CANCER EPIDEMIOLOGY

Cancer associates with risk and severe events of COVID-19: A systematic review and meta-analysis

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Abstract

Evidence is mounting to indicate that cancer patients may have more likelihood of having coronavirus disease 2019 (COVID-19) but lack consistency. A robust estimate is urgently needed to convey appropriate information to the society and the public, in the time of ongoing COVID-19 pandemic. We performed a systematic review and meta-analysis through a comprehensive literature search in major databases in English and Chinese, and two investigators conducted publication selection and data extraction independently. A meta-analysis was used to obtain estimates of pooled prevalence of cancer in patients with COVID-19 and determine the association of cancer with severe events, after assessment of potential heterogeneity, publication bias, and correction for the estimates when necessary. Total 38 studies comprising 7094 patients with COVID-9 were included; the pooled prevalence of cancer was estimated at 2.3% (95% confidence limit [CL] [0.018, 0.029]; *P* < .001) overall and 3.2% (95% CL [0.023, 0.041]; *P* < .001) in Hubei province; the corresponding estimates were 1.4% and 1.9% after correction for publication bias; cancer was significantly associated with the events of severe cases (odds ratio [OR] = 2.20, 95% CL [1.53, 3.17]; *P* < .001) and death (OR = 2.97, 95% CL [1.48, 5.96]; *P* = .002) in patients with COVID-19, there was no significant heterogeneity and a minimal publication bias. We conclude that cancer comorbidity is associated with the risk and severe events of COVID-19; special measures should be taken for individuals with cancer.

KEYWORDS

cancer, comorbidity, COVID-19, meta-analysis, severe events

1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a new respiratory disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1] Because the causative viral pathogen is highly infective and with human-to-human transmission, the COVOD-19 is having a fast spread worldwide. On March 12, 2020, when there were over 20 000 confirmed cases and 1000 deaths in the European region, the World Health Organization (WHO) announced a pandemic of

COVID-19, which has caused the ongoing global public health emergency.

COVID-19 is an infectious disease and almost all people lack specific immunity to the novel coronavirus. Individuals can be infected by contact with respiratory droplets containing SARS-CoV-2 virus or the surfaces contaminated.[2] Older people and individuals with underlying chronic health conditions may increase the risk of developing COVID-19 and being with severe events, likely due to the aging-associated dysregulation of immune systems.[3] The major symptoms of clinical manifestation include fever, cough, fatigue, myalgia or arthralgia, sore throat, headache, shortness of breath (anhelation or dyspnea) and sputum production.[4] A clinical report from one of the hospitals in Wuhan shows that patients who received Intensive Care Unit (ICU) services are more prevalent of respiratory failure (61.1%), arrhythmia (44.4%), and a sudden shock (30.6%).[5] In some severe cases, the coronavirus infection can lead to acute respiratory distress syndrome, acute cardiac or kidney injury, secondary infection, shock and high risk of death.[6] A nationwide report (n = 72 314) from China shows that the severe and critical cases of COVID-19 account for 19% and the case-fatality rate is about 49.0% in the critical cases[7] because of lacking effective treatment for the coronavirus.[8]

In addition, multiple reports have shown that underlying chronic health conditions such as hypertension and diabetes are associated with severe patients with COVID-19.[4,9] This is likely because the receptor of angiotensin-converting enzyme-2 (ACE-2), which the spike proteins of the pathogen SARS-CoV-2 bind to enter the host cells, is associated with hypertension[10] and diabetes.[11] Also, there is a growing interest in the association of cancer with COVID-19.[8,12]

Cancer is a severe underlying condition in patients with COVID-19. Patients with cancer are usually characterized by older age, compromised immune systems, and comorbid with chronic diseases, which might be partially caused by antitumor treatment. Individuals with cancer may be more likely to have COVID-19. One hospital-based study has noted a few cases with cancer,[13] but a robust estimate of cancer prevalence in patients with COVID-19 is lacking. Here, we conducted a systematic review and meta-analysis of cancer prevalence in patients with COVID-19, and examined the association of cancer with severe events, which include severe cases judged by clinical symptoms (SJCS), utilization of ICU services and death.

2 | METHODS

The meta-analysis was conducted in accordance with the guidelines in the Preferred Reporting Items for Systematic Reviews and Meta-analyzes (PRISMA) statement.[14] Conducting of this systematic review and meta-analysis was based on existing literature, and therefore was not registered.

2.1 | Search strategy

A literature search was first performed in major databases of PubMed, Elsevier and Web of Science to identify all published studies with full

What's new?

There is mounting evidence that cancer patients have a greater likelihood of having coronavirus disease 2019 (COVID-19), but consistency is still lacking. This study provides the first estimate after correction for publication bias of cancer prevalence in patients with COVID-19 based on a comprehensive literature search and analysis. The results show that patients with cancer and cancer survivors are at an elevated risk of developing COVID-19 and are also 2- to 3-fold more likely of suffering severe events and death. These findings have implications for public health, calling for the establishment of appropriate measures to manage cancer patients with COVID-19.

text, as of April 23, 2020, and the language was first limited to English. The search terms were as follows: "2019-nCoV" [All fields] or "novel coronavirus" [All fields] or "SARS-CoV-2" [All fields] or "COVID-19" [All fields]. Additional search was performed in the three major Chinese databases—China National Knowledge Infrastructure (CNKI) (https://www.cnki.net), WanFang (http://www.wanfangdata.com.cn), and VIP (http://www.cqvip.com). The above process was performed by two investigators (Y. T. and X. Q.) independently.

2.2 | Inclusion and exclusion criteria

A study was included when met all the following criteria: (a) reporting information on clinical characteristics and epidemiology of the patients with a laboratory-confirmed diagnosis of COVID-19, (b) containing information on cancer and clinical subtypes, or outcomes of the clinically validated death, severe cases, ICU care or disease progression and (c) an original study.

A study was excluded when met one of the following criteria: (a) case report, animal research, review, guideline, expert consensus, letter, protocol, news or comment, (b) with incomplete information on related data, (c) only on special populations such as children, pregnancy, older people or (d) sample size of fewer than 20 individuals and overlapped study samples. Also, we excluded two studies that were conducted in the populations of the United States and Iran.

2.3 | Data extraction

Two investigators (X. J. and X. Q.) screened and extracted data according to the predesigned form of Excel spreadsheet independently. Questions or inconsistencies were resolved through discussion or consultation with a third expert (J. H.) to make a final decision. Information extracted from the included literature includes the name of the first author, year of publication, region, sample size, age, gender, the status of severe cases, utilization of ICU and event of death, where appropriate.

