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# Cancer is associated with coronavirus disease (COVID-19) severity and mortality: A pooled analysis

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## ABSTRACT

**Background:** Coronavirus disease 2019 (COVID-19) is a rapidly escalating pandemic that has spread to many parts of the world. As such, there is urgent need to identify predictors of clinical severity in COVID-19 patients. This may be useful for early identification of patients who may require life-saving interventions. In this meta-analysis, we evaluated whether malignancies are associated with a significantly enhanced odds of COVID-19 severity and mortality.

**Method:** A systematic search of literature was conducted between November 1, 2019, to May 26th, 2020 on PubMed and China National Knowledge Infrastructure (CNKI) to identify studies reporting data on cancers in patients with or without severe COVID-19 were included. The primary outcome of interest was the association between malignancies and COVID-19 severity, while the secondary outcome was the association between malignancies and COVID-19 mortality. Data were pooled into a meta-analysis to estimate pooled odds ratio (OR) with 95% confidence interval (95% CI) for either outcome.

**Results:** A total of 20 studies ( $n = 4549$  patients) were included. Overall, malignancies were found to be associated with significantly increased odds of COVID-19 severity (OR = 2.17; 95% CI 1.47–3.196;  $p < 0.001$ ) and mortality (OR = 2.39; 95% CI 1.18–4.85;  $p = 0.016$ ). No heterogeneity was observed for both outcomes (Cochran's  $Q = 6.558$ ,  $p = 0.922$ ,  $I^2 = 0\%$  and Cochran's  $Q = 2.91$ ,  $p = 0.71$ ,  $I^2 = 0\%$  respectively).

**Conclusion:** Malignancies were significantly associated with a 2-fold increase in the odds of developing severe COVID-19 disease, as well as mortality. Larger studies are needed to corroborate these findings. These patients should be closely monitored for any signs of unfavorable disease progression.

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## 1. Introduction

The coronavirus disease 2019 (COVID-19), which was first reported in Wuhan in December 2019, has achieved a pandemic status. As of 30th July 2020, the disease had spread to over 213 countries and territories, with over 16,812,763 confirmed cases and 662,095 fatalities [1]. Therefore, there is urgent need to identify patient characteristics to enable risk stratification for predicting unfavorable disease progression, and facilitate timely life-saving interventions.

Recently, Zheng and colleagues [2] published a paper on the risk factors of critical and mortal coronavirus disease 2019 (COVID-19) cases in the Journal of Infection. In their analysis, the authors found that the proportion of patients with malignancies was higher in the critical/mortality group “yet without statistical significance” (OR = 1.60; 95% CI 0.81–3.18;  $p = 0.18$ ). Since the publication of their paper, more data on this subject has been published. We performed an updated meta-analysis of currently available literature

to evaluate whether malignancies are associated with increased severity and mortality of COVID-19.

## 2. Methods

### 2.1. Study protocol

This systematic review and meta-analysis were conducted in strict conformity with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [3]. The PRISMA checklist is provided in the supplementary material.

### 2.2. Literature search strategy

A systematic electronic search of literature from November 1, 2019, to May 26th, 2020 was conducted on the electronic databases Medline (PubMed interface) and China National Knowledge Infrastructure (CNKI) to identify studies eligible for inclusion. The electronic search was carried out using the strategy as follows: (1) (((COVID-19) OR (SARS-CoV-2)) OR (2019-nCoV)); (2) ((((((Malignancy) OR (Cancer)) OR (Tumor)) OR (Clinical features)) OR (Outcomes)) OR

