Severity and case fatality rates of COVID-19: A systematic review, meta-analysis and an exploratory meta-regression of risk factors

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ABSTRACT

Background: We estimated the prevalence of severe or critical illness and case fatality of COVID-19 in a systematic review and meta-analysis and examined clinical, biochemical, and radiological risk factors in a meta-regression.

Methods: PRISMA guidelines were followed. PubMed, Scopus and Web of Science were searched using pre-specified keywords. Peer-reviewed empirical studies examining rates of severe illness, critical illness and case fatality among COVID-19 patients were analyzed. Random-effects meta-analyses were performed and adjusted for publication bias. Meta-regression analyses examined the moderator effects of risk factors.

Results: The meta-analysis included 29 studies representing 2,090 individuals. Pooled prevalence rates of severe illness, critical illness and case fatality among COVID-19 patients were 15%, 5%, and 0.8%, respectively. There were significant heterogeneity and publication bias in these studies. Meta-regression analyses revealed that increasing age and elevated LDH consistently predicted severe / critical disease and case fatality. In addition, hypertension, fever and dyspnea at presentation, and elevated CRP predicted increased severity.

Conclusions: These predictors of severity and case fatality should allow clinicians to define at-risk endophenotypes. Differences in unadjusted vs. adjusted pooled estimates indicates limited utility of small-scale studies and underscores the importance of multinational studies to establish the morbidity and mortality rates in pandemics.

Keywords: SARS-CoV-2, COVID-19, case fatality, meta-analysis, meta-regression

INTRODUCTION

A novel corona virus, first identified in Wuhan, China, in late 2019, resulted in a pandemic by the first quarter of 2020; these widespread infections were attributed to the prolonged survival of the virus in the environment and extended length of pre- or post-symptomatic and potential asymptomatic shedding.[1] While the virus is known to cause only a mild illness in a majority of cases, severe illness

characterized by respiratory distress requiring hospital admission is not uncommon.[2] Furthermore, the virus has the potential to precipitate a life-threatening critical illness, characterized by respiratory failure, circulatory shock, and sepsis or other organ failure, requiring intensive care.[3]

An extensive body of literature published since the outset of the epidemic in China has examined the rates of severe and critically severe and the case fatality associated with COVID-19. However, the literature on COVID-19 has several limitations. First, due to lack of awareness and limited availability of training and resources to confirm the diagnosis, failure to recognize and code COVID-19 as the potential cause of morbidity and mortality may have contributed to

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under-estimation of the effects of COVID-19.[4] In fact, a recent estimate suggested that approximately 86% cases of COVID-19 were not documented prior to January 23, 2020.[5] But screening only those who are at high risk may lead to over reporting of morbidity and mortality. Second, given that most datasets and publications are derived from retrospective chart review, as opposed to prospective methods, high measurement error is inevitable.[6] Third, the literature on the outcomes mainly originates from tertiary care settings, distorting the overall clinical picture.[7] Finally, including the same patients in multiple reports examining the same research question without clearly indicating this overlap is a major lapse in methodological and ethical standards.[8]

We conducted a systematic review of the available literature to identify publications with minimal potential overlap to estimate the prevalence of severe illness, critical illness, and case fatality among individuals with COVID-19 in random-effects meta-analyses to enhance generalizability. We adjusted our prevalence estimates by correcting for publication bias and under-reporting. We also examined the effects of clinical, biochemical, and radiological risk factors moderating the between-study heterogeneity of the severity and case fatality rates.

METHODS

SEARCH STRATEGY AND SELECTION CRITERIA

All procedures were conducted in accord with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines. PubMed, Scopus and Web of Science databases were searched on March 7, 2020, to identify studies that have been published in 2020 examining the prevalence of severe illness, critically severe illness, and mortality associated with COVID-19 infection using pre-determined keyword combinations (S1 Table). No language restrictions were applied. Duplicate records were removed, and titles and abstracts were screened for pre-defined eligibility criteria (Figure 1) by two independent raters (CD and CK or SC). Records published in Chinese were translated to American English using Google translator, and a

native Chinese speaker with doctoral level training (SC) examined the original records in Chinese. Full-text manuscripts of records that were considered eligible after the initial screening were re-examined. Two study personnel examined all eligible full-text manuscripts using the 9-item Quality Assessment Tool for Case Series Studies of the National Heart, Lung and Blood Institute.