2.4 | Statistical analysis

The Stata (special edition version 14.0) for Windows (Stata Corp, College Station, Texas) was used to obtain the estimates of cancer prevalence in patients with COVID-19. A pooled odds ratio (OR) was used to measure the strength of association, and 95%

confidence limit (CL) measured the precision of the estimates. Heterogeneity was measured by $I^2 = 100 \times \frac{Q-df}{Q}$, a statistic that measures the proportion of variance in the estimates is due to the heterogeneity between studies, where Q is Cochran's statistic, a classical measure of heterogeneity, which can provide a statistical test based on Chi-square statistic.[15] A threshold of P-value was set at .05. In the

Records identified through PubMed, Elsevier, Web of Science datasets searching
(n=4717)

Additional records identified through CNKI, WanFang and VIP datasets
(n=1007)

5724 records screened

Records after duplicates removed (n=961)

Records pulled following title/abstracts screened
(n=4763)

Records excluded by title and abstract review (n=4567)
• animal research   (n=34)
• protocols   (n=52)
• case reports   (n=94)
• guidelines or consensus
  or recommendations   (n=687)
• news and comments   (n=1322)
• not meet eligibility criteria (n=2378)

Full-text articles assessed for eligibility
(n=196)

Full-text articles excluded with reasons (n=158)
• reviews   (n=3)
• samples outside China   (n=2)
• sample sizes<20   (n=35)
• absense of required data   (n=118)

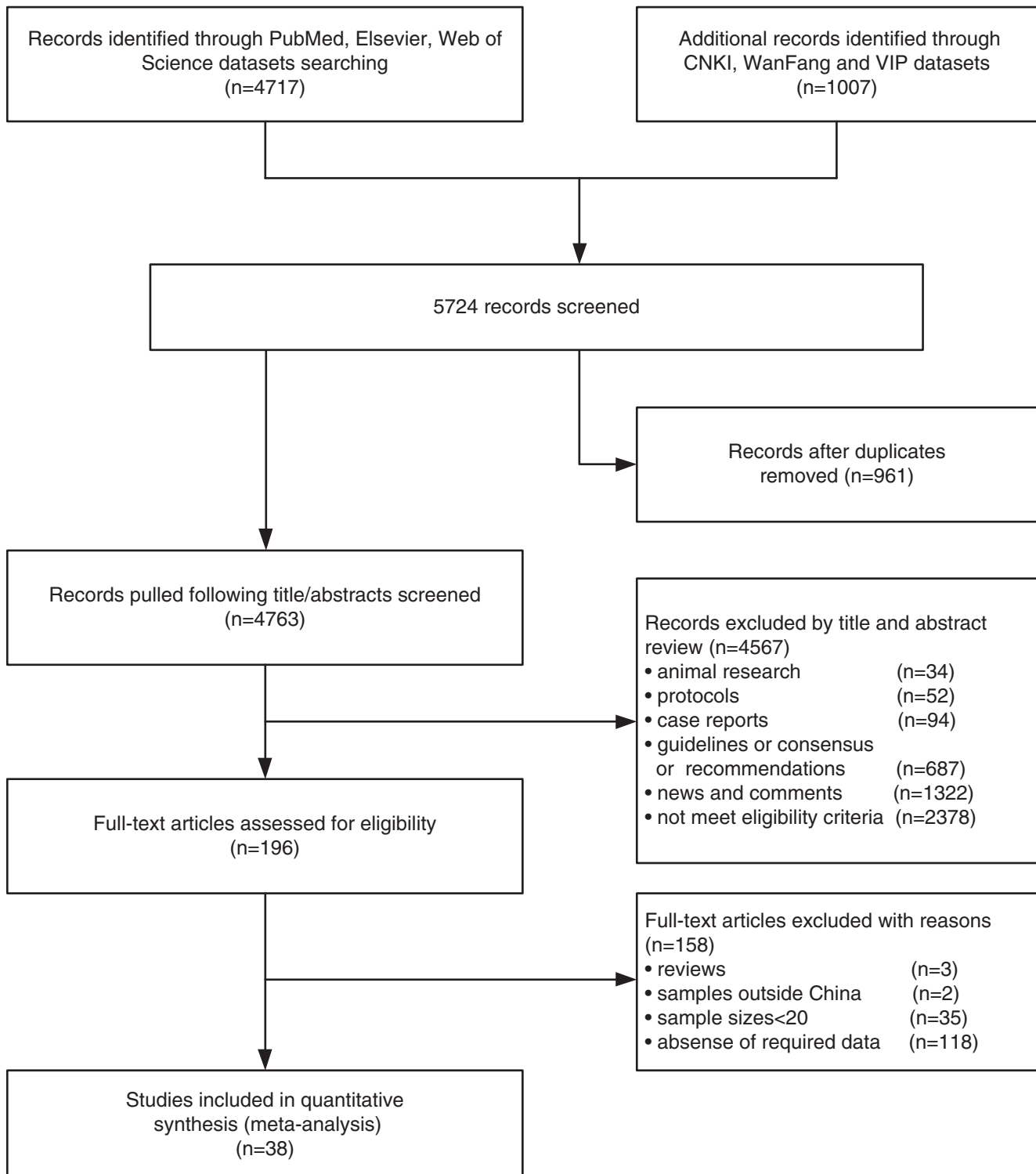Studies included in quantitative synthesis (meta-analysis)
(n=38)

