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L. Palaiodimos

N. Chamorro-Pareja

D. Karamanis

W. Li

P. D. Zavras

See next page for additional authors

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ORIGINAL ARTICLE

Diabetes is associated with increased risk for in-hospital mortality in patients with COVID-19: a systematic review and meta-analysis comprising 18,506 patients

Leonidas Palaiodimos[1,2,3] · Natalia Chamorro-Pareja[2,3] · Dimitrios Karamanis[4] · Weijia Li[2,3] · Phaedon D. Zavras[2,3] · Kai Ming Chang[2,3,5] · Priyanka Mathias[2,3,6] · Damianos G. Kokkinidis[2,3]

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Abstract

Purpose Infectious diseases are more frequent and can be associated with worse outcomes in patients with diabetes. The aim of this study was to systematically review and conduct a meta-analysis of the available observational studies reporting the effect of diabetes on mortality among hospitalized patients with COVID-19.

Methods The Medline, Embase, Google Scholar, and medRxiv databases were reviewed for identification of eligible studies. A random effects model meta-analysis was used, and I^2 was utilized to assess the heterogeneity. In-hospital mortality was defined as the endpoint. Sensitivity, subgroup, and meta-regression analyses were performed.

Results A total of 18,506 patients were included in this meta-analysis (3713 diabetics and 14,793 non-diabetics). Patients with diabetes were associated with a higher risk of death compared with patients without diabetes (OR 1.65; 95% CI 1.35–1.96; I^2 77.4%). The heterogeneity was high. A study-level meta-regression analysis was performed for all the important covariates, and no significant interactions were found between the covariates and the outcome of mortality.

Conclusion This meta-analysis shows that that the likelihood of death seems to be higher in diabetic patients hospitalized with COVID-19 compared with non-diabetic patients. Further studies are needed to assess whether this association is independent or not, as well as to investigate the role of adequate glycemic control prior to infection with COVID-19.

Keywords COVID-19 · SARS-CoV-2 · Diabetes · Mortality · Risk factor · Meta-analysis

Introduction

Diabetes mellitus is one of the leading causes of morbidity and mortality worldwide and is associated with significant cardiovascular and renal complications. The estimated global prevalence was 9.3% in 2019 with an upward trend [1, 2]. In the USA alone, more than 34 million adults had known or undiagnosed diabetes in 2018 [3]. In 2017, diabetes was listed as the underlying or contributing cause of death on 270,702 death certificates, which corresponds to a crude rate of 83.1 per 100,000 persons [3].

Infectious diseases are more frequent and can be associated with worse outcomes in patients with diabetes [4]. Therefore, it is not surprising that diabetes has been considered as a possible risk factor or a predictor for worse outcomes in patients with coronavirus disease 2019 (COVID-19) [5–7]. COVID-19 rapidly reached the level of a pandemic and has caused more than 850,000 deaths worldwide within a few months despite unprecedented mitigation measures [8]. The

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✉ Leonidas Palaiodimos
leonidas.palaiodimos@gmail.com

1 Division of Hospital Medicine, Montefiore Medical Center, Albert Einstein College of Medicine, NW Building, 8th Floor, 111 East 210th Str., Bronx, NY 10467, USA

2 Albert Einstein College of Medicine, 1400 Pelham Parkway South, Bronx, NY 10461, USA

3 Department of Medicine, Jacobi Medical Center, Bronx, NY, USA

4 Department of Economics, University of Piraeus, 72 Ellis Str., Piraeus, 18546 Attica, Greece

5 Division of Infectious Disease, Northwell Health, New Hyde Park, NY, USA

6 Division of Endocrinology, Montefiore Medical Center, 111 East 210th Str., Bronx, NY 10467, USA

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strength of the association between diabetes and COVID-19 has been investigated in observational cohorts around the world.

We aimed to systematically review and conduct a meta-analysis of the available observational studies reporting the effect of diabetes on mortality among hospitalized patients with COVID-19.

