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Diabetes mellitus increases the risk of hospital mortality in patients with Covid-19
Systematic review with meta-analysis

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Abstract

Background: The mortality rate associated with Covid-19 varies considerably among studies and determinants of this variability are not well characterized.

Methods: A systematic review of peer-reviewed literature published through March 31, 2020 was performed to estimate the mortality rate among hospitalized patients in China with a confirmed diagnosis of Covid-19. Hospital mortality rates were estimated using an inverse variance-weighted random-effects meta-analysis model. Funnel plot symmetry was evaluated for small-study effects, a one-study removed sensitivity analysis assessed the influence of individual studies on the pooled mortality rate, and metaregression assessed the association of potential confounding variables with mortality rates.

Results: The review included 16 observational studies involving 1832 hospitalized patients with a diagnosis of Covid-19. The surveillance period among studies ranged from December 16, 2019 to February 23, 2020. The median patient age was 53 years and 53% were males. A total of 38.5% of patients presented with at least 1 comorbidity, most commonly hypertension (24.0%), cardiac disease (15.1%), and diabetes mellitus (14.4%). Fever and cough, reported in 84.8% and 61.7% of patients respectively, were the most common patient symptoms. The pooled mortality rate was 9.9% (95% confidence interval 6.1% to 14.5%). Funnel plot asymmetry was not observed and the meta-analysis results were not substantially influenced by any single study since the pooled mortality rate ranged from 8.9% to 11.1% following iterative removal of one study at a time. Substantial heterogeneity in the mortality rate was identified among studies ($I^2 = 87\%$; $P < .001$). In a metaregression that included demographics, patient risk factors, and presenting symptoms, only a higher prevalence of diabetes mellitus was associated with a higher mortality rate ($P = .03$).

Conclusions: In a meta-analysis of hospitalized patients in China with a diagnosis of Covid-19, the mortality rate was 9.9% and a higher diabetes mellitus prevalence was independently associated with a worse prognosis. The independent influence of diabetes mellitus with Covid-19 mortality should be viewed as hypothesis-generating and warrants further study.

Abbreviations: CI = confidence interval, Covid-19 = coronavirus disease 2019, DM = diabetes mellitus, MERS-CoV = Middle East Respiratory Syndrome Coronavirus, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-analyses, SARS = Severe Acute Respiratory Syndrome, SARS-CoV-2 = Severe Acute Respiratory Syndrome Coronavirus 2.

Keywords: case fatality rate, coronavirus, Covid-19, diabetes mellitus, infectious disease, meta-analysis, mortality, public health, systematic review

1. Introduction

The first human transmission of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), the virus responsible for Coronavirus Disease 2019 (Covid-19), was reported to occur in Wuhan, China on November 17, 2019.[1] On March 11, 2020, following identification of 118,000 Covid-19 cases and nearly 4,300 deaths in 114 countries, the World Health Organization recognized Covid-19 as a global pandemic.[2] The mortality rate associated with Covid-19 varies tremendously among countries with most studies originating from China. Several systematic reviews have reported mortality rates ranging from 4% to 13% in hospitalized patients with Covid-19 in China.[3–5] However, none of these reviews performed analyses to identify potential determinants of mortality rates in affected individuals. The purpose of this systematic review with meta-analysis was to determine the mortality rate of hospitalized patients with Covid-19 in China and to identify factors that may potentially influence this rate. We specifically focused the review to studies from China since most published papers on Covid-19 were derived from that

country and because the mortality rates associated with Covid-19 vary widely among geographic regions.[6,7]

2. Methods

This systematic review was performed according to the PRISMA guidelines[8] and the protocol was registered with the Research Registry (Review Registry UIN: reviewregistry861). Ethical approval and patient consent were not required because this is a systematic review and meta-analysis of previously published studies. The authors agree to make the raw data from this analysis available upon reasonable request.

We performed systematic searches of Medline, Embase, and the Cochrane Central Register of Controlled Trials for observational studies that reported the mortality rate of hospitalized patients in China with a confirmed diagnosis of Covid-19. The searches used the following keywords

2019-nCov, coronavirus, Covid-19, and SARS-CoV-2. We performed manual searches of the Directory of Open Access Journals, Google Scholar, and the reference lists of included papers and relevant meta-analyses. Finally, we searched medRxiv for unpublished manuscript preprints. No language restrictions were applied to the searches; manuscripts published in Chinese-language journals were translated to English by a medical translator. Eligible papers were published between December 1, 2019 and March 31, 2020.