FIGURE 1   Flowchart of the literature search and selection process

TABLE 1 Characteristics of the included studies

| First author | Province | COVID-19 | | | | Severe events | | |
		All	Sex (M/F)	Age(year) (Med/Mean)	Cancer n (%)	Type	Covid19 n (%)	Cancer n (%)
Cao, J. L.[17]	Hubei	102	53/49	54 (37-67)	4 (3.9%)	Death	17 (16.7%)	1 (1%)
Chen, J.[18]	Shanghai	249	126/123	51 (36-64)	1 (0.4%)	ICU	22 (8.8%)	NA
Chen, L.[19]	Wuhan	29	21/8	56 (26-79)	1 (3.4%)	Death	2 (6.9%)	1 (3.4%)
Chen, L.[19]	Wuhan	29	21/8	56 (26-79)	1 (3.4%)	SJCS	14 (48.3%)	1 (3.4%)
Chen, N. S[20]	Hubei	99	76/32	55.5 ± 13.1	1 (1%)	Death	11 (11.1%)	NA
Chen, N. S[20]	Hubei	99	76/32	55.5 ± 13.1	1 (1%)	ICU	23 (23.2%)	NA
Chen, T.[21]	Hubei	274	171 /103	51 (44-70)	7 (2.6%)	Death	113 (41.2%)	5 (1.8%)
Deng, Y.[22]	Hubei	225	124/101	NA	8 (3.6%)	Death	109 (48.4%)	6 (2.7%)
Du, R. H.[23]	Hubei	109	74/35	70.7 ± 10.9	8 (7.3%)	ICU	51 (46.8%)	2 (1.8%)
Fang, X.W.[24]	Anhui	79	45/34	45.1 ± 16.6	1 (1.3%)	SJCS	24 (30.4%)	0
Feng, Y.[25]	Multi-PR	476	271/205	53 (40-64)	12 (2.5%)	SJCS	124 (26.1%)	7 (1.5%)
Guan, W. J.[26]	Multi-PR	1590	904/674	48.9 ± 16.3	18 (1.1%)	Death	50 (3.1%)	3 (0.2%)
Guan, W. J.[26]	Multi-PR	1590	904/674	48.9 ± 16.3	18 (1.1%)	ICU	99 (6.2%)	5 (0.3%)
Huang, C.L.[6]	Hubei	41	30/11	49 (41-58)	1 (2.4%)	ICU	13 (31.7%)	0
Huang, Y. H[27]	Hubei	34	14/20	56.24 ± 17.14	3 (8.8%)	NA	NA	NA
Li, D.[28]	Hunan	80	40/40	47.5 (3-90)	1 (1.3%)	SJCS	17 (21.3%)	1 (1.3%)
Li, X. C[29]	Hubei	548	279/269	60 (48-69)	24 (4.4)	SJCS	269 (49.1%)	14 (2.6%)
Li, Y.L.[30]	Anhui	49	28/21	45 (32-60)	1 (2.0%)	NA	NA	NA
Liu, C.[31]	Multi-PR	32	20/12	38.5 (26.5-5.75)	2 (6.3%)	NA	NA	NA
Liu, K.[32]	Hubei	137	61/76	57 (20-83)	2 (1.5%)	Death	16 (11.7%)	NA
Liu, W.[33]	Hubei	78	39/39	38 (33-57)	4 (5.1%)	SJCS	7 (9%)	2 (2.6%)
Mao, L.[34]	Hubei	214	87/127	52.7 ± 15.5	13 (6.1%)	SJCS	88 (41.1%)	5 (2.3%)
Mo, P. Z.[35]	Hubei	155	86/69	54 (42-66)	7 (4.5%)	SJCS	85 (54.8%)	5 (3.2%)
Shi, H. S.[36]	Hubei	81	42/39	49.5 ± 11.0	4 (4.9%)	NA	NA	NA
Sun, D.F.[37]	Zhejiang	30	15/15	49 (30-71)	1 (3.3%)	NA	NA	NA
Wan, S. X[38]	Chongqing	135	72/63	47 (36-55)	4 (3.0%)	SJCS	40 (29.6%)	3 (2.2%)
Wang, D. W.[5]	Hubei	138	75/63	56 (42-68)	10 (7.2%)	ICU	36 (26.1%)	4 (2.9%)
Wang, F.[39]	Ningxia	29	19/10	NA	1 (3.4%)	NA	NA	NA
Wang, L. Z.[40]	Shandong	26	15/11	42.0 (33.5-53.3)	1 (3.8%)	NA	NA	NA
Wang, R. R[41]	Anhui	125	71/54	38.76 ± 13.79	1 (0.8%)	Death	0	NA
Wang, Z. L[42]	Hubei	69	32/37	42.0 (35.0-62.0)	4 (5.8%)	SJCS	14 (20.3%)	NA
Wang, Z. L[42]	Hubei	69	32/37	42 (35-62)	4 (5.8%)	Death	5 (7.2%)	NA
Wu, C. M[43]	Hubei	201	128/73	51 (43-60)	1 (0.5%)	Death	44 (21.9%)	NA
Wu, C. M[43]	Hubei	201	128/73	51 (43-60)	1 (0.5%)	ICU	53 (26.4%)	NA
Wu, J.[44]	Jiangsu	80	39/41	46.10 ± 15.42	1 (1.3%)	Death	0	NA
Wu, J.[44]	Jiangsu	80	39/41	46.10 ± 15.42	1 (1.3%)	SJCS	3 (3.8%)	NA
Xu, X.[45]	Guangdong	90	39/51	50 (18-86)	2 (2.2%)	SJCS	38 (42.2%)	NA
Yang, W.J[46]	Zhejiang	149	81/68	45.11 ± 13.35	2 (1.3%)	NA	NA	NA
Yang, X. B.[9]	Hubei	52	35/17	59.7 ± 13.3	2 (3.8%)	Death	32 (61.5%)	1 (1.9%)
Zhang, G. Q[47]	Hubei	221	108/113	55.0 (39.0-66.5)	9 (4.1%)	SJCS	55 (24.9%)	3 (1.4%)
Zhang J. X.[48]	Hubei	663	321/342	55.6 (44-69)	14 (2.1%)	SJCS	409 (61.7%)	4 (0.6%)
Zhang J. X.[48]	Hubei	663	321/342	55.6 (44-69)	14 (2.1%)	Death	25 (3.8%)	11 (1.7%)
Zhang, J. J.[49]	Hubei	140	71/69	57 (25-87)	6 (4.3%)	SJCS	58 (41.4%)	0
Zhang, W.[50]	Beijing	74	45/34	52.7 ± 19.1	2 (2.7%)	SJCS	18 (24.3%)	2 (2.7%)
Zhou F.[51]	Hubei	191	119/72	56 (46-67)	2 (1.0%)	Death	54 (28.3%)	0

Note: M, male; F, female; ICU, intensive care unit; Multi-PR (multi-province), means the sample source including both Hubei and one or more other provinces; SJCS, severity judged by clinical symptoms; NA, not available.

presence of a significant heterogeneity, a random-effect meta-analysis was performed. Also, cumulative meta-analysis, sensitivity analysis, subgroup analysis was performed to assess the systematic bias, and meta-regression modeling was performed to adjust for potential covariates.

Publications bias was assessed using the Begg's rank correlation test and Egger's linear regression test. A threshold of P-value was set at .05. In the presence of publication bias, "trim and fill" method was used to estimate the number of expected missing studies and to obtain a corrected estimate.[16]

Study power was calculated using PS (Power and Sample Size Calculations, version 3.0) software.