Materials and methods

This study was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [9], although only observational studies were included.

Literature search

We conducted a systematic literature search of the Medline, Embase, Google Scholar, and medRxiv (the preprint server for health sciences) databases up to May 10, 2020 for observational studies providing data concerning any kind of association between diabetes and mortality in hospitalized patients with COVID-19. The reference lists of the possibly eligible articles and the relevant secondary research studies were reviewed manually. Two investigators (LP and DGK) independently searched for eligible studies. In cases where there was a disagreement regarding the eligibility of a study, a third investigator (FZ) was involved in order for consensus to be reached. The reference list of pertinent reviews and observational studies were also manually searched for further potentially eligible studies. A combination of the following keywords was used to perform our search: "COVID-19," "SARS-CoV-2," "novel coronavirus," "risk factor," "mortality," and "death." The search algorithms that were used for each database are provided in Supplementary Methods. The pre-specified inclusion criteria were as follows: (i) studies which included adult patients hospitalized for COVID-19 and (ii) studies that provided data on any kind of association between diabetes and mortality in the aforementioned population. The pre-specified exclusion criteria were as follows: (i) certainly or possibly duplicated or overlapping patient populations and (ii) studies that included pre-specified patient populations based on a specific diagnosis (e.g., only hypertensives or only patients with cancer). In the case of duplicated or overlapping populations, the studies with a larger sample size were included.

Data extraction and outcomes

Data extraction was performed based on a pre-defined data extraction form by two independent investigators (NCP and WL) blinded to each other. The pre-specified outcome was in-hospital mortality.

Risk of bias assessment

Two independent reviewers (NCP and PM) assessed the risk of bias of the included studies with the Quality in Prognosis Studies (QUIPS) tool [10]. Studies were assessed as having low, moderate, serious, or critical risk of bias for the following domains: study participation, study attrition, prognostic factor measurement, confounding measurement and account, outcome measurement, analysis, and reporting.

Statistical analysis

We estimated the odds ratios (ORs) and their respective 95% confidence intervals (CI) for all the individual studies. When neither OR nor event rates were provided, we used the unadjusted hazard ratios and converted them to ORs given the short follow-up period. For studies that provided both adjusted and unadjusted ORs, we used the unadjusted effect estimate. We performed a meta-analysis using the random effects model according to the method of Der Simonian and Laird. Heterogeneity among trials for each outcome was assessed with the I^2 test. Values < 25% indicated low, 25 to 70% moderate, and > 70% high heterogeneity [11]. Egger's test and funnel plots were used to assess for publication bias. Subgroup and sensitivity analyses were performed based on the location where the studies were conducted and the mean/median age. A meta-regression analysis was performed for important covariates in order to address high heterogeneity among the included studies. Statistical significance level was set at 0.05 with CI calculated at the 95% level. Stata 14.1 (Stata Corp., College Station, TX, USA) was used for statistical analysis.

Results

Out of 1721 studies screened from the literature and online sources, 14 observational studies (12 retrospective and two prospective) met the pre-specified criteria for inclusion in the analysis (Fig. 1) [12–25]. The characteristics of these studies are summarized in Table 1. Overall, all the studies were found to have a low risk of bias (Fig. 2). Five studies were conducted in Asia, five in the USA, and four in Europe. The total number of patients included in the final dataset was 18,506 patients, 3713 being diabetics and 14,793 non-diabetics. The mean or median age was above 60 years in 12 studies; 43% (7967) of the population were women (Table 2). Among studies which reported their results in event rates, the overall frequency of death events in diabetics was 41.1% (991 out of 2413) compared with