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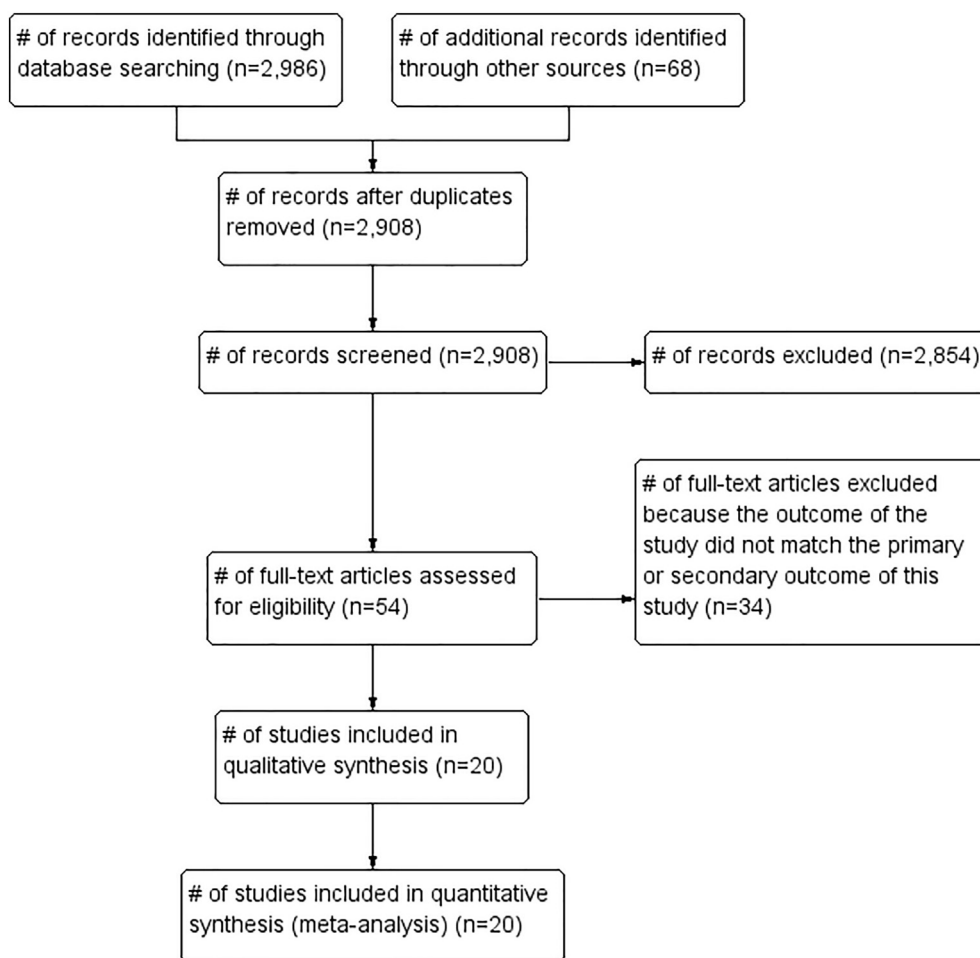


Fig. 1. PRISMA flow chart for the included studies.

(Risk factors)); (3) 1 AND 2. No language restriction was made. When the articles were published by the same study group and there was an overlap of the search period, only the most recent article was included to avoid duplication of data. The PubMed function “related articles” was used to extend the search. Also, we searched major infectious disease

(Lancet Infectious Disease, Journal of Medical Virology, Journal of Infection, International Journal of Infectious Diseases), oncology (Journal of Clinical Oncology, Lancet Oncology), and general medicine journals (The Lancet, New England Journal of Medicine, British Medical Journal) reporting articles about COVID-19 infection to look for additional