Study selection was performed by 2 independent reviewers and discrepancies were resolved by consensus. Titles and abstracts were initially screened to exclude review articles, commentaries, non-research letters, studies with less than 20 patients, studies that exclusively enrolled special populations (e.g., children, pregnant women, elderly, critically ill patients, etc.), studies in which mortality was not reported, and clinical trials of experimental drugs for Covid-19. We additionally excluded papers derived from surveillance databases since hospital and out-patient records were not reported separately. Full-texts of the remaining articles were retrieved and reviewed.

Researchers independently extracted data from eligible studies using standardized data collection forms. For each study, we recorded metadata, patient characteristics (age, sex, comorbidities, presenting symptoms), study characteristics (sample size, number and location of participating hospitals, study design, Covid-19 diagnosis method, range of diagnosis dates), treatment data, risk of bias elements, and mortality rates. To account for multiple papers derived from the same primary study or subsamples of the primary study, we preferentially extracted data from the paper with the largest sample size and then supplemented missing data using other papers published from the same study as needed.

The primary outcome of this review was the mortality rate of hospitalized patients in China with a confirmed diagnosis of Covid-19. The mortality rate was calculated for each study and the overall pooled result was reported along with the 95% confidence interval (CI). Meta-analysis estimates were calculated from a random-effects restricted maximum likelihood model with inverse variance weighting to account for anticipated heterogeneity among studies. Because the mortality rate was expected to be proportionally near zero, we used the Freeman-Tukey double arcsine transformation for variance stabilization.[9] The I^2 statistic was used to assess heterogeneity in the mortality rate among studies. Substantial heterogeneity was considered present when I^2 exceeded 50%. We performed prespecified metare-gression analyses to explore potential sources of heterogeneity that included patient demographics, risk factors, and presenting symptoms. Variables that were included in the models were patient age, patient sex, risk factors (presence of at least one risk factor, hypertension, cardiac disease, diabetes mellitus [DM], respiratory disease), and presenting symptoms (fever, cough, dyspnea, myalgia, headache). Treatment regimens were largely individualized based on patient symptoms and, therefore, these data were reported descriptively and their associations with mortality were not analyzed due to the considerable risk of confounding. We evaluated the robustness of the meta-analysis conclusions with a one-study removed sensitivity analysis where the analysis was recalculated following iterative one-at-a-time removal of each study. Funnel plot asymmetry was evaluated by visual inspection only since statistical testing of asymmetry for prevalence outcomes in a single group yields biased results.[10] The level of agreement between reviewers evaluating studies for inclusion, data abstraction, and quality assessment was assessed using simple and weighted kappa statistics. A two-sided P value of less than .05 was considered statistically significant. Analyses were performed with Stata v16.1 (Stata Corp, College Station, TX, United States).

3. Results

The literature review included 950 records identified by systematic literature searches and 21 records identified by searches of the grey literature and articles published ahead-of-print from journal websites. Among the 971 papers, we retrieved the full text of 123 papers and ultimately included 16 papers involving 1832 hospitalized patients in China with a confirmed diagnosis of Covid-19 in the meta-analysis. The most common types of papers that were excluded from consideration were commentaries and non-research letters. A schematic of the study identification and selection process is shown in Figure 1.

Among the 16 observational studies,[11–26] 12 were performed at a single center and 4 were multicenter studies. The sample sizes ranged widely across studies (median 90 patients; range 24 to 416 patients). Patients were prospectively enrolled in 1 study and retrospectively enrolled in the remainder of studies. The surveillance period among all studies ranged from December 16, 2019 to February 23, 2020 (Table 1). The median age of patients was 53 years and 53% were males. A total of 38.5% of patients presented with at least one comorbidity, most commonly hypertension (24.0%), cardiac disease (15.1%), and DM (14.4%). Fever and cough, reported in 84.8% and 61.7% of patients respectively, were the most commonly reported symptoms. Patient treatments were not standardized but were tailored to individual symptoms. Antivirals (90.8%), antibiotics (84.9%), and oxygen therapy (71.2%) were most commonly utilized (Fig. 2). The primary risks of bias pertaining to mortality rates were attributed to predominant retrospective patient enrollment and variability in patient age and risk factors among studies. Cohens inter-rater kappa statistic for inclusion agreement, abstraction, and quality assessment was 0.82, 0.86, and 0.80, respectively, indicative of excellent inter-rater agreement.

