pacific region, the prevalence was slightly lower (0.04) than in North America (0.06), whereas the prevalence was significantly higher in Europe (0.22). Moreover, studies from China showed a lower overall prevalence (0.04), compared with studies from other countries (0.10). Statistical analyses from 2015 [9] revealed that the prevalence of cancer in the overall Chinese population was 285.83 per 100 000 people (0.29%), which is much lower than the prevalence of cancer in COVID-19 patients in China.

In May 2020, a pre-print of a meta-analysis by Venkatesulu et al., which included 31 studies concerning outcomes in cancer patients affected by COVID-19, demonstrated that cancer patients with COVID-19 had a higher likelihood of death (odds ratio [OR] 2.54) and that cancer patients were more likely to be intubated. They also showed that cancer patients with COVID-19 were older than the normal population and had higher rates of comorbidities. However, that study lacked pooled prevalences by some key variables, such as age and geographic region. Here, we conducted multiple subgroup analyses of cancer prevalence by continent, country, mean patient age, sample size, and study design, which yielded more detailed information; the findings also provided pooled prevalence data regarding cancer morbidity among patients with COVID-19. Notably, we found that age was associated with the prevalence of cancer in COVID-19 patients. Cancer prevalence among COVID-19 patients also differed across geographic regions, presumably for the following reasons:

1) In response to the COVID-19 pandemic, many countries implemented policies such as screening of healthcare staff and patients with respect to COVID-19 symptoms and travel history, placement of restrictions on employee business travel, establishment of COVID-19 hotline and response teams, engagement in telehealth and online meetings, education of staff to effectively use personal protective equipment, and minimisation of admissions and follow-up visits [21, 132]. Both prevalence and clinical outcomes might be affected by national or regional public health and epidemic prevention policies, which may also partially account for differences across geographic regions. Situations in Asian countries (e.g., China, South Korea, and Singapore) may partly be due to the government's policy, which included aggressive action involving the use of social-distancing measures to slow disease spread, as well as extensive testing and isolation of infected people to reduce the potential for transmission. This strategy helped the countries to contain the outbreak. However, several countries in Europe and North America required considerably longer intervals to address the spread of COVID-19. Some evidence suggests that patients with multiple morbidities (e.g., cancer) were more susceptible to COVID-19 and more likely to experience severe illness and worse outcomes. Therefore, in locations where the disease has not been well-controlled for an extended interval, inadequate public health measures (e.g., absence of mask use and premature large-scale gatherings) might cause cancer patients in these areas to experience a greater risk of COVID-19.
2) The subtypes of COVID-19 that are prevalent on different continents may exhibit considerable differences in terms of molecular structure, virulence, and invasiveness. In a phylogenetic network analysis of 160 COVID-19 genomes, Forster et al. found three central variants distinguished by amino acid alterations, which they regarded as subtypes A, B, and C [22]. The A and C subtypes were significantly