Table 1 Characteristics of the included studies

Study	Country	Region	Institution	Study design	First patient	Last patient	Number of included patients
Guan	China	31 regions (including Wuhan)	Multicenter	Retrospective	December 25	January 31	1590
Han	China	Wuhan	Tongji Hospital	Retrospective	February 2	February 15	306
Zeng	China	Xi'an and Wuhan	Multicenter (not Tongji Hospital)	Retrospective	February 5	March 20	97
Nikpouraghdam	Iran	Tehran	Baqiyatallah Hospital	Retrospective	February 19	April 15	2964
Javanian	Iran	Babol	Babol University of Medical Sciences	Retrospective	February 25	March 12	100
Rossi	Italy	Reggio Emilia	Multicenter	Prospective	February 27	April 2	1075[a]
Borobia	Spain	Madrid	La Paz University Hospital	Retrospective	February 25	April 19	2226
Perez Guzman	UK	London	Imperial College Healthcare NHS Trust	Retrospective	February 25	April 5	520
Tomlins	UK	Bristol	North Bristol NHS Trust	Retrospective	March 1	March 30	95
Levy	USA	New York	Northwell Health	Retrospective	March 1	April 12	5233
Wang	USA	New York	Mount Sinai Health System	Retrospective	March 7	April 15	3273
Cummings	USA	New York	New York-Presbyterian	Prospective	March 2	April 1	257
Palaiodimos	USA	New York	Montefiore Medical Center	Retrospective	March 9	March 22	200
Bode	USA	10 states (not New York)	Multicenter	Retrospective	March 1	April 6	570[b]

[a] Only the subset of patients who were hospitalized were included

[b] Only the subset of patients who had been discharged or died were included

17.6% (2113 out of 12,012) in the non-diabetic group. (The numbers of death events in the groups of interest were not provided in three studies; instead, odds or hazard ratios were provided) In our meta-analysis of 14 studies, we found that patients with diabetes were associated with a higher risk of death compared with patients without diabetes, but with significant heterogeneity (OR 1.65; 95% CI 1.35–1.96; I^2 77.4%; Fig. 3).

Sensitivity and subgroup analyses

Sensitivity analyses were conducted for studies that were performed in the USA ($N = 5$), Asia (5), and Western countries (Europe-USA) ($N = 9$). Similarly, in the overall analysis, our sensitivity analysis for studies conducted in the USA revealed a greater risk of death among diabetic patients compared with the non-diabetes group (OR 1.34; 95% CI 1.04–1.85; I^2 73.7%). We found a similar association for studies conducted in Asia (OR 2.12; 95% CI 1.09–3.16; I^2 61.1%) and among studies conducted in the Western countries (USA or Europe) (OR 1.60; 95% CI 1.27–1.93; I^2 82.8%; Fig. 4). Subgroup analysis of the studies that had a mean or median age less than 60 years ($N = 2$, both from Asia) did not show a significant difference in mortality between diabetics and non-diabetics (OR 2.3; 95% CI 0.01–4.92; I^2 75.5%; Fig. 4) but were likely limited by the small sample given the wide range in confidence intervals.

Publication bias assessment findings

Assessment for publication bias was performed in two different ways. Visual assessment of the funnel plot suggested possible publication bias given the asymmetry noted among smaller studies. However, Egger's test was non-significant; thus, it was not suggestive of publication bias ($p = 0.255$) (Fig. 5).

Meta-regression analysis

A study-level meta-regression analysis was performed for all the important covariates (age: $p = 0.474$, female sex: $p = 0.766$, hypertension: $p = 0.524$, coronary artery disease: $p = 0.808$, heart failure: $p = 0.263$, chronic kidney disease: $p = 0.875$, history of stroke: $p = 0.252$, smoking history: $p = 0.639$, COPD history: $p = 0.620$, and malignancy history: $p = 0.329$). No significant interactions were found between the covariates mentioned above and the outcome of mortality. The detailed meta-regression results can be found in Table 3.