**Table 1**  
Characteristics of the studies included in the severity analysis cohort

Study	Country & City	Sample Size	Severe patients				Non-severe patients			
			n (%)	Age (yrs)	Women (%)	Cancer (%)	n (%)	Age (yrs)	Women (%)	Cancer (%)
Guan et al. [5]	Outside Hubei, China	1099	173 (15.7%)	52 (40–65)	73 (42%)	3 (1.7%)	926 (84.3%)	45 (34–57)	386 (42%)	7 (0.76%)
Huang et al. [6]	Wuhan, China	41	13 (31.7%)	49 (41–61)	2 (15%)	0 (0%)	28 (68.3%)	49 (41–57.5)	15 (53.6%)	1 (3.6%)
Zhang Guqin et al. [7]	Wuhan, China	221	55 (24.9%)	62 (52–74)	20 (36.4%)	4 (7.3%)	166 (75.1%)	51 (36–64.3)	93 (56%)	5 (3.0%)
Yao et al. [8]	Dabieshan, China	108	25 (23.1%)	–	12 (48%)	2 (8%)	83 (76.9%)	50.0 (34.0 56.0)	53 (63.9%)	0 (0%)
Aggarwal et al. [9]	Iowa, USA	16	8 (50%)	67 (38–70)	3 (38%)	2 (25%)	8 (50%)	68.5 (41–95)	1 (13%)	1 (13%)
Wang D et al. [10]	Wuhan, China	138	36 (26.1%)	66 (57–78)	14 (38.9)	4 (11.1%)	102 (73.9%)	51 (37–62)	49 (48%)	6 (5.8%)
Hong et al. [11]	Daegu, South Korea	98	13 (13.2%)	63.2 ± 10.1	7 (53.8%)	1 (7.7%)	85 (86.8%)	54.2 ± 17.7	53 (62.4%)	3 (3.5%)
Li X et al. [12]	Wuhan, China	548	269 (49.3%)	65 (54–72)	116 (43.1%)	14 (5.2%)	279 (50.7%)	56 (44–66)	153 (54.8%)	10 (3.5%)
Wang Z et al. [13]	Wuhan, China	69	14 (20.9%)	70.5 (62–77)	7 (50%)	1 (7.1%)	55 (79.1%)	37 (32–51)	30 (55%)	3 (5.4%)
Wan S et al. [14]	Chongqing China	135	40 (29.6%)	56 (52–73)	19 (47.5%)	3 (7.5%)	95 (70.4%)	44 (33–49)	43 (45.3%)	1 (1%)
Goyal et al. [15]	New York, USA	393	130 (33.1%)	64.5 (51.7–73.6%)	38 (29.2%)	10 (7.6%)	263 (66.9%)	61.5 (47–75)	117 (45.5%)	13 (4.9%)
Feng et al. [16]	Wuhan, Shanghai and Anhui	476	124 (26.1%)	58 (48–67)	43 (34.7%)	7 (5.6%)	352 (73.9%)	51 (37–63)	162 (46%)	5 (1.4%)
Colaneri et al. [17]	Pavia, Italy	44	17 (38.6%)	–	4 (23.5%)	4	27 (61.4%)	–	12 (44.4%)	2
Zhu et al. [18]	Ningbo, China	127	16 (12.5%)	57.50 ± 11.70	7 (43.8%)	1	111 (87.5%)	49.95 ± 15.52	38 (34.2%)	4

**Table 2**  
Characteristics of the studies included in the mortality cohort

Study	Country & City	Sample Size	Survivors				Non-survivors			
			n (%)	Age (yrs)	Women (%)	Cancer (%)	n (%)	Age (yrs)	Women (%)	Cancer (%)
Zhou F et al. [19]	Wuhan, China	191	137 (71.7%)	52 (45–58)	56 (41%)	0 (0%)	54 (28.3%)	69 (63–76)	16 (30%)	2 (3.7%)
Chen T et al. [20]	Wuhan, Chins	274	161 (58.8%)	51 (37–66)	73 (45%)	2 (1.2%)	113 (41.2%)	68 (62–77)	30 (27%)	5 (4.4%)
Yang et al. [21]	Wuhan, China	52	20 (38.5%)	51.9 ± 12.9	6 (30%)	1 (1.9%)	32 (61.5%)	64.6 ± 11.2	11 (34%)	1 (3.1%)
Deng et al. [22]	Wuhan, China	225	116 (51.6%)	40 (33–57)	65 (56%)	2 (1.7%)	109 (48.4%)	69 (62–74)	36 (33%)	6 (5.5%)
Ruan et al. [23]	Wuhan, China	150	82 (54.7%)	50 (44–81)	29 (35%)	1 (1.2%)	68 (45.3%)	67 (15–81)	19 (28%)	2 (2.9%)
Bonetti et al. [24]	Valcamonica, Italy	144	74 (51.4%)	62.1 (53–72.8)	24 (31.1%)	6 (8.1%)	70 (48.6%)	78 (64.2–84)	25 (35.7%)	9 (12.9%)