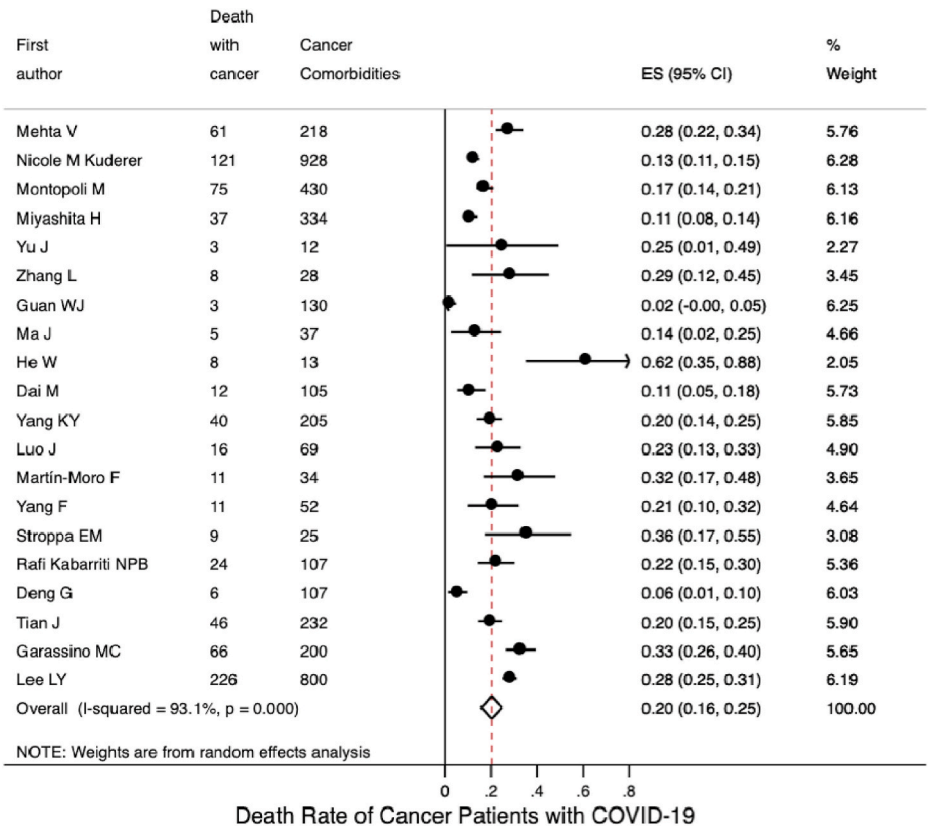

Fig. 4(A). Mortality rate of COVID-19 patients with cancer.

more prevalent mainly in Europeans and Americans. In contrast, the B subtype was most common in East Asia; its ancestral genome appears not to have spread outside East Asia prior to mutation into derived B subtypes, which indicates founder effects or immunological/environmental resistance against this subtype outside of Asia [22].

3) There are disparities in COVID-19 susceptibility and clinical outcomes across ethnic backgrounds. There has been debate concerning the extent to which the effects of COVID-19 differ among ethnic groups; thus far, relevant studies have explored the impact of ethnicity on COVID-19 mortality and morbidity. For instance, Santorelli et al. analysed the mortality rates in 1276 inpatients in Bradford with test results for COVID-19 across ethnic groups [23]. The age-adjusted risk of dying from COVID-19 was slightly lower in South Asian patients than in British patients (risk ratio [RR] 0.87; 95% CI 0.41–1.84) [23]. Similarly, Public Health England (PHE) reported disparities concerning the risks and outcomes of COVID-19 [24]. After adjustments for sex, age, and region, people from a Black, Asian, and Minority Ethnic (BAME) background had a higher risk of death from COVID-19 than British people; however, following adjustments for comorbidities, there were no differences in COVID-19 mortality among ethnic groups [24]. Few studies have compared the prevalence or incidence rates of COVID-19 among ethnic groups. In May 2020, Niedzwiedz et al. linked participants in the UK Biobank [25] to COVID-19 testing data from PHE. Of 392,116 participants in the cohort, 2658 were tested for COVID-19; 948 had positive test results. The incidences of COVID-19 were higher in Irish (RR 1.42; 95% CI 1.00–2.03), South Asian (RR 2.42; 95% CI 1.75–3.36), and Black (RR 3.35; 95% CI 2.48–4.53) individuals, compared with British individuals [25]. Our meta-analysis indicated that Caucasian patients with cancer were more likely to be infected with COVID-19, compared with Asian patients with cancer, which contrasted with the findings of previous epidemiological studies.