Discussion

Our study was a systematic review and meta-analysis of observational studies looking at the association between diabetes and mortality in adult hospitalized patients with COVID-19. The findings of our study can be summarized as follows: (i) overall, death was 65% more likely to occur in diabetic

Table 2 Baseline characteristics of patients per included study

Study	Age	Female (*n*, %)	DM (*n*, %)	HTN (*n*, %)	HLD (*n*, %)	CAD (*n*, %)	HF (*n*, %)	CKD (*n*, %)	CVA (*n*, %)	Smoking (*n*, %)	COPD (*n*, %)	Malignancy (*n*, %)
Guan	48.9 ± 16.3[a]	674 (42.7)	130 (8.2)	269 (16.9)	NA	59 (3.7)	NA	NA	30 (1.9)	111 (7.0)	24 (1.5)	NA
Han	60 (49–70)[b]	132 (43.1)	129 (42.2)	119 (38.9)	NA	25 (8.2)	NA	4 (1.3)	11 (3.6)	5 (1.6)	18 (5.9)	18 (5.9)
Zeng	67 (57–75)[b]	38 (39.2)	26 (26.8)	47 (48.5)	NA	NA	NA	8 (8.2)	NA	NA	8 (8.2)	NA
Nikpouraghdam	55.5 ± 15.2[a]	1009 (34.0)	113 (3.8)	59 (1.9)	NA	37(1.3)	NA	18 (0.6)	NA	NA	60 (2.0)	17 (0.6)
Javanian	60.1 ± 13.9[a]	49 (49.0)	37 (37.0)	32 (32.0)	NA	NA	NA	12 (12.0)	3 (3.0)	NA	12 (12.0)	4 (4.0)
Rossi	63.2[c]	418 (38.9)	175 (16.3)	280 (26.0)	85 (7.9)	115 (10.6)	96 (8.9)	45 (4.2)	NA	NA	91 (8.5)	167 (15.5)
Borobia	61 (46–78)[b]	1152 (51.8)	381 (17.1)	920 (41.3)	NA	NA	NA	174 (7.8)	NA	157 (7.1)	153 (6.9)	385 (17.3)
Perez Guzman	67 (41–93)[b]	198 (38.0)	138 (26.5)	187 (36.0)	82 (16.0)	43 (8.2)	21 (4.0)	70 (13.4)	34 (6.5)	NA	20 (3.8)	46 (8.8)
Tomlins	75 (59–82)[b]	35 (37.0)	37/95 (38.9)	35 (37.0)	NA	21 (22.0)	15 (16.0)	22 (23.0)	8 (8.4)	NA	10 (11.0)	20 (21.0)
Levy	21–106[d]	2176 (41.6)	1414 (27.0)	2474 (50.2)	NA	454 (9.2)	219 (4.4)	326 (6.6)	NA	NA	NA	NA
Wang	60 (46–71) vs. 75 (65–84)[e]	1399 (42.7)	768 (23.5)	1082 (33.0)	NA	NA	NA	NA	NA	116 (3.5)	NA	233 (7.1)
Cummings	62 (51–72)[b]	87 (34.0)	92 (35.8)	162 (63.0)	NA	NA	NA	37 (14.0)	NA	NA	24 (9.0)	18 (7.0)
Palaiodimos	64 (50–73.5)[b]	102 (51.0)	79/200 (39.5)	152 (76.0)	92 (46.2)	33 (16.5)	34 (17.0)	58 (29.0)	22 (11.0)	65 (32.5)	28 (14.0)	11 (5.5)
Bode	65 (24–95) vs. 61 (18–101)[f]	498 (44.4)	184 (32.3)	NA	NA	NA	NA	NA	NA	NA	NA	NA

Abbreviations: *DM* diabetes mellitus, *HTN* hypertension, *HLD* hyperlipidemia, *CAD* coronary artery disease, *HF* heart failure, *CKD* chronic kidney disease, *CVA* cerebrovascular accident, *COPD* chronic obstructive pulmonary, *NA* non-available