Among the 1832 patients, 251 died (crude mortality 13.7%). The mortality rate in individual studies ranged from 0% to 37.0%. In a random effects meta-analysis, the pooled mortality rate was 9.9% (95% CI 6.1%–14.5%) (Fig. 3). The mortality rate was minimally influenced by any single study and ranged from a low of 8.9% after removal of Zhou et al[26] to a high of
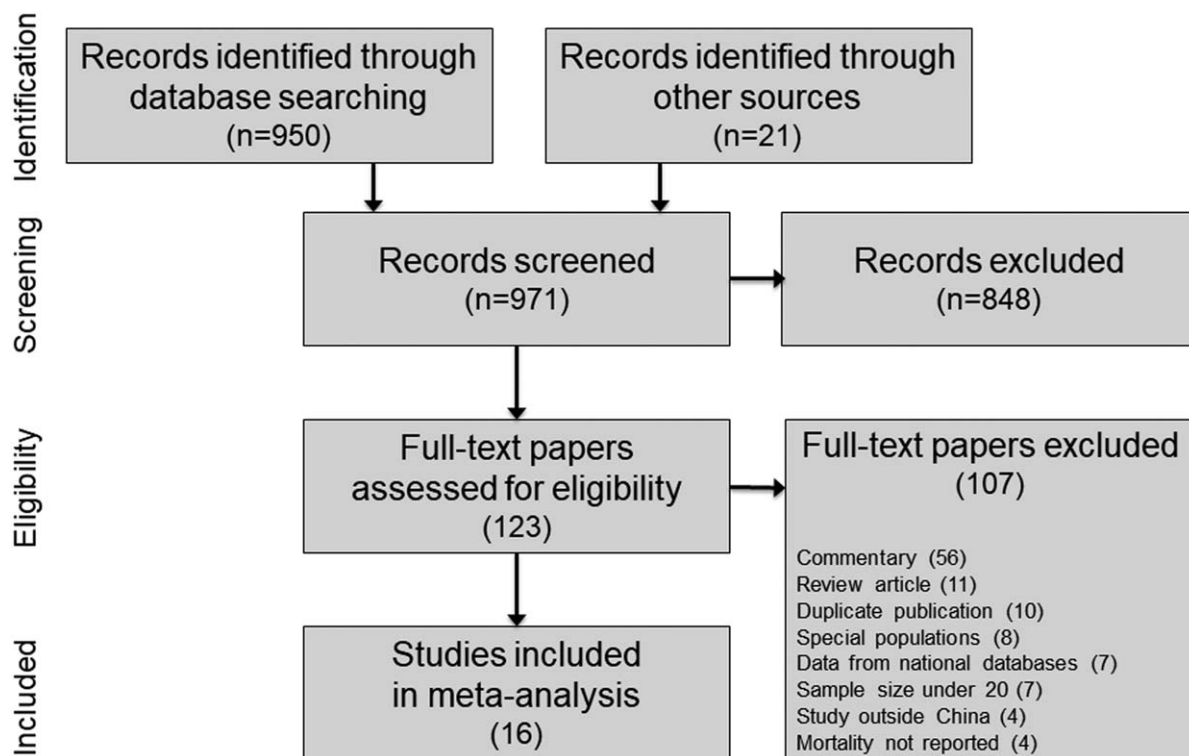
Figure 1. PRISMA Study Flow Diagram. PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-analyses.

11.1% after removal of Xu et al 24 (Table 2). Substantial funnel plot asymmetry was not apparent by visual inspection (Fig. 4). Significant heterogeneity was identified in the mortality rate among studies ($I^2 = 87\%$; $P < .001$). We subsequently undertook a metaregression analysis to identify possible sources of study-to-study variability in this rate. Among the demographics, risk factors, and symptoms, the only variable that statistically significantly influenced the mortality rate was the prevalence of DM, where each 1% increase in DM prevalence was associated with a 1.5% absolute increase in the mortality rate ($P < .001$) (Table 3). A bubble plot that visually conveys the association between DM and mortality is provided in Figure 5.


Table 1

Study and patient characteristics in observational Covid-19 studies in China.