3 | RESULTS

3.1 | Characteristics of included studies

Through a comprehensive literature search, 5724 relevant articles were identified. Duplications were found by carefully scanning the
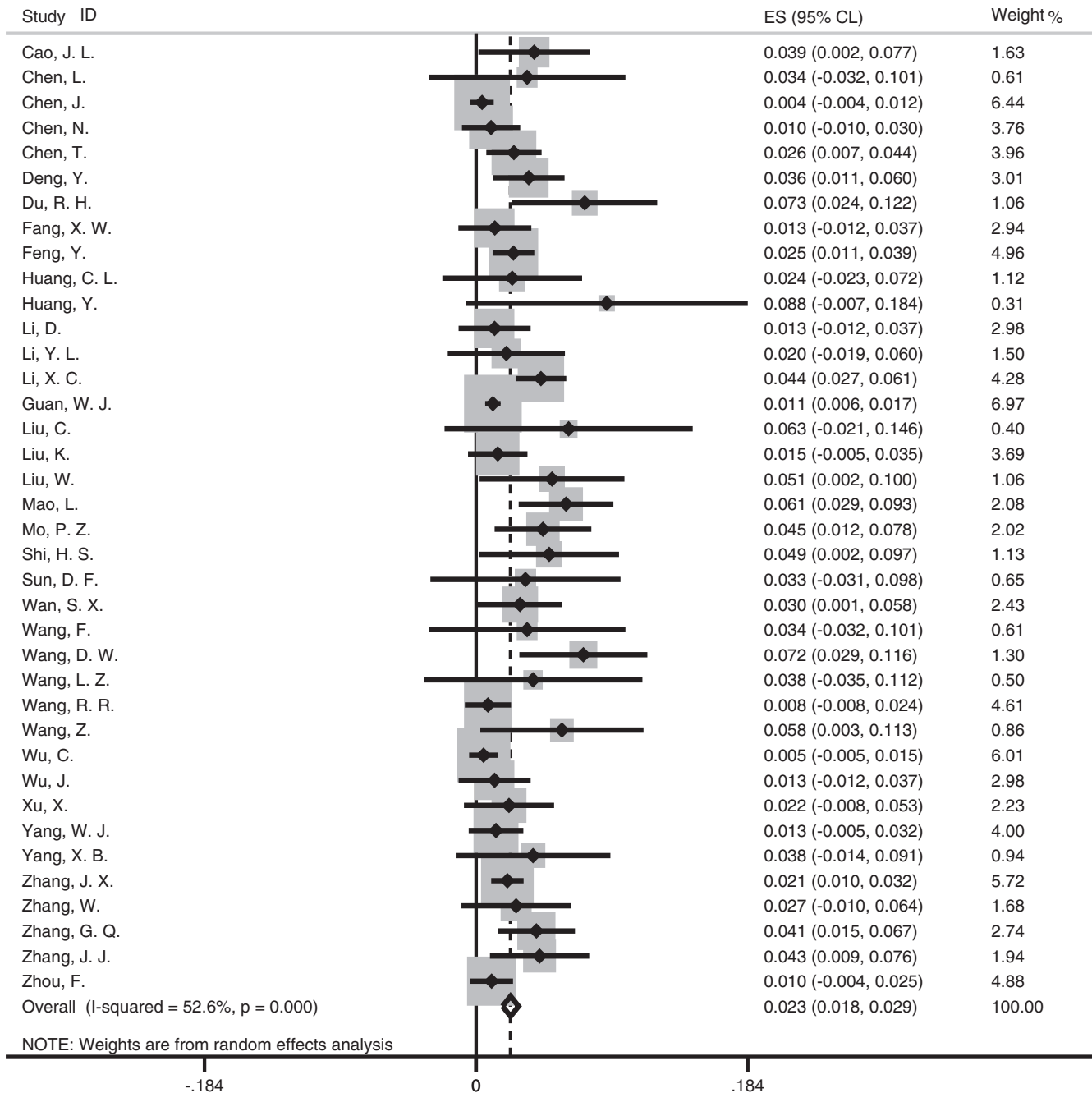
Study ID		ES (95% CL)	Weight %
Cao, J. L.		0.039 (0.002, 0.077)	1.63
Chen, L.		0.034 (-0.032, 0.101)	0.61
Chen, J.		0.004 (-0.004, 0.012)	6.44
Chen, N.		0.010 (-0.010, 0.030)	3.76
Chen, T.		0.026 (0.007, 0.044)	3.96
Deng, Y.		0.036 (0.011, 0.060)	3.01
Du, R. H.		0.073 (0.024, 0.122)	1.06
Fang, X. W.		0.013 (-0.012, 0.037)	2.94
Feng, Y.		0.025 (0.011, 0.039)	4.96
Huang, C. L.		0.024 (-0.023, 0.072)	1.12
Huang, Y.		0.088 (-0.007, 0.184)	0.31
Li, D.		0.013 (-0.012, 0.037)	2.98
Li, Y. L.		0.020 (-0.019, 0.060)	1.50
Li, X. C.		0.044 (0.027, 0.061)	4.28
Guan, W. J.		0.011 (0.006, 0.017)	6.97
Liu, C.		0.063 (-0.021, 0.146)	0.40
Liu, K.		0.015 (-0.005, 0.035)	3.69
Liu, W.		0.051 (0.002, 0.100)	1.06
Mao, L.		0.061 (0.029, 0.093)	2.08
Mo, P. Z.		0.045 (0.012, 0.078)	2.02
Shi, H. S.		0.049 (0.002, 0.097)	1.13
Sun, D. F.		0.033 (-0.031, 0.098)	0.65
Wan, S. X.		0.030 (0.001, 0.058)	2.43
Wang, F.		0.034 (-0.032, 0.101)	0.61
Wang, D. W.		0.072 (0.029, 0.116)	1.30
Wang, L. Z.		0.038 (-0.035, 0.112)	0.50
Wang, R. R.		0.008 (-0.008, 0.024)	4.61
Wang, Z.		0.058 (0.003, 0.113)	0.86
Wu, C.		0.005 (-0.005, 0.015)	6.01
Wu, J.		0.013 (-0.012, 0.037)	2.98
Xu, X.		0.022 (-0.008, 0.053)	2.23
Yang, W. J.		0.013 (-0.005, 0.032)	4.00
Yang, X. B.		0.038 (-0.014, 0.091)	0.94
Zhang, J. X.		0.021 (0.010, 0.032)	5.72
Zhang, W.		0.027 (-0.010, 0.064)	1.68
Zhang, G. Q.		0.041 (0.015, 0.067)	2.74
Zhang, J. J.		0.043 (0.009, 0.076)	1.94
Zhou, F.		0.010 (-0.004, 0.025)	4.88
Overall (I-squared = 52.6%, p = 0.000)		0.023 (0.018, 0.029)	100.00

NOTE: Weights are from random effects analysis

-.184   0   .184

FIGURE 2 Forest plot for meta-analysis of cancer prevalence in patients with COVID-19

titles and abstracts, and then removed. Thirty-eight studies met the inclusion and exclusion criteria were included in the meta-analysis, and 22 of which were from the Hubei province. Of the included studies, 7094 patients with COVID-19, and 206 (2.90%) patients had cancer. The search process is shown in Figure 1, and the characteristics of all included studies are presented in Table 1.