In May 2020, Kuderer et al. published a cohort study based on 928 cancer patients with COVID-19 [3]. They found that independent factors associated with mortality included age, male sex, smoking status, number of comorbidities, Eastern Cooperative Oncology Group performance status of $\geq$2, active cancer, and treatment with azithromycin plus hydroxychloroquine. In our study, because data regarding potential risk factors associated with mortality were limited among the included studies, we did not assess associations of clinical outcome with potential prognostic variables mentioned above, a considerable limitation of this study. However, a novel aspect and strength of the present meta-analysis is that we performed subgroup analysis by continent to assess the severe illness incidence and mortality rate among COVID-19 patients with cancer. There were some notable findings (Fig. 6): *1)* European COVID-19 patients had both the highest cancer prevalence (0.22) and highest cancer patient mortality (0.26); *2)* North American COVID-19 patients had a cancer prevalence similar to that of patients from the Asia-Pacific region, but had the lowest severe illness incidence among cancer patients (0.26); *3)* compared with patients from the Asia-Pacific region, European COVID-19 patients had a much higher cancer prevalence, whereas the incidences of severe illness among cancer patients were similar in these two groups (Asia-Pacific region, 0.38; Europe, 0.39); and *4)* compared with patients from the Asia-Pacific region, North American COVID-19 patients had a much lower severe illness incidence among cancer patients (0.26), whereas cancer prevalence and cancer patient mortality were similar. Overall, European COVID-19 patients were most likely to both develop cancer and experience cancer progression to severe illness and death. Although COVID-19 patients in the Asia-Pacific region had the lowest cancer prevalence, their severe illness incidence was similar to that of European patients. Finally, a continent-stratified analysis of severe illness incidence and mortality rate among COVID-19 patients with cancer is shown in Figs. S8A–B; given that the included studies were limited, subgroup analysis of patients without cancer was not performed. Another strength of this

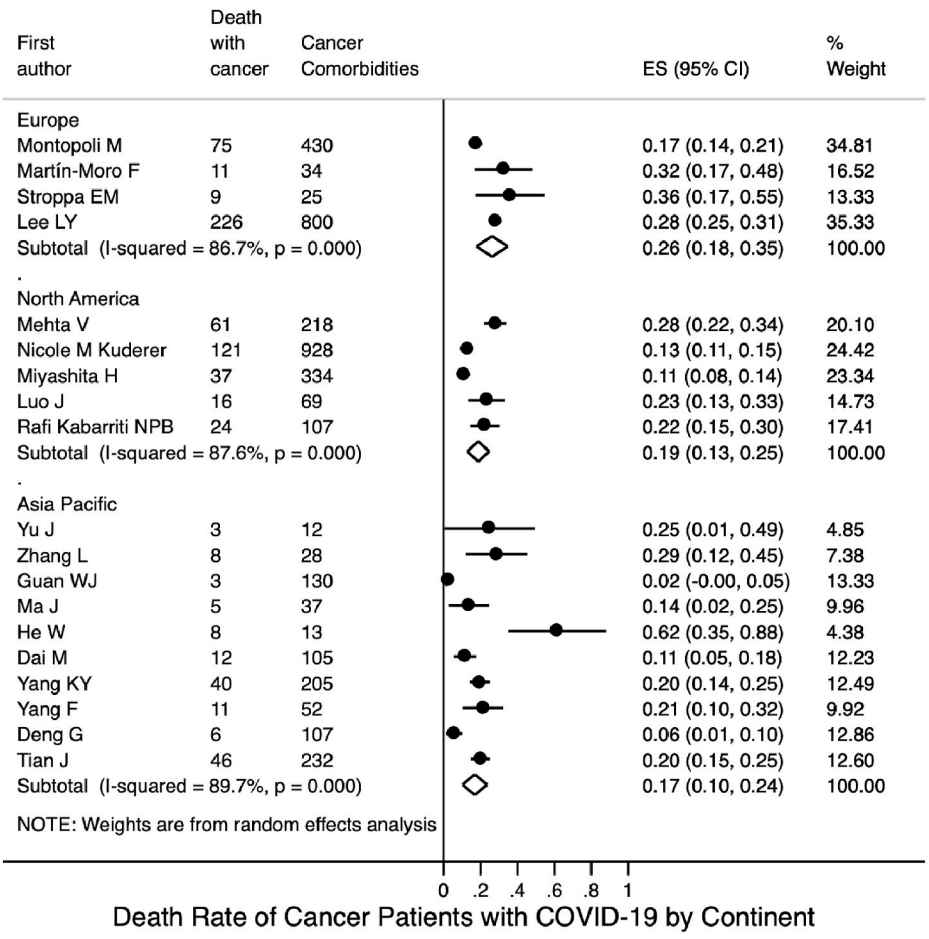

Fig. 4(B). Mortality rate of COVID-19 patients with cancer stratified by continent.