[a] Mean ± SD

[b] Median (IQR)

[c] Mean

[d] Range

[e] Median (IQR) in discharged vs. deceased

[f] Median (range) in diabetics vs. non-diabetics

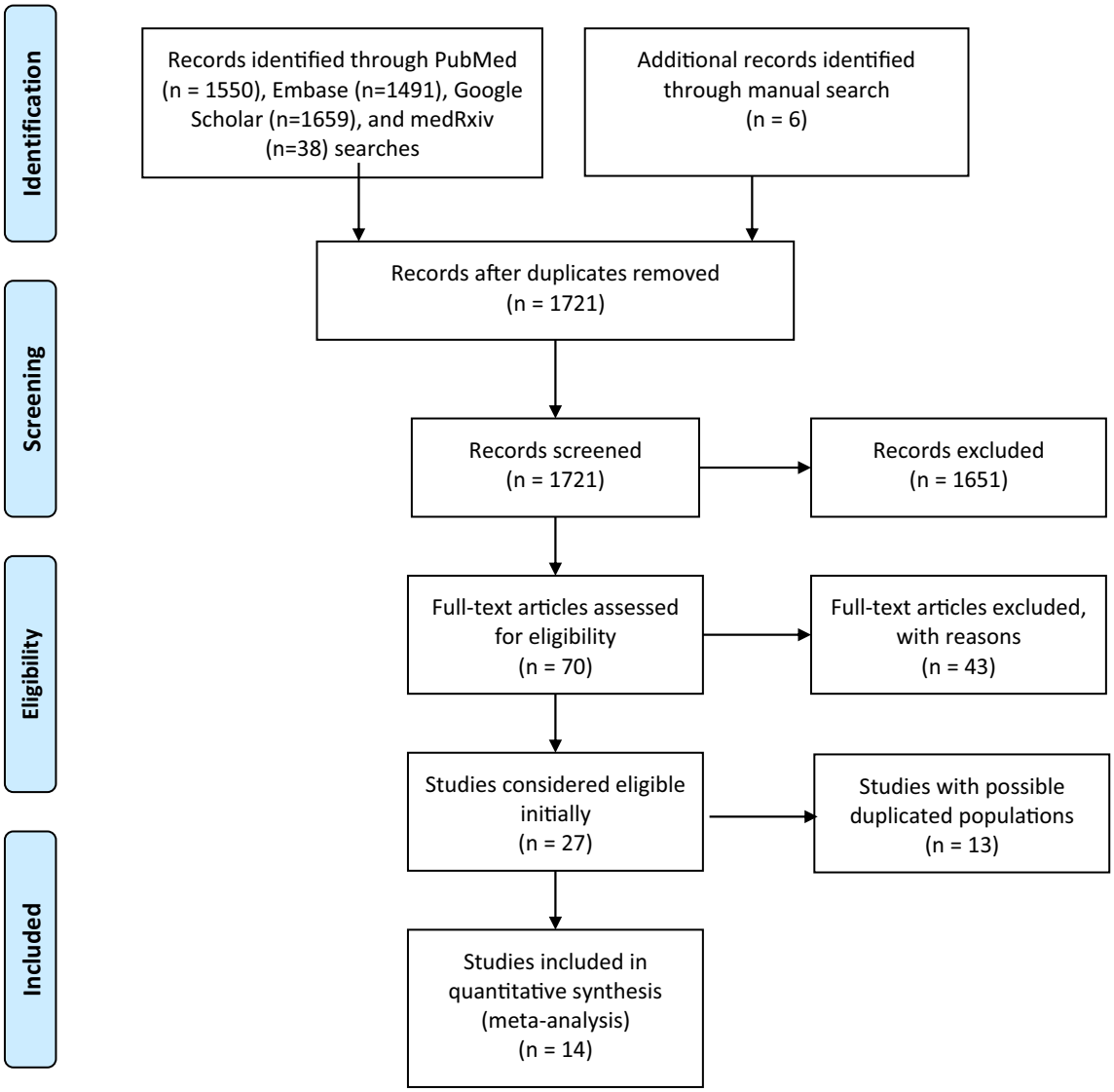

Fig. 1 PRISMA 2009 flow diagram

inpatients compared with non-diabetic patients but was limited by significant heterogeneity; (ii) this association remained significant when the analysis focused on geographical regions of study origin with, once again, significant heterogeneity; and (iii) our meta-regression analysis did not show an association between how frequent the other significant comorbidities were across different studies and our results.

The findings of our meta-analysis are consistent with the results of several large observational cohorts. In one of the largest retrospective studies of hospitalized patients with COVID-19 conducted in New York, diabetic patients comprised 33.8% (1808/5700) of the total inpatient population [26], whereas the prevalence of diabetes in the general population in New York is approximately 10.5% [27]. An early cohort of 1099 patients with COVID-19 from China revealed that 17.8% of the entire cohort developed severe disease, while the respective rate in the diabetic