DATA EXTRACTION

Data from the eligible manuscripts were organized into pre-defined data fields. The data fields included the total sample size and number of participants with severe illness, critically severe illness, and mortality. Severe illness was operationally defined as having either respiratory distress with RR $\geq$ 30 /min, resting peripheral oxygen saturation of $\leq$ 93%, or arterial partial pressure of oxygen $\leq$ 300 mmHg, or requiring hospitalization. Critical illness was defined as having respiratory failure, circulatory shock, end-organ failure, any combination of the above, or requiring intensive care. In addition, the following variables were extracted as potential covariates of the above outcomes. Central tendency (i.e., mean or median) and dispersion (i.e., SD, SE, 95% CI, IQR or range) of age were extracted. When not reported, study level means and standard deviations for age were imputed from the available statistics (i.e., median, IQR or range).[9] Proportions of the following variables within a study sample were extracted: age $\leq$ 18 years, age $\geq$ 60 years, female sex, diabetes mellitus, hypertension, heart disease, chronic liver disease, chronic kidney disease, chronic obstructive pulmonary disease, malignancy, immunosuppression (e.g., HIV), smoking and pregnancy. Proportions of patients with specific presenting symptoms (i.e., fever, cough, sore throat, shortness of breath, headache, diarrhea), asymptomatic cases, specific laboratory parameters (i.e., positive nucleic acid test for COVID-19, leukopenia, leukocytosis, thrombocytopenia, lymphopenia, elevated lactate dehydrogenase (LDH), elevated C-reactive protein (CRP), elevated erythrocyte sedimentation rate (ESR), high procalcitonin and high D-dimer based on reference ranges considered in each study) and radiographic features (i.e., no
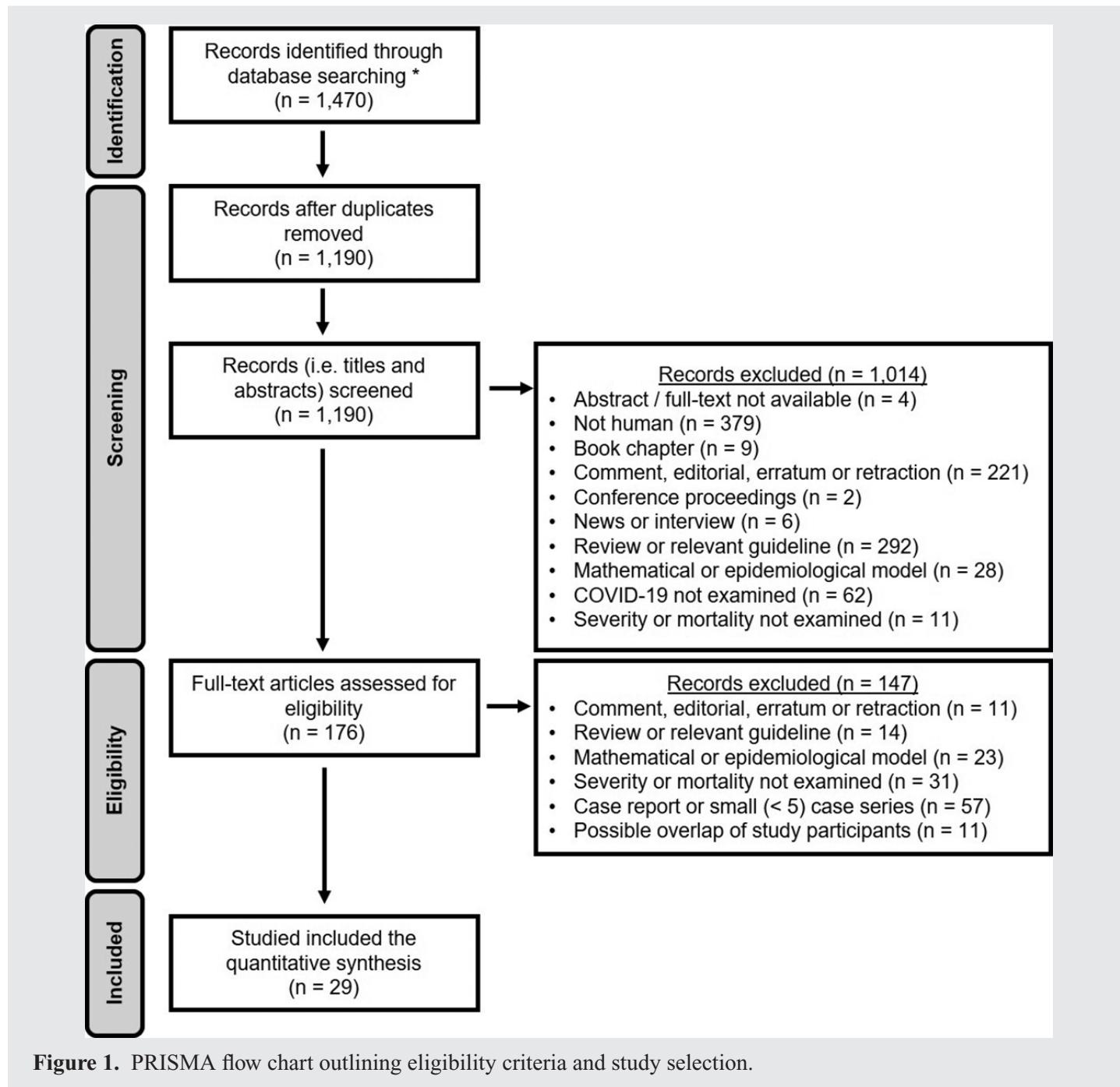
Figure 1. PRISMA flow chart outlining eligibility criteria and study selection.