3.2 | Cancer prevalence of patients with COVID-19

The pooled prevalence of cancer in patients with COVID-19 (Figure 2) was estimated at 2.3% (95% CL [0.018, 0.029]; $I^2 = 52.6\%$, $P < .001$), which was obtained with a random-effect meta-analysis. Cumulative analysis showed the estimates of early studies were fluctuating and with larger variance. However, by the last few studies, the estimates and precision approached a constant (Figure S1).

Separate analysis by sample location estimated that the pooled cancer prevalence in Hubei (Figure 3) was at 3.2% (95% CL [0.023, 0.041]; $I^2 = 59.3\%$; $P < .001$) with a random-effect meta-analysis, while it was at 1.0% in the samples outside Hubei and 1.8% in the samples from multiple provinces.

3.3 | Assessment of the source of heterogeneity

To determine additional source of heterogeneity in the studies, we performed a sensitivity and subgroup analysis. Sensitivity analysis showed the effect size had no noted deviation when an individual study was omitted at a time (Figure S2). Subgroup analysis indicated that the estimates were not significantly different by gender and sample size, but were affected by age and sample location (Table 2). Meta-regression analyses showed that the cancer prevalence in patients with COVID-19 was significantly affected by sample location ($P = .016$), but not gender ($P = .403$), age ($P = .257$) and sample size ($P = .740$), which were also confirmed by multiple meta-regression analysis that only sample location ($P = .036$) was a significant factor causing the overall heterogeneity, supporting our analysis performed above by Hubei-only.

3.4 | Association of cancer with the severe events of COVID-19

Seventeen studies, including 11 of which were from Hubei province, reported the information on severe cases defined by clinical symptoms and ICU experience. No significant heterogeneity ($I^2 = 19.2\%$;
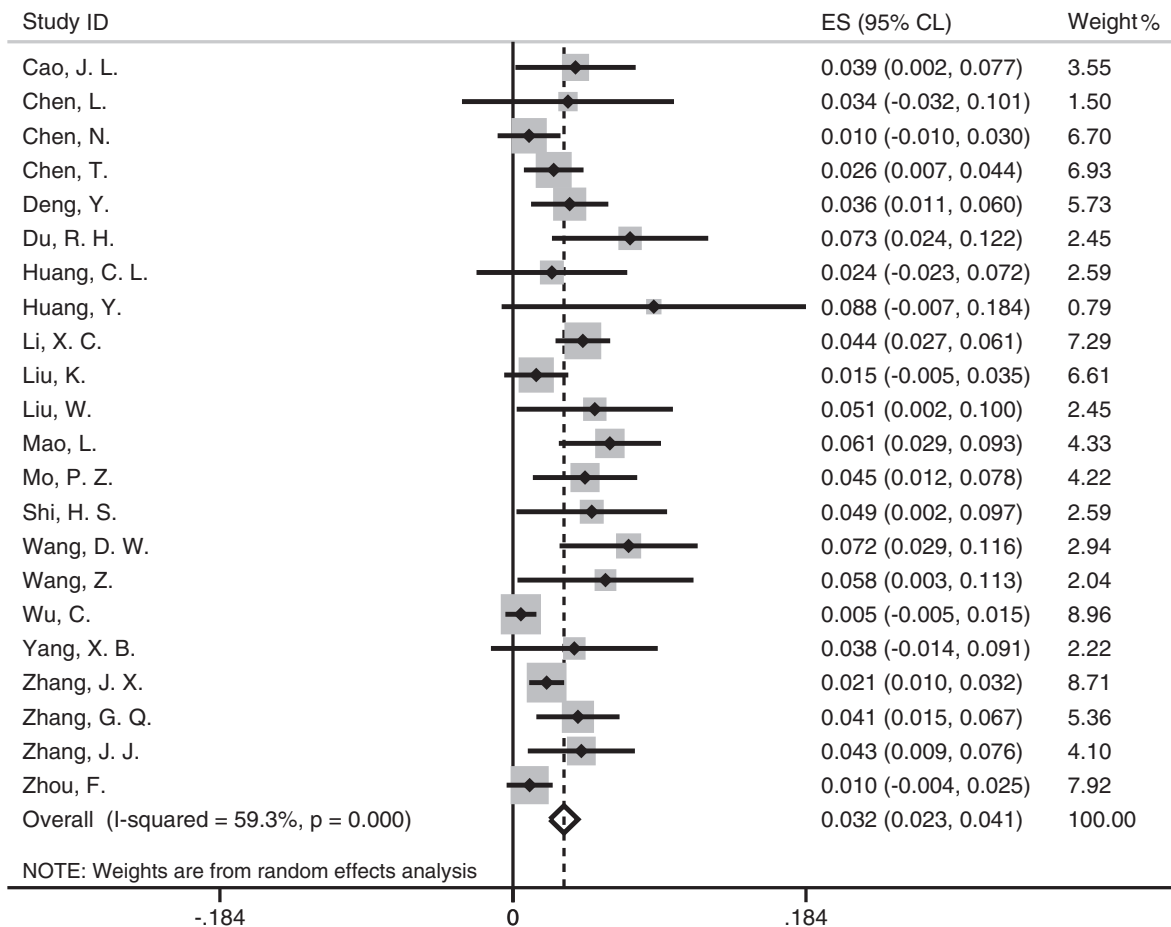
Study ID		ES (95% CL)	Weight%
Cao, J. L.		0.039 (0.002, 0.077)	3.55
Chen, L.		0.034 (-0.032, 0.101)	1.50
Chen, N.		0.010 (-0.010, 0.030)	6.70
Chen, T.		0.026 (0.007, 0.044)	6.93
Deng, Y.		0.036 (0.011, 0.060)	5.73
Du, R. H.		0.073 (0.024, 0.122)	2.45
Huang, C. L.		0.024 (-0.023, 0.072)	2.59
Huang, Y.		0.088 (-0.007, 0.184)	0.79
Li, X. C.		0.044 (0.027, 0.061)	7.29
Liu, K.		0.015 (-0.005, 0.035)	6.61
Liu, W.		0.051 (0.002, 0.100)	2.45
Mao, L.		0.061 (0.029, 0.093)	4.33
Mo, P. Z.		0.045 (0.012, 0.078)	4.22
Shi, H. S.		0.049 (0.002, 0.097)	2.59
Wang, D. W.		0.072 (0.029, 0.116)	2.94
Wang, Z.		0.058 (0.003, 0.113)	2.04
Wu, C.		0.005 (-0.005, 0.015)	8.96
Yang, X. B.		0.038 (-0.014, 0.091)	2.22
Zhang, J. X.		0.021 (0.010, 0.032)	8.71
Zhang, G. Q.		0.041 (0.015, 0.067)	5.36
Zhang, J. J.		0.043 (0.009, 0.076)	4.10
Zhou, F.		0.010 (-0.004, 0.025)	7.92
Overall (I-squared = 59.3%, p = 0.000)		0.032 (0.023, 0.041)	100.00