Table 3
Summary of meta-regression results for the 90 included studies.

Regression Variables	Number of Studies	Random Effect Pooled Prevalence (95% CI)	I^2 (%)	τ^2	P-value
1) Continent					
Asia-Pacific	66	0.04 (0.03–0.06)	62.37	0.0015	0.04*
Europe	15	0.22(0.17–0.28)			
North America	9	0.05 (0.04–0.06)			
2) Country					
China	63	0.04 (0.03–0.06)	46.74	0.0011	<0.001*
Other Countries	27	0.13 (0.11–0.16)			
3) Age Group (Years)					
≤60	54	0.05 (0.03–0.06)	70.49	0.0016	0.2
>60	36	0.10 (0.07–0.14)			
4) Study Design					
Cohort	64	0.07 (0.05–0.09)	57.22	0.0015	0.35
Non-Cohort	26	0.07 (0.05–0.09)			
5) Sample Size					
≤100	54	0.10 (0.07–0.14)	70.17	0.0015	0.075
>100	36	0.05 (0.04–0.07)			

Note: I^2, percent residual variation due to heterogeneity; τ^2, residual maximum likelihood estimates of between-study variance; CI, confidence interval.

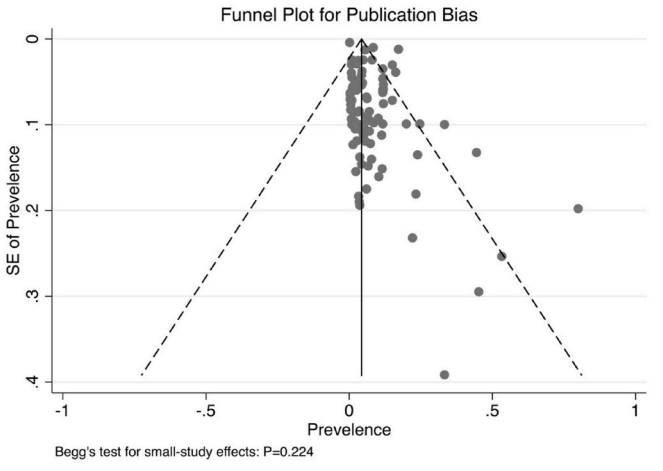

Fig. 5. Funnel plot with pseudo 95% confidence limits and Begg's test.

meta-analysis is that it descriptively demonstrated the severe illness incidence and mortality rate in COVID-19 patients with and without cancer. Cancer patients typically exhibit systemic immunosuppressive states caused by the malignancy itself and anticancer treatments (e.g., chemotherapy, surgery, or immunomodulatory drugs such as PD-1/PD-L1 inhibitors) [4,6,8]; thus, their ability to resist the virulence and invasiveness of the infection is considerably weaker. In addition, these patients are often older and exhibit one or more major comorbidities, such that they are at increased risk for COVID-19-related mortality [7].

Our systematic review and meta-analysis had several limitations: *1)* Heterogeneity was observed in the included studies, both for the estimation of prevalence and for the analyses of severe illness and mortality.

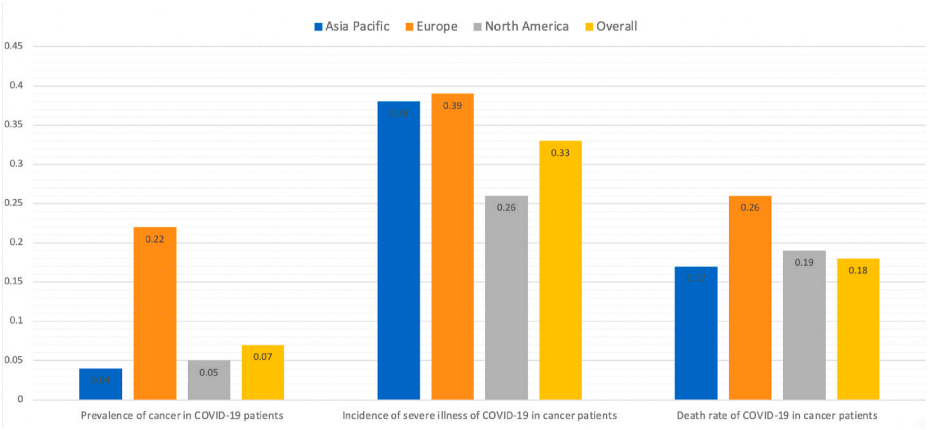

Fig. 6. Prevalence, severe illness incidence, and mortality rate of COVID-19 patients with cancer, stratified by continent.