Study	No. patients	Male: female	Median age (yr)	No. hospitals	Hospital; location	Study design	Diagnosis method	Diagnosis dates
Chen, L. et al[11]	29	21:8	56	1	Tongji Hospital; Wuhan	R	RT-PCR	Jan 14-Jan 29
Chen, N. et al[12]	99	67:32	56	1	Jin Yintan Hospital; Wuhan	R	RT-PCR	Jan 1-Jan 20
Fu et al[13]	36	16:20	45	1	Third People's Hospital; Kunming	R	RT-PCR	Jan 31-Feb 15
Guo et al[14]	187	91:96	59*	1	Seventh Hospital; Wuhan	R	RT-PCR	Jan 23-Feb 23
Huang et al[15]	41	30:11	49	1	Jin Yintan Hospital; Wuhan	P	RT-PCR or NGS	Dec 16-Jan 2
Liu, K. et al[16]	137	61:76	57	9	Nine hospitals; Hubei province	R	RT-PCR	Dec 30-Jan 24
Liu, L. et al[17]	24	8:16	43*	1	Hunan Provincial People's Hospital; Changsha	R	RT-PCR	Jan 8-Feb 8
Peng et al[18]	112	53:59	62*	2	Western Hospital & Union Medical College; Wuhan	R	†	Jan 20-Feb 15
Shi, H. et al[19]	81	42:39	50*	2	Jin Yintan Hospital & Tongii Medical College; Wuhan	R	RT-PCR or NGS	Dec 20-Jan 23
Shi, S. et al[20]	416	205:211	64	1	Renmin Hospital; Wuhan	R	RT-PCR	Jan 20-Feb 10
Tang et al[21]	183	98:85	54*	1	Tongji Hospital; Wuhan	R	RT-PCR	Jan 1-Feb 3
Wang, D. et al[22]	138	75:63	56	1	Zhongnan Hospital; Wuhan	R	RT-PCR	Jan 1-Jan 28
Wang, Z. et al[23]	69	32:37	42	1	Union Hospital; Wuhan	R	RT-PCR	Jan 16-Jan 29
Xu et al[24]	62	35:27	41	7	Seven hospitals; Zhejiang province	R	RT-PCR	Jan 10-Jan 26
Yuan et al[25]	27	12:15	60	1	Central Hospital; Wuhan	R	RT-PCR	Jan 1-Jan 25
Zhou et al[26]	191	119:72	56	2	Jin Yintan Hospital & Wuhan Pulmonary Hospital; Wuhan	R	RT-PCR or NGS	Dec 29-Jan 31