lesions on computed tomography, patchy consolidation, ground glass opacities, peripheral distribution, and bilateral lung involvement or involvement of ≥ 3 lobes).

DATA ANALYSIS

Three separate DerSimonian-Laird random-effects meta-analyses were performed using the 'meta'

package (version 4.11-0) in R statistical software (version 3.6.2) to examine three primary outcomes: the prevalence of a) combined severe or critical COVID-19 infection, b) critically severe COVID-19 infection, and c) COVID-19-associated mortality.[10] Studies with both zero or 100% proportions were not excluded to ensure incorporation of all available data, which is known to ensure analytic consistency and minimize bias.[11] Consistency of the findings of the meta-analyses were confirmed by leave-one-out sensitivity analyses.[12] Given that under-reporting and publication bias could result in biased (i.e., smaller) prevalence estimates, publication bias was examined using funnel plots. Funnel plot asymmetry was confirmed using the traditional Egger tests and the Peters test, which is robust to small-study effects (i.e., biases caused by the likelihood of studies with extreme results despite small sample sizes getting published) and seems to perform better when using proportions or log odds as outcomes.[13,14] The effect-sizes were imputed for estimated missing (i.e., unpublished / unreported) studies via the trim-and-fill method.[15] The trim-and-fill method relies heavily on the assumption that the funnel plot of a meta-analysis should be symmetric and corrects for asymmetric distributions of effect-sizes by removing smaller studies that may contribute to asymmetric funnel plots, estimating a center of effect-sizes using the remaining effect-sizes and imputing effect-sizes until the funnel plot becomes symmetric. The meta-analyses were repeated including the effect-sizes of potentially missing studies imputed using the trim-and-fill method for each primary outcome.[15] Heterogeneity of effect-sizes was quantified by calculating the Higgins' I^2 statistic for each meta-analysis.[16] To explain the heterogeneity of the studies,[17] exploratory univariate random-effects meta-regression analyses were performed to examine the moderator effects of each of the covariates described above.

RESULTS

Results of database search, subsequent screening, and eligibility assessment are summarized in a PRISMA flow diagram (Figure 1). Out of 2,564 records identified in the initial database search, 29 studies including data for 2,090 patients with COVID-19 were considered eligible. The proportions of females in the study samples ranged from 27.59% to 100.00%. The mean age of the participants included in the studies ranged from 2 to 66 years. Four studies entirely recruited children, and one study exclusively recruited pregnant women. The included studies and their quality ratings are summarized in Table 1. The summary statistics of all covariates are summarized in S2 Table.

Pooled prevalence of severe or critically severe illness among individuals with COVID-19 infection was estimated to be 14.6% (95% CI, 8.9%–23.1%) in the random-effects meta-analysis (Figure 2a). Excluding any single study from the meta-analysis (i.e., leave-one-out sensitivity analyses) did not significantly change the pooled prevalence estimate. However, the funnel plot of the effect-sizes was severely asymmetric, suggesting underreporting or publication bias (Figure 2b). Egger test indicated asymmetry (t = −2.208, p = 0.037), yet the Peters test was not significant, indicating that the funnel plot asymmetry may be driven by the small-study effect (t = 1.874, p = 0.073). Seven effect-sizes were imputed to correct for the publication bias. When the random-effects meta-analysis was performed including these imputed effect-sizes (i.e., after correcting for publication bias), the prevalence of severe or critical illness increased to 25.8% (95% CI, 17.2%–36.8%) (Figure 2c).