We minimised the influence of heterogeneity by using a random-effects model; we also performed exploratory subgroup analyses by continent, country, age, sample size, and study design. Furthermore, we used both Metan and Metaprop approaches to test the robustness of the results. *2)* This study might have been limited by the retrospective nature of most of the included studies. To minimise possible inaccuracies, we conducted subgroup analysis by study design, separately pooling the prevalences of cohort and non-cohort studies (e.g., case-series, case-control, and cross-sectional studies). *3)* The definitions of "severe illness" were not uniform and differed among the included studies, which might lead to heterogeneities to some extent. Generally, severe illness referred to a composite of severe illness requiring mechanical ventilation, admission to an ICU, admission to hospital, or a combination of these; mechanical ventilation; admission to an ICU; admission to hospital; and need for supplemental oxygen during the course of COVID-19. *4)* Most included studies did not indicate a specific time period for the mortality rate; hence, the objectivity of the mortality comparison might have been influenced by reporting bias due to the lack of conformity concerning the time interval. In addition, longer-term follow-up and larger sample sizes are needed to understand the epidemiological and clinical characteristics of cancer patients more completely during the course of COVID-19 [133,134]. *5)* When performing continent-stratified analysis for severe illness incidence and mortality rate, the included studies for each subgroup were limited due to data availability. *6)* Although we performed a thorough assessment of literature quality, illustrating that the problem of bias was not serious and within the acceptable range, we acknowledge the likely effect of selection bias in the primary studies included in this meta-analysis, especially given that many of the studies use convenience sampling. *7)* The datalock used was July 15 2020. Given the pace at which COVID-19 data is being published, we will update our analysis in a timely fashion.

5. Conclusions

Taken together with previously published results, our meta-analysis provides a comprehensive picture of the epidemiological and clinical characteristics of cancer patients with COVID-19. The estimated cancer prevalence among COVID-19 patients was 0.07 (95% CI 0.05–0.09); this prevalence increased with age. The prevalence was much higher in Europe than in the Asia-Pacific region or North America. COVID-19 patients with cancer were at risk of more severe illness and a higher mortality rate. These findings concerning cancer patients with COVID-19 reinforce important considerations for clinical care and emphasise the urgent need for more data with longer-term follow-up, larger sample sizes, and more detailed sociodemographic and clinicopathological variables. In the future, with the availability of additional data, it will be important to investigate differences across more sociodemographic and clinicopathological features (e.g., sex, race, smoking status, symptoms and signs, cancer type, laboratory results, and tumour stage) in COVID-19 patients with and without cancer.

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Author contributions

Conceptualization, Yu Jiang, Lin Zhang, Xiangyi Kong, Yi Fang, Jing Wang; Data Collection, Yihang Qi, Lin Zhang, Xiangyi Kong; Methodology, Junjie Huang, Yang Zhao, Xuzhen Qin, Zhihong Qi, Adejare (Jay) Atanda, Lei Zhang, Peng Jia; Supervision, Yu Jiang, Asieh Golozar; Writing - original draft, Xiangyi Kong, Lin Zhang, Yihang Qi; Writing - review & editing, Asieh Golozar, Adejare (Jay) Atanda, Lei Zhang, Xiangyi Kong, Lin Zhang. All authors have read and agreed to the published version of the manuscript.

Ethical approval

The analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences, and Peking Union Medical College institutional review board provided a waiver (exemption) for approval.

Declaration of competing interest

The authors declare that they have no conflicts of interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.canlet.2021.02.012.

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