* Mean value reported.
† Value missing.
NGS = next-generation sequencing, P = prospective, R = retrospective, RT-PCR = reverse transcription polymerase chain reaction.
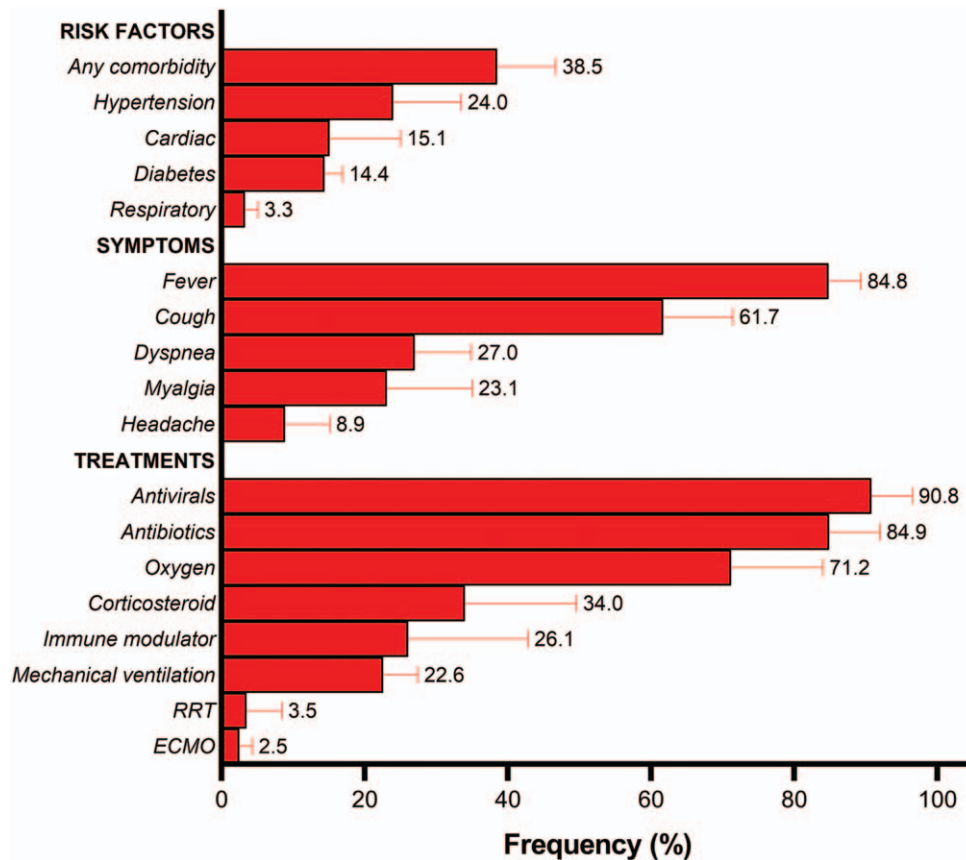
Figure 2. Prevalence of patient risk factors, presenting symptoms, and administered treatments in observational Covid-19 studies in China. Plotted values represent the weighted frequency and 95% confidence interval among included studies.
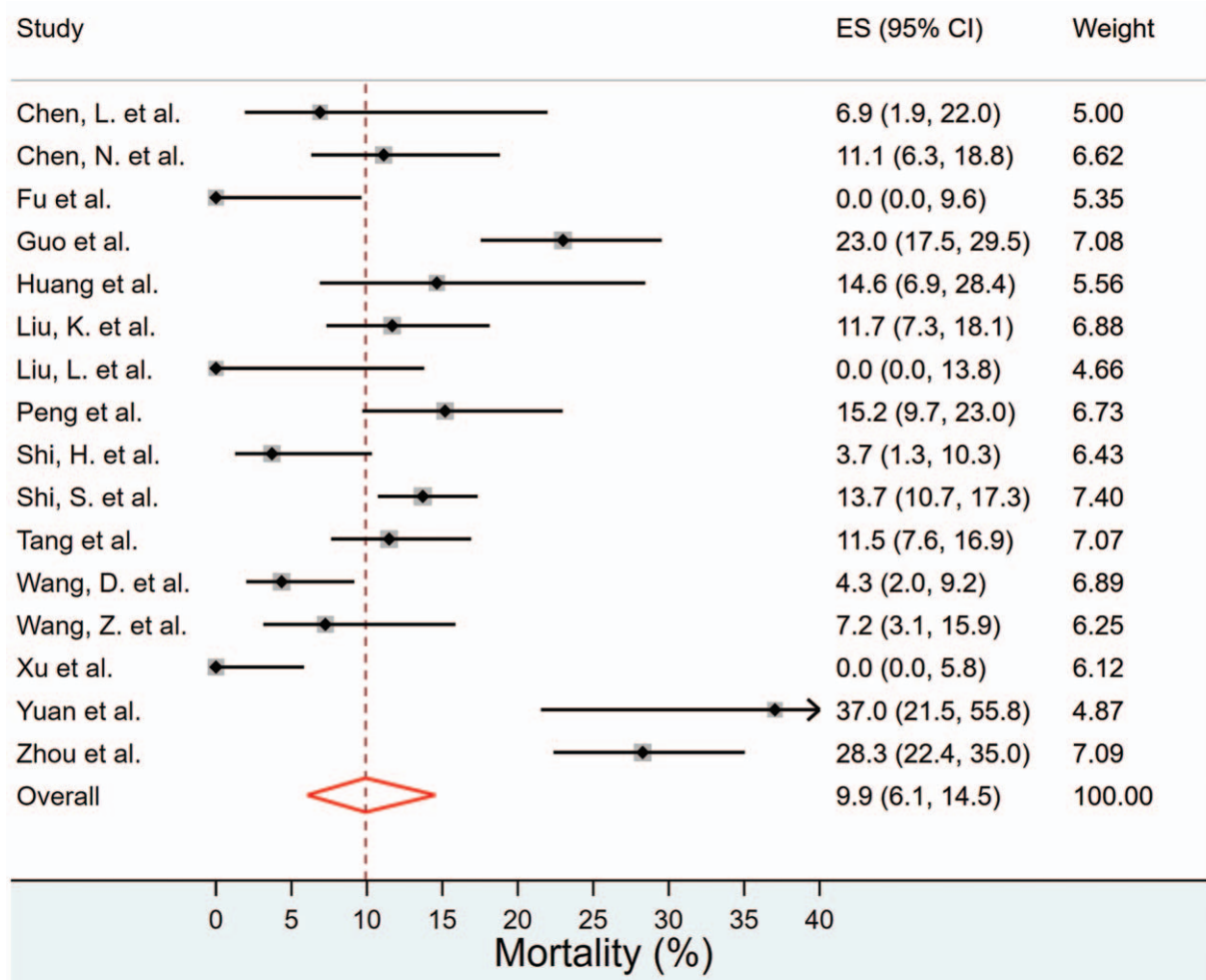
4. Discussion