NOTE: Weights are from random effects analysis

-.184   0   .184

FIGURE 3 Forest plot for meta-analysis of cancer prevalence in patients with COVID-19 from Hubei

TABLE 2   Meta-analysis of cancer prevalence in patients with COVID-19 by subgroup

Group	No. Study	n	ES	95% CL	P	I^2	P
Overall							
Prevalence	38	7094	0.023	0.018-0.029	<.001	52.60%	<.001
Subgroup							
Gender							
M/F < 1	9	1534	0.028	0.017-0.039	<.001	33.00%	<.001
M/F ≥ 1	29	5560	0.022	0.016-0.028	<.001	53.50%	<.001
Age group							
<51	16	2734	0.013	0.009-0.018	<.001	0	<.001
≥51	22	4360	0.028	0.020-0.036	<.001	67.00%	<.001
Location							
Within Hubei	22	3801	0.032	0.023-0.041	<.001	59.30%	<.001
Outside Hubei	13	1195	0.010	0.004-0.015	<.001	0	.001
Multi-province	3	2098	0.018	0.004-0.032	<.001	56.70%	.01
Sample size							
<106	19	1154	0.022	0.014-0.031	<.001	0	<.001
≥106	19	5940	0.023	0.016-0.030	<.001	71.70%	<.001

Note: 95% CL, 95% confidence limit; ES, effect size; F, female; M, male; Multi-PR (multi-province), means the sample source including both Hubei and one or more other provinces.

P = .230) was presented between the studies (Figure 4A). A fixed-effect meta-analysis showed that cancer was significantly associated with the severe cases of COVID-19 (OR = 2.20, 95% CL [1.53, 3.17]; P < .001). The power to detect this significant association was estimated to be 85.9%.

In addition, eight studies reported the outcome of death, and all were from Hubei province. No heterogeneity (I^2 = 0%, P = .447) was observed (Figure 4B). A fixed-effect meta-analysis showed that cancer was associated with the risk of death (OR = 2.97, 95% CL [1.48, 5.96]; P = .002) in patients with COVID-19, with the estimated power to detect this association at 80.1%.

3.5 | Publication bias and correction

Assessment of publication bias is a crucial step to present the findings from a meta-analysis objectively. We noted a significant (P < .01) publication bias in the meta-analysis of 38 studies; correction for the publication bias was made with the "filled" studies for overall sample (Figure 5A) and Hubei-only (Figure 5B), separately. The random-effect meta-analysis was then used to obtain an adjusted estimate of pooled prevalence of cancer was at 1.4% (95% CL [0.8, 2.0]; heterogeneity P < .01) overall and at 1.9% (95% CL [1.0, 2.8], heterogeneity P < .01) in the Hubei-only.

We did not find evidence for publication bias in the association of cancer with severe events of COVID-19 based on Begg's test (P = .761) and Egger's test (P = .592) (Figure 5C,D), and no evidence for a significant publication bias (P > .5, n = 17) in the association of cancer with the severe cases, either.

4 | DISCUSSION

To the best of our knowledge, this is a more comprehensive meta-analysis that has investigated the association between cancer with COVID-19 so far. The analysis of 38 eligible studies comprising 7094 patients with COVID-19 showed that the pooled prevalence of cancer comorbidity was estimated at 2.3%, and 1.4% after correction for publication bias, which was more than 4-fold high as the cancer prevalence (0.26%) in the general populations in China.[52] In addition, cancer significantly increased the risk for being severe cases or death. Our study provides a solid evidence that patients with cancer were more susceptible to the coronavirus infection and significantly associated with severe events.

The study provides the first estimate with correction for publication bias of the pooled prevalence of cancer in patients with COVID-19. Desai et al[53] had estimated the pooled prevalence of cancer at 2.0%, based on publications of 11 studies that were noted with the presence of heterogeneity, but the estimate was obtained without assessing publication bias. The increased cancer prevalence in patients with COVID-19 may be less likely caused by the difference in the exposure. On the contrary, patients with cancer may have limited social and daily activities, which could have reduced the chance of exposure to the pathogen compared to the general populations. We suspect that the higher prevalence of cancer is due to an increase in the susceptibility to the infection with the SARS-CoV-2 virus, which can be attributed to the underlying health conditions, including older age and dysregulated immune systems.

However, we observed a noted regional difference in the cancer prevalence, which is likely due to the chance of exposure. The sample
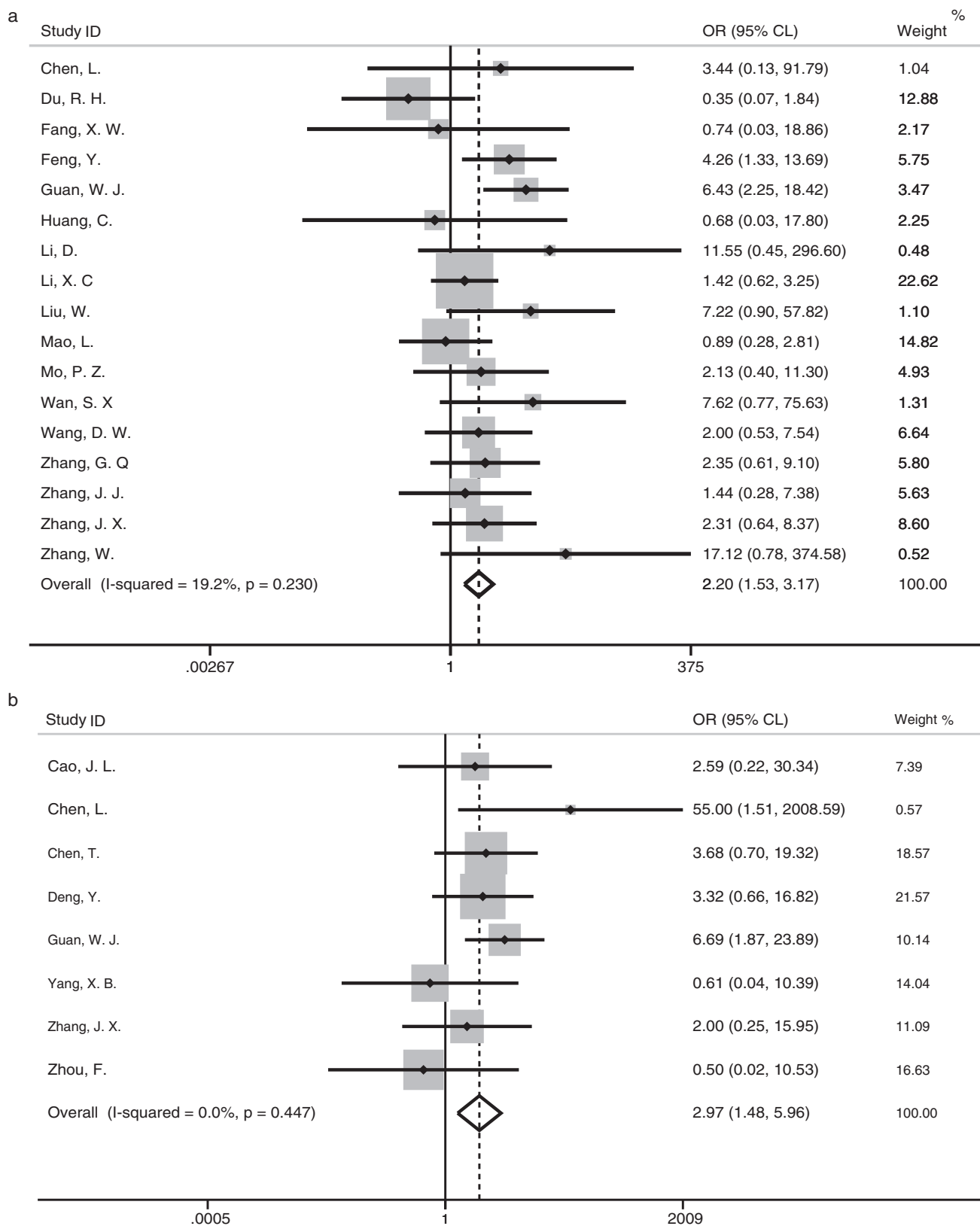
a