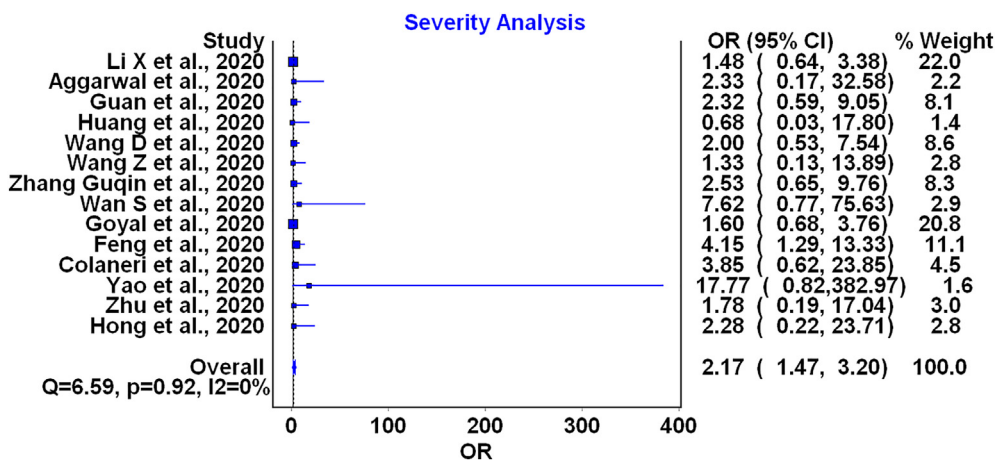


Fig. 2. A forest plot for the meta-analysis of malignancies and COVID-19 severity.

studies. We then hand-searched the bibliographies of included studies to detect other potentially eligible investigations.

2.3. Eligibility criteria

All studies were screened and assessed for eligibility by three independent reviewers (I-C, B-N and V-K). The search results were screened by title and abstract, with those of potential relevance evaluated by full text. Studies were deemed eligible for inclusion if they fulfilled the following criteria: (1) observational cohort or case-control studies reporting malignancy frequency data in COVID-19 patients (>18 years old), (2) used appropriate definition of severe disease or compared survivors to non-survivors, (3) disease severity was monitored throughout the study, (4) clearly outlined the definition of “severe disease” and

(5) sample size >10. A clinically valid definition of ‘severe disease’ (i.e. a composite of (1) respiratory distress, respiratory rate ≥ 30 per min; (2) oxygen saturation on room air at rest ≤93%; (3) partial pressure of oxygen in arterial blood/fraction of inspired oxygen ≤300 mmHg; (4) patients requiring mechanical ventilation/vital life support/intensive care unit admission (ICU); (5) death/ mortality) was required for a study to be included. Reviews and studies with incomplete or irrelevant data were excluded. Any disagreements between reviewers arising during the eligibility assessment were settled through consensus.

2.4. Data extraction & quality assessment

Data extraction and quality assessment were conducted by three independent reviewers (I-C, B-N and V-K). For each study, the following

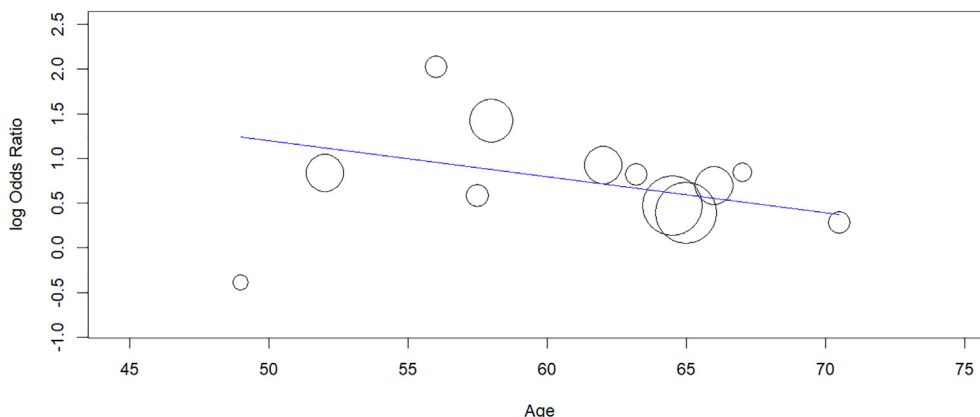


Fig. 3. Meta-regression plot on the impact of age on association of malignancies and COVID-19 severity.