subgroup was 34.6% [28]. In contrast, a large study also from New York, which included 4103 patients, showed that diabetes was not an independent risk factor for the development of critical illness from COVID-19, although a trend was noted (OR 1.14, 95% CI 0.83–1.58) [29]. Smaller cohorts included in this meta-analysis did not show an association of diabetes with in-hospital mortality, but these studies had relatively small sample sizes and were likely underpowered (19, 23, 24). Given the heterogeneity of the results across the literature, our meta-analysis sought to answer this significant question by utilizing a total sample of 18,506 patients.

Diabetes is associated with higher susceptibility to infectious diseases and higher infection-related mortality [30]. A retrospective matched control study from Canada of more than one million participants demonstrated that diabetics had a significantly higher risk of being hospitalized due to an infection, develop sepsis, and die regardless of the affected system or organ or whether the infection was viral or bacterial

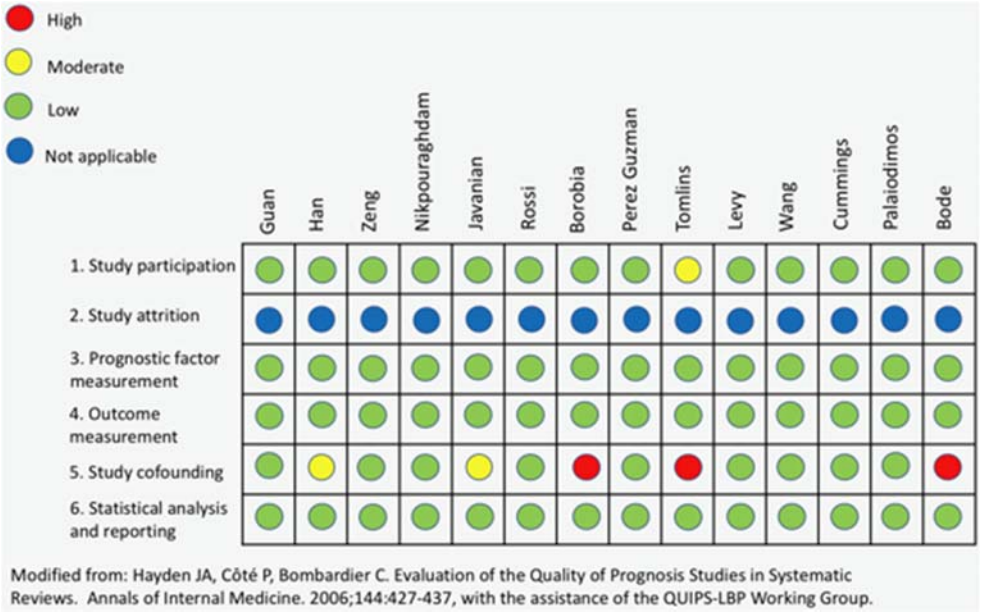

Fig. 2 Risk of bias assessment based on the Quality in Prognosis Studies (QUIPS) tool