Significant heterogeneity was observed among the prevalence estimates of severe illness ($\tau^2 = 1.679$; $I^2 = 94\%$, p < 0.001). Correcting for publication bias decreased this heterogeneity ($I^2 = 85\%$, 95% CI, 80%–89%); however, heterogeneity remained significant (p < 0.001). Exploratory univariate random-effects meta-regression analyses conducted with the aim of explaining the heterogeneity using the moderator effects of the considered covariates suggested that each of increasing mean age (p = 0.006) and prevalence of age $\geq$ 60 years (p < 0.001), hypertension (p < 0.001), chronic kidney disease (p = 0.038), malignancy (p = 0.023), and chronic obstructive pulmonary disease (p = 0.025) were associated with a greater risk of severe or critical illness associated with COVID-19, while the prevalence of age $\leq$ 18 years

Table 1. Studies Meeting Eligibility Criteria

Study*	Study Setting	Study Period	Sample Size	Severe / Critical Illness	Critical Illness	Mortality	Quality†	
							Rater 1	Rater 2
Cai (24)	In-patient[1]	Jan19–Feb03	10	0	0	0	Good	Good
Chen C (25)	Out patient	Jan–Feb	150	NA	24	11	Good	Good
Chen H (26)	In-patient[2]	Jan20–Jan31	9	0	0	0	Good	Good
Chen L (27)	In-patient	Jan14–Jan29	29	14	5	2	Good	Good
Chen N (28)	In-patient	Jan01–Jan20	99	33	23	11	Good	Good
Chen W (29)	In-patient	NA	57	18	NA	NA	Fair	Poor
Feng (30)	In-patient[1]	Jan16–Feb06	15	0	0	0	Fair	Good
Li K (31)	In-patient	Jan–Feb	83	25	0	NA	Good	Good
Li Y (32)	In-patient	Jan–Feb	54	14	NA	0	Good	Good
Liu C (33)	In-patient	Jan23–Feb08	32	4	NA	0	Fair	Fair
Liu K (34)	In-patient	Dec30–Jan24	137	34	26	16	Good	Good
Liu W (35)	In-patient	Dec30–Jan15	78	20	8	2	Good	Good
Liu Y (36)	In-patient	Jan11–Jan20	12	9	3	0	Good	Good
Tian (37)	Emergency	Jan20–Feb10	262	46	0	3	Good	Good
Wang D (a) (38)	In-patient[1]	Jan25–Feb21	31	0	0	0	Fair	Good
Wang D (b) (39)	In-patient	Jan01–Jan28	138	36	36	6	Good	Good
Wang L (40)	In-patient	Jan21–Feb05	18	NA	2	0	Good	Good
Wu J (41)	In-patient	Jan22–Feb14	80	3	3	0	Good	Good
Wu W (42)	Out patient	Jan19–Jan25	40	17	4	2	Good	Good
Xia W (43)	In-patient[1]	Jan23–Feb8	20	1	0	0	Fair	Good
Xu X (44)	Public health data	Jan10–Jan26	62	1	1	0	Good	Good
Xu Y (45)	In-patient	Jan–Feb	50	13	3	0	Good	Good
Yang (3)	In-patient	Jan17–Feb10	149	23	23	0	Good	Good
Yao (46)	Public health data	Jan01–Feb07	195	5	5	0	Fair	Good
Young (47)	Public health data	Jan22–Jan31	18	6	2	0	Good	Good
Zhang J (48)	In-patient	Jan16–Feb03	140	58	NA	NA	Good	Good
Zhang M (49)	In-patient	Jan18–Feb03	9	0	0	0	Good	Good
Zhao (50)	In-patient	NA	101	14	NA	NA	Good	Fair
Zhu (51)	In-patient	Dec01–Feb15	12	0	0	0	Good	Good