Covid-19 is an emerging infectious disease in which evidence related to disease transmission, susceptibility, and risk factors for mortality and morbidity are not well characterized and likely substantially influenced by multiple factors such as patient characteristics, geography, and adherence to social distancing recommendations. We undertook a systematic review and meta-analysis intended to characterize the mortality rate in a relatively homogenous group of patients, all of whom were hospitalized for Covid-19 in China. In 16 studies of 1832 patients with a confirmed diagnosis of Covid-19 between December 16, 2019 and February 23, 2020, the pooled mortality rate was 9.9%. This rate varied considerably among studies and the variability was partially explained by a significant relationship between DM prevalence and mortality rate. The association of Covid-19 treatment with mortality rate was unclear and meta-analysis on this topic was not attempted since treatments were individualized and directed at alleviating symptoms and associated manifestations of the disease. Overall, the results of this meta-analysis highlight the mortality burden of hospitalized patients in China receiving a diagnosis of Covid-19 and, for the first time in a meta-analysis, demonstrate a strong association of DM with patient mortality.

Several other meta-analyses have reported mortality rates with Covid-19 and a comparison of key findings and methodological considerations among these reviews is warranted. Our mortality estimate of 9.9% is comparable to the findings from prior reviews

where mortality estimates ranged from 7.0%[3] to 13.9%[5] in hospitalized patients. The meta-analysis of Sun et al[4] reported a lower mortality rate of 4.3%, but 89% of the patients in that analysis were derived from a single paper of a government surveillance database where hospitalization status was not reported. It is likely that their mortality estimate of 4.3% reflected a mixed cohort of hospitalized and non-hospitalized patients. Further evidence of this discrepancy can be observed by an analysis where the mortality rate was higher when Covid-19 first emerged, but steadily decreased to approximately 4.3% as more cases were identified.[27] Therefore, it appears that the mortality rate of hospitalized patients in China is approximately 10%, but less than 5% overall when considering the mortality rate among all infected individuals regardless of hospitalization status.

Our systematic review is the first to evaluate the relationship of patient-related factors on mortality rates and, in this respect, this review provides new information. Among all variables related to demographics, comorbidities, and presenting symptoms, only the prevalence for DM was associated with mortality rates. While this finding was novel, it was not unexpected since individuals with DM have been shown to have a worse prognosis with other coronaviruses such as with the Severe Acute Respiratory Syndrome (SARS) outbreak in China in 2002[28,29] and Middle East Respiratory Syndrome Coronavirus (MERS-CoV) in the Middle East in 2012.[30] Additionally, Zhou and colleagues[26] reported that mortality risk due to Covid-19 was three-fold

| Study		ES (95% CI)	Weight
Chen, L. et al.		6.9 (1.9, 22.0)	5.00
Chen, N. et al.		11.1 (6.3, 18.8)	6.62
Fu et al.		0.0 (0.0, 9.6)	5.35
Guo et al.		23.0 (17.5, 29.5)	7.08
Huang et al.		14.6 (6.9, 28.4)	5.56
Liu, K. et al.		11.7 (7.3, 18.1)	6.88
Liu, L. et al.		0.0 (0.0, 13.8)	4.66
Peng et al.		15.2 (9.7, 23.0)	6.73
Shi, H. et al.		3.7 (1.3, 10.3)	6.43
Shi, S. et al.		13.7 (10.7, 17.3)	7.40
Tang et al.		11.5 (7.6, 16.9)	7.07
Wang, D. et al.		4.3 (2.0, 9.2)	6.89
Wang, Z. et al.		7.2 (3.1, 15.9)	6.25
Xu et al.		0.0 (0.0, 5.8)	6.12
Yuan et al.		37.0 (21.5, 55.8)	4.87
Zhou et al.		28.3 (22.4, 35.0)	7.09
Overall		9.9 (6.1, 14.5)	100.00

Figure 3. Forest plot of mortality in hospitalized patients in China diagnosed with Covid-19. The mortality rate and 95% confidence interval are plotted for each study. The pooled mortality rate (diamond apex) and 95% confidence interval (diamond width) is calculated using a random effects model. Pooled mortality = 9.9%. Heterogeneity: $I^2 = 87\%$; $P < .001$.