Study ID		OR (95% CL)	% Weight
Chen, L.		3.44 (0.13, 91.79)	1.04
Du, R. H.		0.35 (0.07, 1.84)	12.88
Fang, X. W.		0.74 (0.03, 18.86)	2.17
Feng, Y.		4.26 (1.33, 13.69)	5.75
Guan, W. J.		6.43 (2.25, 18.42)	3.47
Huang, C.		0.68 (0.03, 17.80)	2.25
Li, D.		11.55 (0.45, 296.60)	0.48
Li, X. C		1.42 (0.62, 3.25)	22.62
Liu, W.		7.22 (0.90, 57.82)	1.10
Mao, L.		0.89 (0.28, 2.81)	14.82
Mo, P. Z.		2.13 (0.40, 11.30)	4.93
Wan, S. X		7.62 (0.77, 75.63)	1.31
Wang, D. W.		2.00 (0.53, 7.54)	6.64
Zhang, G. Q		2.35 (0.61, 9.10)	5.80
Zhang, J. J.		1.44 (0.28, 7.38)	5.63
Zhang, J. X.		2.31 (0.64, 8.37)	8.60
Zhang, W.		17.12 (0.78, 374.58)	0.52
Overall (I-squared = 19.2%, p = 0.230)		2.20 (1.53, 3.17)	100.00

.00267   1   375

b

Study ID		OR (95% CL)	Weight %
Cao, J. L.		2.59 (0.22, 30.34)	7.39
Chen, L.		55.00 (1.51, 2008.59)	0.57
Chen, T.		3.68 (0.70, 19.32)	18.57
Deng, Y.		3.32 (0.66, 16.82)	21.57
Guan, W. J.		6.69 (1.87, 23.89)	10.14
Yang, X. B.		0.61 (0.04, 10.39)	14.04
Zhang, J. X.		2.00 (0.25, 15.95)	11.09
Zhou, F.		0.50 (0.02, 10.53)	16.63
Overall (I-squared = 0.0%, p = 0.447)		2.97 (1.48, 5.96)	100.00

.0005   1   2009

FIGURE 4   Forest plots of the meta-analysis of the association of cancer with severe events of COVID-19 (A, severe cases; B, death)

location, whether or not a study sample was from the epicenter of COVID-19, accounted for major heterogeneity. The estimates of pooled cancer prevalence (unadjusted 3.2%, n = 22) in patients with COVID-19 from Hubei was 3.2-fold high (unadjusted 1.0%, n = 13) in the samples outside Hubei. Because the prevalence of cancer in the general populations of central China, including Hubei, is at a middle
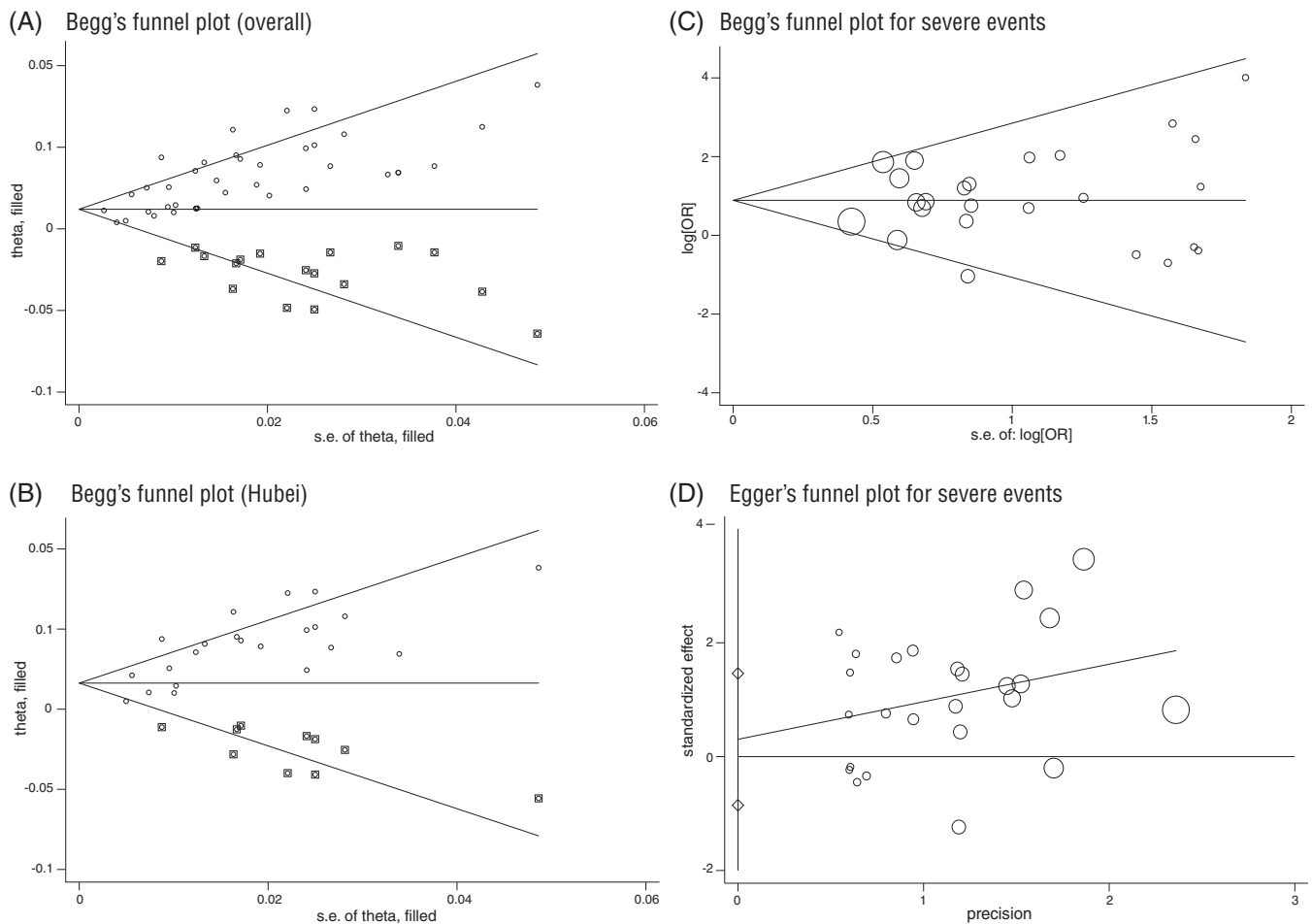
FIGURE 5   Plots for publication bias assessment (x-axis, precision or SE; y-axis, effect size; dot, individual study; circle size represents the weight of individual study). A, Begg's plot with filled studies for meta-analysis of cancer prevalence in all samples; B, Begg's plot with filled studies for Hubei only of cancer prevalence in Hubei; C, Begg's plot for meta-analysis of association with severe events; D, Egger's publication plot for publication bias in studies of severe events