* All studies were published in year 2020. Young et al. (2020) was based on data collected in Singapore. All the studies were based on data collected in China.
† Quality of studies were examined using the National Heart, Lung and Blood Institute's 9-item Quality Assessment Tool for Case Series Studies.
[1] Study sample was made-up exclusively of children.
[2] Study sample was made-up exclusively of pregnant women.
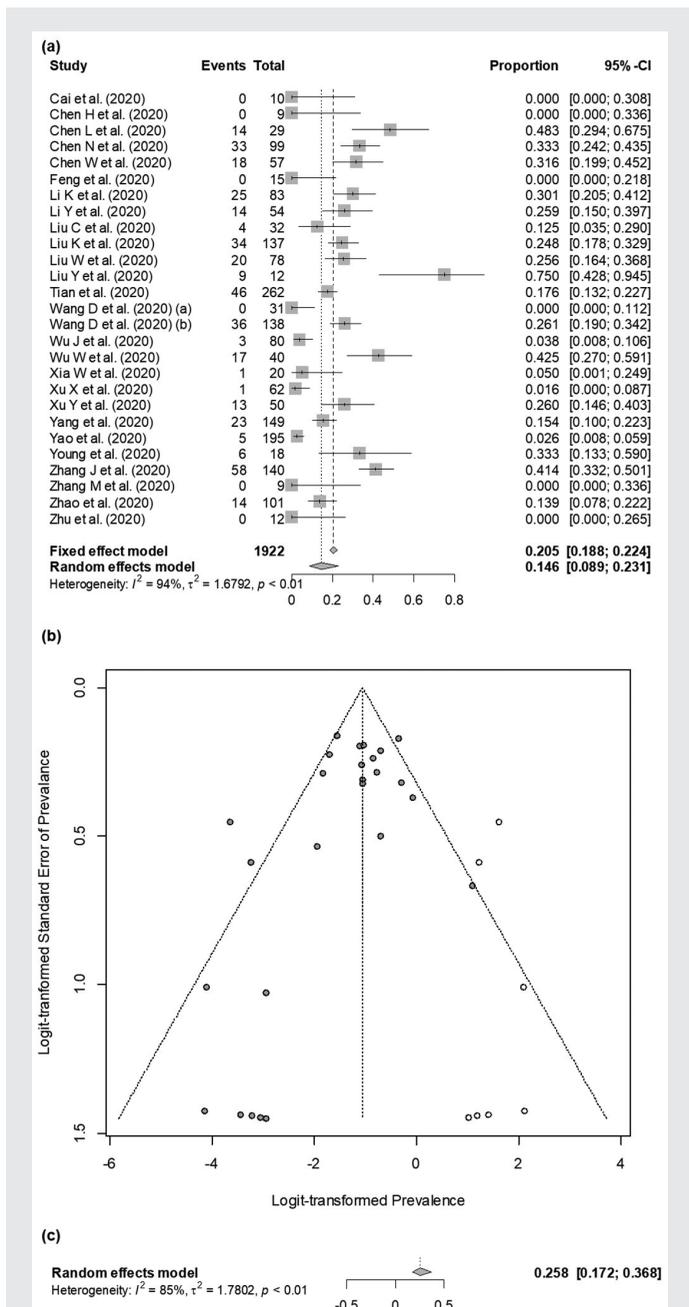
Figure 2. Results of random-effects meta-analysis examining the pooled prevalence of combined severe and critical illness among individuals with COVID-19. a) Forest plot; b) Funnel plot depicting publication bias and imputed effect-sizes to correct for publication bias; c) Results corrected for publication bias.

(p = 0.007) within a sample was associated with a reduced risk of severe or critical illness. The prevalence of the presenting clinical features of fever (p < 0.001), dyspnea (p = 0.028), and diarrhea (p = 0.026); laboratory findings of lymphocytopenia (p = 0.003), elevated LDH (p < 0.001), CRP (p < 0.001), and D-dimer levels (p < 0.001); and bilateral lung involvement or involvement of ≥ 3 lung lobes (p = 0.006) was associated with increased risk of severe or critically severe illness, while having no radiological features on chest CT was associated with decreased risk of severe illness (p = 0.003). The results of all univariate meta-regression analyses examining the moderator effects of the covariates on the prevalence of severe or critical illness in COVID-19 infection and their effects on heterogeneity are summarized in S3 Table.

The random-effects meta-regression analyses revealed a pooled estimate of 4.8% (95% CI, 2.4%–9.5%) for the prevalence of critical illness in COVID-19 infection (Figure 3a). Leave-one-out meta-regression analyses did not significantly change this estimate. The funnel plot (Figure 3b) was suggestive of underreporting or publication bias. This was confirmed in an Egger test (t = −5.099, p < 0.001), yet the Peters test was not significant (t = −0.319, p = 0.758). Eleven effect-sizes had to be imputed to statistically correct for this bias and after correction, the pooled prevalence of critical illness in COVID-19 infection increased to 16.3% (95% CI, 9.8%–25.7%) (Figure 3c).