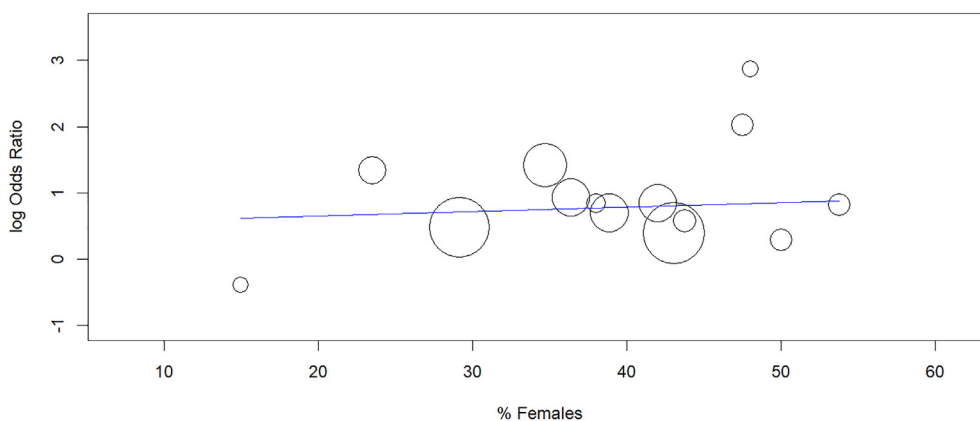


Fig. 4. Meta-regression plot on the impact of sex on association of malignancies and COVID-19 severity.

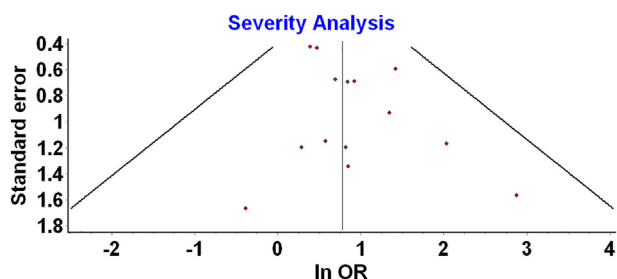


Fig. 5. A funnel plot for the meta-analysis of malignancies and mortality in COVID-19 patients.

information was extracted: the surname of the first author and the year of publication, the geographical region where the study was performed, the type of study, sample size, baseline demographic characteristics, proportion of cancer patients with severe and non-severe COVID-19/ survivors and non-survivors. Any variances were resolved by consensus. Quality assessment and analysis of risk of bias of all selected full-text articles were performed using the methodological index for non-randomized studies (MINORS) tool.

2.5. Outcomes of interest

The primary outcome of interest was the association between malignancies and COVID-19 severity, while the secondary outcome was the association between malignancies and COVID-19 mortality.

2.6. Statistical analysis

The statistical analysis was carried out using MetaXL (software version 5.3, EpiGear International Pty Ltd., Sunrise Beach, Australia) and

Meta-Analyst (software version 5.26.14, Center for Evidence-Based Medicine, Brown University, Providence, USA). The strength of association between malignancies and COVID-19 severity and mortality was estimated using the odds ratio (OR). A random-effects model was applied. The magnitude of heterogeneity among the included studies was assessed using the chi-squared test (Chi [2]) and I-squared statistic (I<sup>2</sup>). For the Chi [2] test, a Cochrane's Q p-value of <0.10 was considered significant. The values of the I<sup>2</sup> statistic were interpreted as follows at a 95% confidence interval: Thresholds of 25%, 50%, and 75% to designate low, moderate, and high heterogeneity were applied [4]. Random-effects meta-regression using log OR was performed to evaluate the impact of baseline characteristics (age and sex) on the study outcomes. Publication bias was assessed using funnel plots. Additionally, a leave-one-out sensitivity analysis was performed to assess the robustness of the results and to further probe the sources of inter-study heterogeneity.

3. Results

3.1. Study identification and characteristics of the included studies

The initial search produced 2986 potentially relevant articles. Following the removal of duplicates and primary screening, 54 articles were assessed by full text for eligibility in the meta-analysis. Of these, 34 were excluded because the primary and secondary outcomes of the study did not match that of this review. Thus, a total of 20 studies (n = 4549 patients) were included in this systematic review and meta-analysis (Fig. 1). Most of the studies were from China (15 studies), while the rest were from the United States (2 studies), Italy (2 studies) and South Korea (1 study). Fourteen studies reported data on malignancies in severe vs non-severe COVID-19 patients, while the rest reported data in COVID-19 survivors vs non-survivors. The characteristics of the included are summarized in Tables 1 and 2. Summary of the