level behind the east and southwest China,[54] the elevated prevalence of cancer in the patients with COVID-19 in Hubei is less likely caused by the general prevalence of cancer. Of note, the mean age of the study samples in Hubei and non-Hubei was similar around 50 years, and the corresponding cancer incidence at this age group is reported at 0.37%[55] and 0.39%[56] in Hubei and China, respectively. We can reasonably speculate that the regional difference is due to the chance of exposure, that is, lower awareness of personal protection in the early stage of the outbreak. When the outbreak of COVID-19 first started in Wuhan and then Hubei, people, even medical professionals, might have had lower awareness of the high infectivity and had inadequate equipment to protect themselves from exposure. It is documented that there were 3387 medical and health professionals from 476 medical institutions or hospitals across the country of China, infected with COVID-19, 3062 cases (91%) of whom were from Hubei, according to the *Beijing Evening Daily*[1] (Official news online in Chinese).

In contrast, people outside Hubei may have more time to acquire related knowledge and adequate personal protection equipment to avoid effective exposure to the pathogens. It is expected that

individuals with cancer, later outside Hubei, may have taken more careful protection from being exposed. This is supported by a significant regional difference in other comorbid conditions such as hypertension (18.1% vs 10.5%; *P* = .003) and diabetes (8.8% vs 4.7%; *P* = .025) between Hubei and outside Hubei.[57]

Besides cancer prevalence, our study shows that cancer is associated with severe cases and the risk of death in patients with COVID-19. Liang et al[13] observed that patients with cancer tend to have a higher risk of severe events, a composite endpoint defined by patients in ICU that required invasive ventilation, or death, compared to patients of COVID-19 without cancer. However, a meta-analysis of a small number of studies (n = 4) indicated that malignance was not significantly associated with the risk of COVID-19.[58] Less is known about the progression and survival outcome of the patients with cancer and CVOID-19. Our analysis provides robust evidence that cancer is associated with the risk of severe cases and death, based on the samples from Hubei province, in which relevant information is available and collected from the published studies.

To speculate the possible mechanisms underlying the association of cancer with COVID-19, we believe that both initial innate immune response and specific adaptive immune response determine the outcome after infection. In response to coronavirus infection, typically, the regulated inflammation and adaptive immune response can eradicate the pathogen, and develop antibody and protective immunity. Patients with cancer, likely with advanced age and on active treatment or even during watchful observation, may have dysregulated immune systems, including a reduced innate immunity due to age,[59] or compromised immune system by using immunosuppressive or immune-stimulating drugs for antitumor treatments.[8] They may have reduced the ability to develop an effective immune response to eradicate the pathogen successfully. Therefore, patients with cancer are more susceptible and likely to develop COVID-19 after exposure to the pathogen virus.

However, the mechanism underlying the association of cancer with severe events of COVID-19 seem more complicated without a rigorous study. A pathological study of a single individual with COVID-19 indicates that inflammation and cytokines-associated lung injury may be associated with severe events of COVID-19.[60] This observation is supported by an analysis of more clinical samples that severe events or death of COVID-19 are significantly associated with an increase in innate immune cells such as neutrophils and inflammatory cytokines, and lymphopenia,[29,51] indicating immunopathology is involved. However, people argue that the "cytokine storm" seems not to explain the association of cancer with the severe event of COVID-19,[61] as the development of cancer is caused by blunted immune status such as immunosuppression[62]; and also, a case report showed that immunosuppression might be with favorable outcomes in cancer patients with COVID-19.[63]

4.1 | Limitations

The study has limitations. First, most of the included studies were based on hospital-based case-series, selection bias may exist and affect the estimates, although the publication bias was assessed and corrected. Second, due to limited clinical information, we were unable to perform the study by the site of cancer. Finally, while we had carefully investigated all articles, the included studies were limited to the study samples in China to reduce the heterogeneity. Even though two studies in non-Chinese populations met our criteria for inclusion and exclusion, one from Iran and one from the United States of American, they reported two extreme cases of cancer prevalence in patients with COVID-19; they were excluded from the analysis as outliers.

5 | CONCLUSION

Despite the limitations, our analysis provides the first objective findings after adjusted for heterogeneity and correction for publication bias. Our study indicates that patients with cancer or cancer survivors are at an elevated risk for infection with the SARS-CoV-2 and are associated with severe cases and risk of death. Special preventive measures should be taken to protecting individuals, especially cancer survivors, with compromised immune systems or underlying health conditions, from exposure to the SRAS-CoV-2 virus.

CONFLICT OF INTEREST

All authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Only publicly available data were used in our study, and data sources and handling of these data are described in Table 1 and in the Materials and Methods, respectively. Further details are available from the corresponding author upon request.

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ENDNOTE

1 https://baijiahao.baidu.com/s?id=1659420755263370520&wfr=spider&for=pc

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.