Significant heterogeneity of effect-sizes was also a concern for the meta-analysis of prevalence of critical illness ($\tau^2 = 1.994$; $I^2 = 92\%$, p < 0.001). Correcting for publication bias decreased this heterogeneity ($I^2 = 78\%$, 95% CI, 69%–84%); however, heterogeneity remained significant (p < 0.001). Univariate meta-regression analyses suggested increased risk of critical illness associated with sample characteristics of increasing mean age (p = 0.002), prevalence of age ≥ 60 years (p < 0.001), comorbid hypertension (p < 0.01), cardiac disease (p = 0.023), and malignancy (p = 0.041). Similarly, the prevalence of fever (p = 0.044), dyspnea (p = 0.042), and fatigue (p = 0.036) on presentation; the prevalence of increased LDH (p = 0.003), CRP
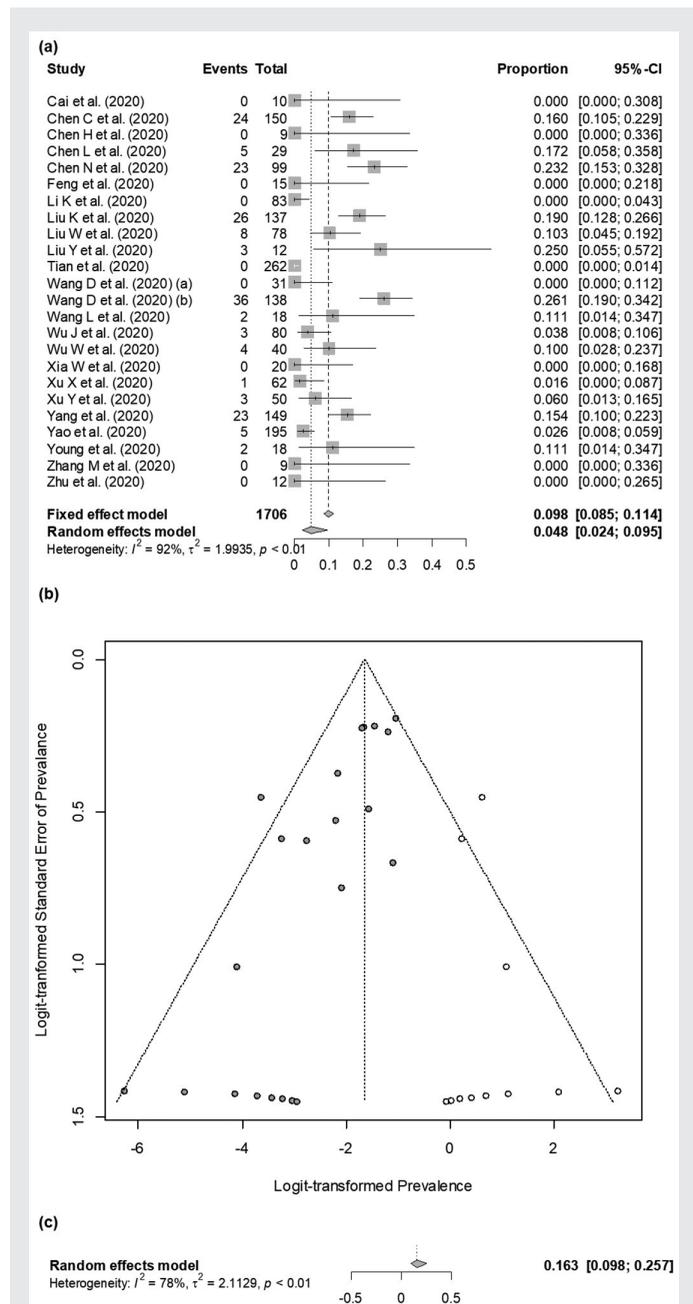
Figure 3. Results of random-effects meta-analysis examining the pooled prevalence of critical illness among individuals with COVID-19. a) Forest plot; b) Funnel plot depicting publication bias and imputed effect-sizes to correct for publication bias; c) Results corrected for publication bias.

(p = 0.008), and D-dimer (p = 0.021) were associated with a greater risk of critical illness (S4 Table).

Prevalence of COVID-19 associated mortality was 0.8% (95% CI, 0.2%–2.9%) based on the random-effects meta-analysis (Figure 4a), and this estimate was minimally affected by leave-one-out sensitivity analyses. However, as with severe and critically severe illness, publication bias and potential under-reporting were apparent based on significant funnel plot asymmetry (t = −5.203, p < 0.001) (Figure 4b). A Peters test was not significant and suggested the high likelihood of the funnel asymmetry being driven by small-study effect (t = 0.097, p = 0.924). Trim-and-fill method, which corrects for both publication bias and small-study effect, imputed 13 effect-sizes to account for missing / unreported effects in an attempt to statistically correct for the publication bias. Conducting the meta-regression analyses with the addition of these effect-sizes revealed a pooled estimate of 7.4% (95% CI, 4.5%–11.9%) for the mortality rate associated with COVID-19 infection (Figure 4c).

Heterogeneity of effect-sizes on prevalence of mortality in COVID-19 was also a concern ($\tau^2 = 2.996$; $I^2 = 86\%$, p < 0.001). Correction for publication bias decreased the heterogeneity ($I^2 = 61\%$, 95% CI, 45%–73%), yet the heterogeneity remained significant (p < 0.001). Univariate meta-regression analyses modeling heterogeneity indicated increased mortality risks associated with increasing mean age (p < 0.001), prevalence of age $\geq$ 60 years (p = 0.011), presenting with fatigue (p = 0.048), leukocytosis (p = 0.007), high LDH (p = 0.030), and low albumin (p < 0.001). The prevalence of age $\leq$ 18 years (p = 0.036) was associated with a decreased risk of COVID-19-associated mortality (S5 Table).