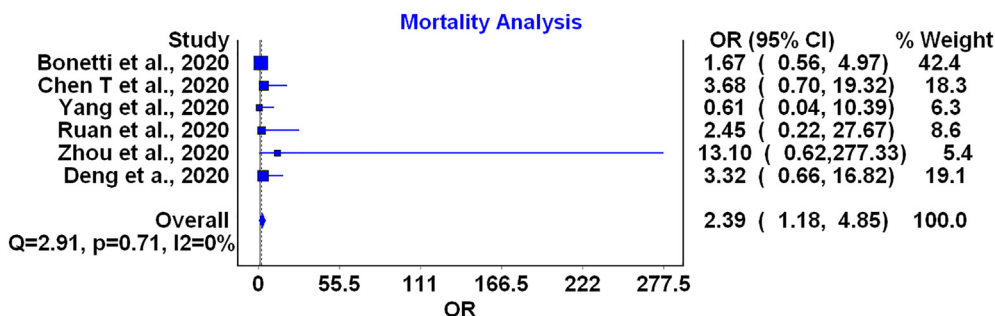


Fig. 6. A forest plot for the meta-analysis of malignancies and COVID-19 mortality.

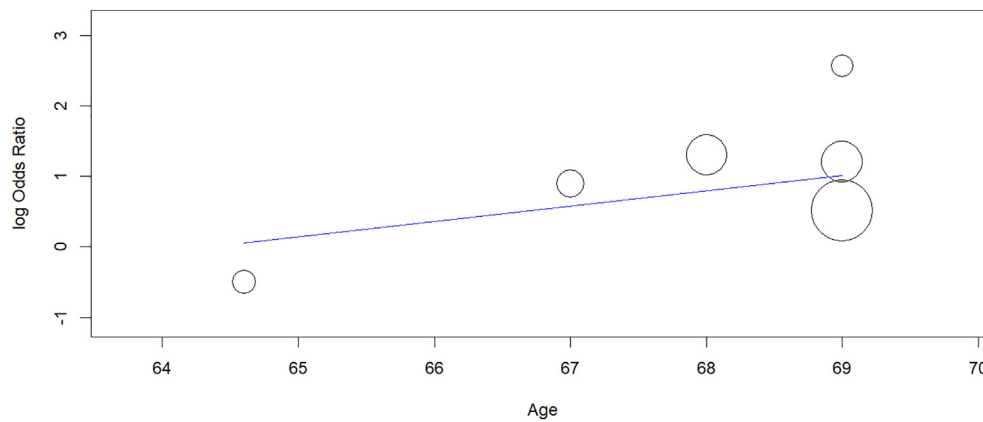


Fig. 7. Meta-regression plot on the impact of age on association of malignancies and COVID-19 mortality.

methodological index for non-randomized studies (MINORS) assessment for the included studies is provided in supplementary material.

### 3.2. Primary outcome: meta-analysis of association of malignancies with COVID-19 severity

A total of 14 studies ( $n = 3513$  patients [933 severe & 2580 non-severe]) reported data on the association between malignancies and COVID-19 severity. In the pooled analysis, malignancies were found to be associated with significantly increased odds of severe COVID-19 ( $OR = 2.17$ ; 95% CI 1.47–3.196;  $p < 0.001$ ), with no evidence of inter-study heterogeneity being observed for this outcome (Cochran's  $Q = 6.558$ ,  $p = 0.922$ ,  $I^2 = 0\%$ ) (Fig. 2). No significant changes in the OR could be seen in the leave-one-out sensitivity analysis. In the meta-regression analysis, neither age (co-efficient =  $-0.040$ ; 95% CI  $-0.125$ - $0.044$ ;  $p = 0.351$ ) nor sex (co-efficient =  $0.007$ ; 95%  $-0.045$ - $0.058$ ;  $p = 0.797$ ) of patients in the severe group had significant influence on association of malignancies and severity of COVID-19 (Figs. 3 and 4). Funnel plot revealed only mild asymmetry (Fig. 5).