Table 2

One-study removed sensitivity analysis of mortality in hospitalized patients in China diagnosed with Covid-19[*].

study	mortality rate (%)	95% CI
Overall	9.9	6.1, 14.5
Chen, L. et al[11]	10.1	6.1, 14.9
Chen, N. et al[12]	9.8	5.7, 14.8
Fu et al[13]	10.9	6.9, 15.6
Guo et al[14]	9.1	5.3, 13.7
Huang et al[15]	9.7	5.7, 14.4
Liu, K. et al[16]	9.8	5.7, 14.8
Liu, L. et al[17]	10.7	6.7, 15.5
Peng et al[18]	9.5	5.5, 14.4
Shi, H. et al[19]	10.4	6.4, 15.3
Shi, S. et al.[20]	9.6	5.3, 14.9
Tang et al[21]	9.8	5.6, 14.8
Wang, D. et al[22]	10.4	6.4, 15.3
Wang, Z. et al[23]	10.1	6.0, 15.0
Xu et al[24]	11.1	7.2, 15.6
Yuan et al[25]	9.0	5.3, 13.4
Zhou et al[26]	8.9	5.4, 13.0

[*] Values represent mortality rate in meta-analysis following removal of indicated study.
CI = confidence interval.

higher in diabetes versus nondiabetic patients. While the role of hyperglycemia in the development and prognosis of Covid-19 remains speculative, potential mechanisms by which susceptibility for Covid-19 might be increased in patients with DM include higher affinity cellular binding for more efficient virus entry, inhibition of viral clearance, impaired T-cell function.[31] Chronic hyperglycemia and association inflammation may also contribute to an abnormal and ineffective immune response, thereby increasing susceptibility to hyperinflammation and cytokine storm syndrome. Diabetics with viral infection also have a greater risk of diabetic ketoacidosis, which inhibits the ability to mitigate sepsis, a major contributor to death among persons with Covid-19. Others have suggested that poor in-hospital glycemic control during hospital quarantine for Covid-19 may further contribute to mortality risk,[32] potentially owing to prioritization of life-saving treatments, limited medical personnel, unavailability of personalized diets, and limited physical activity. Thus, the findings of this meta-analysis inform working hypotheses that individuals with hyperglycemia may have a worse prognosis with Covid-19, improved glycemic control during hospitalization may improve prognosis, and individuals with DM represent a vulnerable population whose propensity for or severity of infection may be blunted with vaccination. The accumulating
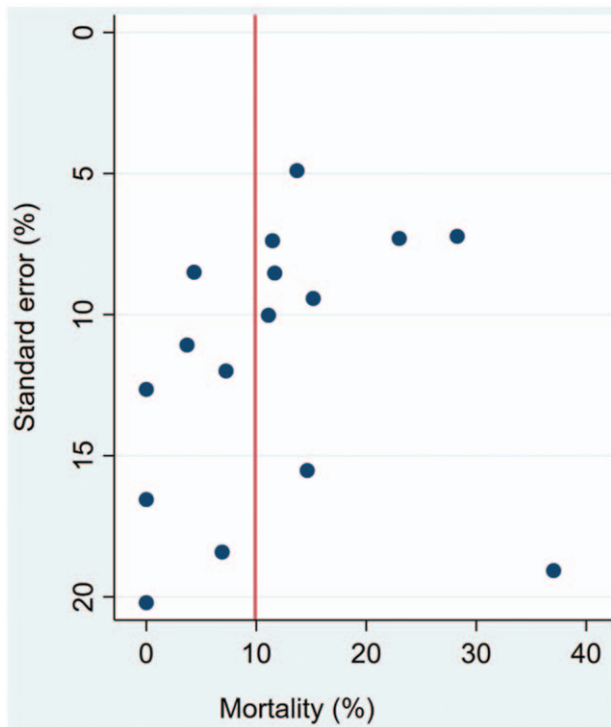
Figure 4. Funnel plot of mortality in hospitalized patients in China diagnosed with Covid-19. Funnel plot asymmetry due to small-study effects was not apparent by visual inspection.