DISCUSSION

In this systematic review and meta-analysis, we comprehensively and systematically examined the available literature to estimate the prevalence of morbidity and mortality associated with SRAS-CoV-2 infection. Despite the large number of articles that were reviewed, our quantitative synthesis was limited to 29 studies representing data from 2,090 individuals.
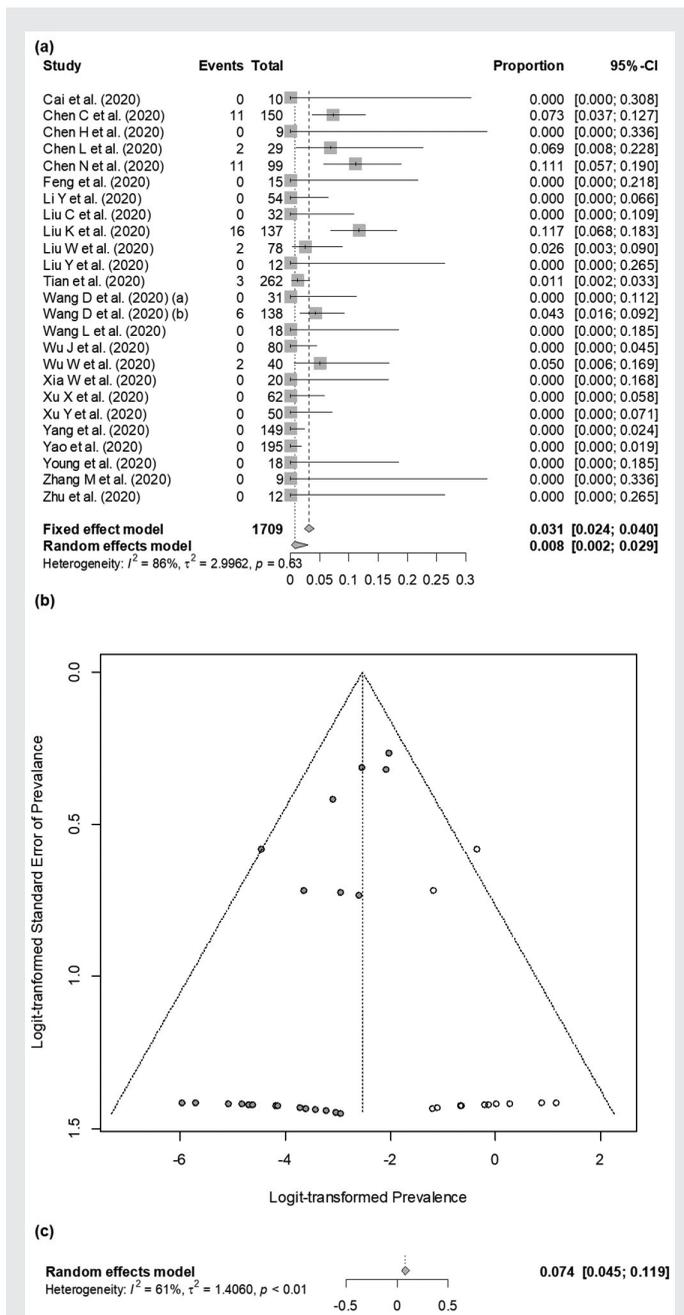
Figure 4. Results of random-effects meta-analysis examining the pooled case fatality rate among individuals with COVID-19. a) Forest plot; b) Funnel plot depicting publication bias and imputed effect-sizes to correct for publication bias; c) Results corrected for publication bias.

Our literature-based estimates of severe illness, critical illness, and case fatality rates among patients with COVID-19 were 15%, 5%, and 0.8%, respectively. After adjusting for underreporting and publication bias, COVID-19-associated prevalence of severe illness, critical illness and case fatality increased to 26%, 16%, and 7.4%, respectively.

Our unadjusted random-effects estimates of severe illness requiring hospitalization (15%) and critical illness requiring intensive care admission (5%) are consistent with the estimates of COVID-19-associated morbidity based on large individual-level datasets.[18] Therefore, the unadjusted findings of our meta-analysis regarding severity of illness corroborate the inferences made based on current surveillance systems. However, the unadjusted mortality rate observed in our analysis (0.8%, 95% CI, 0.2%–2.9%) is lower than the COVID-19-associated mortality rates in China (3.6%) or globally (3.4%) at the end of February 2020 (i.e., the time represented in the reviewed publications).

Retrospective patient data and the literature derived from such data could be systematically biased toward both overestimating and / or underestimating morbidity and mortality. The reviewed studies largely represent tertiary care settings, of which the capacity may have been overridden minimally, if at all, despite the high reproductive number (R_0) at the time of sampling. As such, the outcomes of our unadjusted random-effects meta-analyses, which accounts for the random variability of effects between studies, can be inferred to be a generalizable representation of morbidity and mortality rates applicable to well-trained and equipped healthcare settings in which resources are not overwhelmed. This estimate, therefore, represents COVID-19 associated mortality in regions with a low R_0.