### 3.3. Secondary outcome: meta-analysis of association of malignancies with COVID-19 mortality

A total of 6 studies ( $n = 1036$  patients [590 survivors & 446 non-survivors]) reported data on the association between malignancies and mortality in COVID-19 patients. In the pooled analysis, malignancies were found to be associated with significantly increased odds of mortality in COVID-19 patients ( $OR = 2.39$ ; 95% CI 1.18–4.85;  $p = 0.016$ ). No evidence of inter-study heterogeneity was observed for this outcome (Cochran's  $Q = 2.91$ ,  $p = 0.71$ ,  $I^2 = 0\%$ ) (Fig. 6). No significant changes

in the OR could be seen in the leave-one-out sensitivity analysis. In the meta-regression analysis, neither age (co-efficient =  $0.217$ ; 95% CI  $-0.395$ - $0.829$ ;  $p = 0.487$ ) nor sex (co-efficient =  $-0.084$ ; 95% CI  $-0.411$ - $0.243$ ;  $p = 0.615$ ) had significant influence on the association of malignancies and mortality in COVID-19 patients (Figs. 7 and 8). Due to the small number of studies, analysis for publication bias was not performed for this outcome.

## 4. Discussion

The results of this meta-analysis demonstrate that malignancies are associated with a worse prognosis in COVID-19 patients, with a 2-fold increase in the odds of severity and mortality.

Generally, cancer patients are known to have a higher susceptibility to life-threatening infections and sepsis from many pathogens, including viruses [25]. Williams and colleagues in 2004 demonstrated that compared to the general population, cancer patients are much more likely to be with severe sepsis (relative risk, 3.96; 95% confidence interval, 3.94–3.99) [26]. Mortality rates for these patients are also higher [25,26]. These observations are consistent with the findings of the current study. Similar findings have also been reported in previous epidemics such as the Middle-East Respiratory Syndrome Coronavirus (MERS-CoV) [27].

The increased risk of a severe form of COVID-19, as well as mortality in cancer patients could be a function of their immunosuppressed status, either due to the malignancy itself or treatment [28]. Further, cancer patients tend to be older and have more co-morbid conditions, both of which are established risk factors for poor outcomes in COVID-19 [29]. Recent studies have demonstrated a high level of expression of angiotensin converting enzyme 2 (ACE2) receptor, the transmembrane

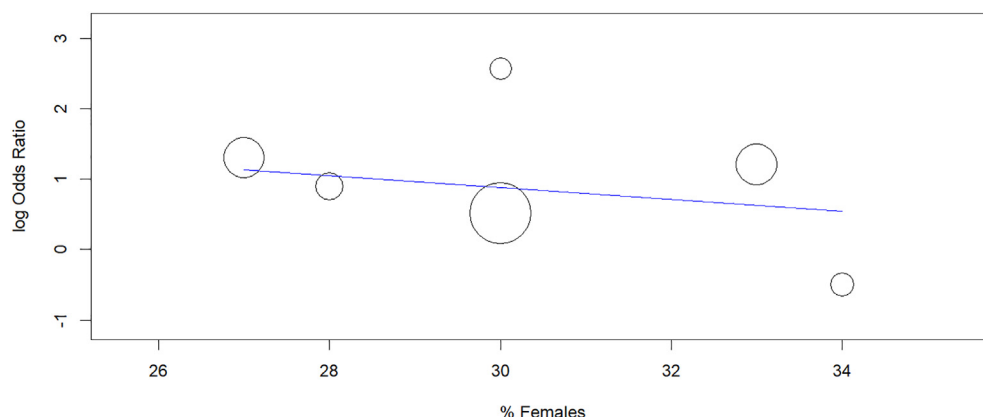


Fig. 8. Meta-regression plot on the impact of sex on association of malignancies and COVID-19 mortality.

receptor used by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) for entry into cells, in various types of cancers [30–32]. This could also partly explain the higher susceptibility of cancer patients to COVID-19, as well as the poor outcomes.

Our meta-analysis was limited by several factors, such as the small sample sizes of the studies included, particularly in the analysis of the secondary outcome (mortality). We could not perform a sub-group analysis to determine which cancers carried the highest odds of severe form of COVID-19 due to lack of adequate data. Further, most of the studies were from China, hence there is a possibility of patient overlap. Nonetheless, our study was strengthened by the lack of inter-study heterogeneity, robust analysis including leave-one out sensitivity analysis, meta-regression and analysis for potential publication bias. Larger studies are needed to confirm the findings of the current study.

## 5. Conclusion

The findings of this updated meta-analysis suggest that malignancies may be associated with a 2-fold increase in the odds of developing severe COVID-19 disease, as well as mortality. These patients should be closely monitored for any signs of unfavorable disease progression.

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No funding was sought for this study.

## Declaration of Competing Interest

None of the authors have any conflicts of interests with regard to this publication.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ajem.2020.08.025>.

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