Figure 5. Metaregression of the association between diabetes mellitus and mortality in hospitalized patients in China diagnosed with Covid-19. Open circles represent values of individual studies where circle size is proportional to the study weight in the random-effects model. The red line represents the regression line of best fit. $P = .03$.
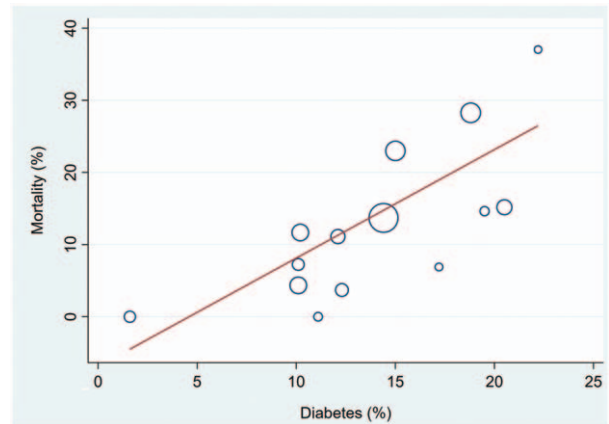
evidence regarding increased Covid-19 risk among diabetics prompted the American Association of Clinical Endocrinologists to issue a position statement specifically related to Covid-19 and diabetics where additional recommendations are provided.[33]

The main strengths of this review were prospectively defined methodology, adherence to PRISMA guidelines, inclusion of patients from a single geographic region, and robust conclusions that were unchanged in sensitivity analyses. There were also several important limitations that warrant further discussion. First,

Table 3

Predictors of mortality in hospitalized patients in China diagnosed with Covid-19.

Variable	Studies	Regression coefficient*	95% CI	P value
Diabetes mellitus (%)	14	1.5%	0.2, 2.8	.03
Age, yr	16	0.6%	−0.2, 1.4	.14
Fever (%)	14	0.3%	−0.3, 0.9	.31
Headache (%)	11	−0.4%	−1.3, 0.5	.33
Any pre-existing comorbidity (%)	15	0.1%	−0.2, 0.5	.42
Hypertension (%)	13	0.1%	−0.2, 0.5	.44
Respiratory disease (%)	11	−1.0%	−3.9, 1.8	.44
Myalgia (%)	14	−0.1%	−0.4, 0.2	.51
Cough (%)	14	0.1%	−0.2, 0.5	.51
Male sex (%)	16	0.2%	−0.5, 0.8	.61
Dyspnea (%)	13	0.1%	−0.4, 0.6	.64
Cardiac disease (%)	11	−0.1%	−0.2, 0.4	.70

* Indicates absolute increase in mortality rate for each unit of change in the independent variable. For example, each 1% increase in the prevalence of diabetes mellitus among studies was associated with a 1.5% increase in mortality.
CI = confidence interval.

definitive causal relationships cannot be established from metaregression findings and, therefore, the observed association of DM with mortality should be considered as hypothesis-generating for future studies. Second, it is plausible that other factors were associated with mortality but were not detected due to aggregation bias whereby real associations observed at the patient level (e.g., age of each patient) may not agree with those observed at the study level (e.g., mean patient age in each study) when data are pooled in a meta-analysis.[34] Third, the generalizability of these results to other geographic regions is unclear owing to factors such as differences in healthcare resources, population age and health, and adherence to social distancing recommendations. Fourth, we excluded studies that only enrolled highly selected populations such as pregnant women and critically ill patients. Although these selection criteria were implemented to minimize selection bias, we were unable to derive conclusions regarding Covid-19 mortality in special populations from this analysis. Finally, most patients with Covid-19 in this review represented the initial cluster prior to declaration of a worldwide pandemic and surveillance data suggest that the mortality rate appeared to plateau in China after only a few months following the initial outbreak. The factors that led to this decrease are unknown and there are undoubtedly additional factors that influenced mortality rates but were not amenable to formal analysis such as unmeasured or rarely reported comorbidities (e.g., chronic kidney disease), variability in treatments that likely differed by hospital and disease stage, and hospital preparedness/response status.

5. Conclusion

In a meta-analysis of hospitalized patients in China with a diagnosis of Covid-19, the mortality rate was 9.9% and a higher diabetes mellitus prevalence was independently associated with a worse prognosis. The independent influence of diabetes mellitus with Covid-19 mortality should be viewed as hypothesis-generating and warrants further study.

services. The authors had no writing assistance in the preparation of this manuscript.

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