However, reverse-causation bias caused by failing to capture the deaths that may not reach healthcare facilities / be diagnosed prior to death could contribute to underestimation.[19] The effect-sizes imputed to correct for publication bias may, in fact, represent severity and case fatality rates of settings in which the demand exceeds the available resources.[20] While optimized utilization of healthcare facilities by

maintaining a low R_0 may reduce the mortality rates to as low as 0.8%, overwhelming healthcare resources may increase the overall case fatality rate to 7.4%, or even greater as represented by the effect-sizes we have imputed.[21]

In our meta-regression analyses that examined risk factors, increasing age and age $\geq$ 60 years consistently stood out as a risk factor, while age $\leq$ 18 years consistently remained a protective factor, being consistent with the current literature. Angiotensin converting enzyme (ACE)-2 receptors are generally up regulated in patients with hypertension or heart failure who receive ACE-inhibitors and angiotensin-II receptor blockers.[22] COVID-19 enters cells by binding to ACE-2 receptors, increasing their risk of infection and development of severe clinical illness.[22] Consistently, we observed an increased risk of severity with hypertension and cardiovascular disease. Presenting with fever emerged as a risk factor for severe and critical illness and mortality, underscoring the importance of body temperature as a screening tool.

This systematic review and meta-analysis was conducted at the outset of the COVID-19 pandemic in an effort to determine morbidity and mortality rates associated with the disease. At the time the literature was reviewed, almost all the studies reporting morbidity and mortality data originated in China. Thus, the generalizability of the findings of this study are limited. In addition, our systematic review has some methodological limitations. First, while we eliminated studies with overlapping samples by screening for overlaps of institutes, study dates, and authors, we cannot be 100% certain of exclusion of all overlapping data. Second, a high degree of heterogeneity was a concern. However, this should be expected in any meta-analysis due to the variability in methodology and study samples. This limitation was mitigated partially by conducting random-effects meta-analyses to pool the estimates. More important, we used heterogeneity to explore the risk factors in meta-regression analyses.[16] Third, the reviewed literature contained hardly any information regarding the types of medications used by patients (e.g., ACE inhibitors, angiotensin II receptor blockers), anthropometric parameters (e.g., BMI, fat mass) or the dietary patterns of the patients. Furthermore, the reviewed articles lacked data on specific treatment protocols or specific medications used for management of COVID-19. As such, the contribution of these moderator effects of these important variables could not be evaluated. Fourth, the protocol was not pre-registered. Finally, funnel plots of all three meta-analyses were visually asymmetric and the statistical tests indicated that these asymmetries might be driven mostly by small-study effects. While the trim-and-fill analysis can correct for asymmetries in funnel plots due to both small-study effect and underreporting, the analysis strongly assumes the symmetry of funnel plot,[15] which may not hold true in the absence of publication bias. Furthermore, the accuracy of the estimates of trim-and-fill analysis is questionable in the presence of between-study heterogeneity, and the imputed data may contribute to artificially decrease the uncertainty of the pooled estimates.[23] Thus, we emphasize the need to exercise caution when interpreting the findings that have been corrected for publication bias using the trim-and-fill analyses.

Conclusions

In conclusion, COVID-19 associated overall rates of hospitalization, intensive care, and case fatality were estimated to be 15%, 5%, and 0.8%, respectively, in our meta-analysis. Adjusting for potential underreporting and publication bias increased these estimates to 26%, 16%, and 7.4%, respectively, yet caution is advised in interpreting these adjusted outcomes due to limitations associated with the statistical methods used for adjustment. These differences in unadjusted vs. adjusted pooled estimates and the high between study heterogeneity indicate the limited generalizability of prevalence estimates derived from small-scale studies and underscore the importance of relying on multinational studies to establish the morbidity and mortality rates in pandemics (e.g., COVID-19). Hypertension, fever and dyspnea at presentation, and elevated CRP seem to predict increased disease severity, while increasing age and elevated LDH seem to consistently predict severity and case fatality. These risk factors should inform clinicians to define endophenotypes possessing a greater risk.

Supporting information- Supplementary tables

S1 Table. Keywords and keyword combinations used to screen the PubMed, Scopus, and Web of Science electronic databases.

S2 Table. Summary statistics of all covariates used in univariate meta-regression analyses.

S3 Table. Results of all univariate meta-regression analyses examining the moderator effects of covariates on the prevalence of combined severe or critical illness in COVID-19.

S4 Table. Results of all univariate meta-regression analyses examining the moderator effects of covariates on the prevalence critical illness in COVID-19.

S5 Table. Results of all univariate meta-regression analyses examining the moderator effects of covariates on the case-fatality rate in COVID-19.

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