[31]. Similarly, a UK cohort of more than 100,000 diabetics and 200,000 control subjects revealed that diabetic patients had significantly higher rates of all types of infections with an almost double risk for hospitalization and death compared with non-diabetics [32]. Among others, diabetics had 40% higher rates of lower respiratory infections (101.1 vs. 73.3;

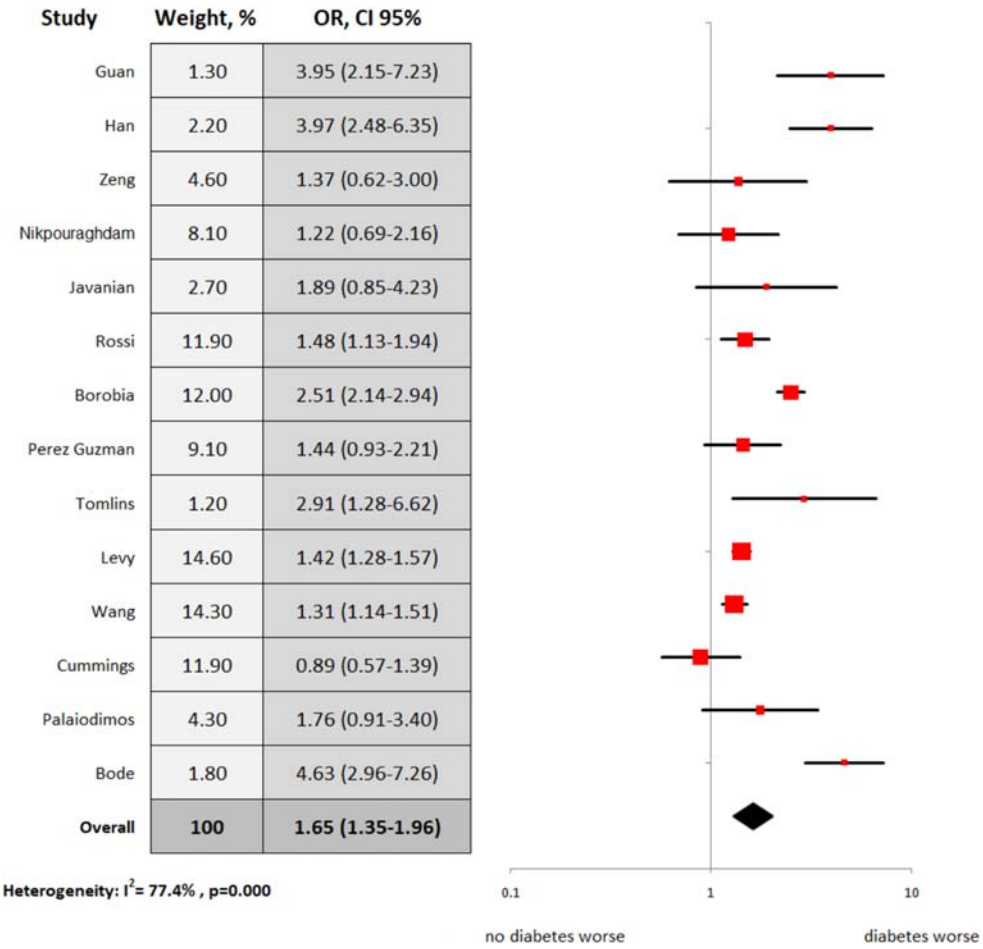

Fig. 3 Overall analysis: diabetes vs. no diabetes for in-hospital mortality

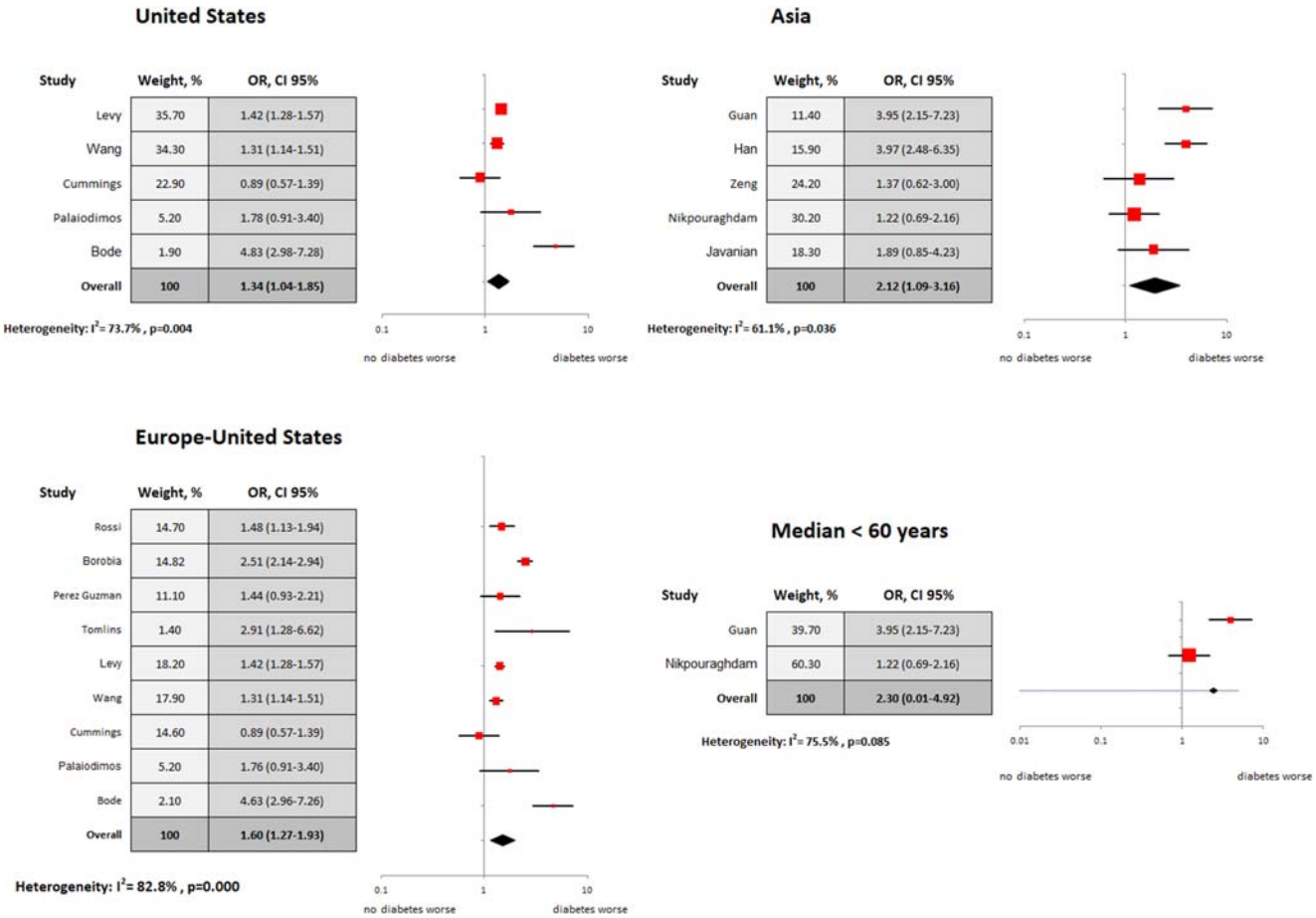

Fig. 4 Sensitivity and subgroup analyses based on the region of the study origin and the mean/median age of the study population: diabetes vs. no diabetes for in-hospital mortality

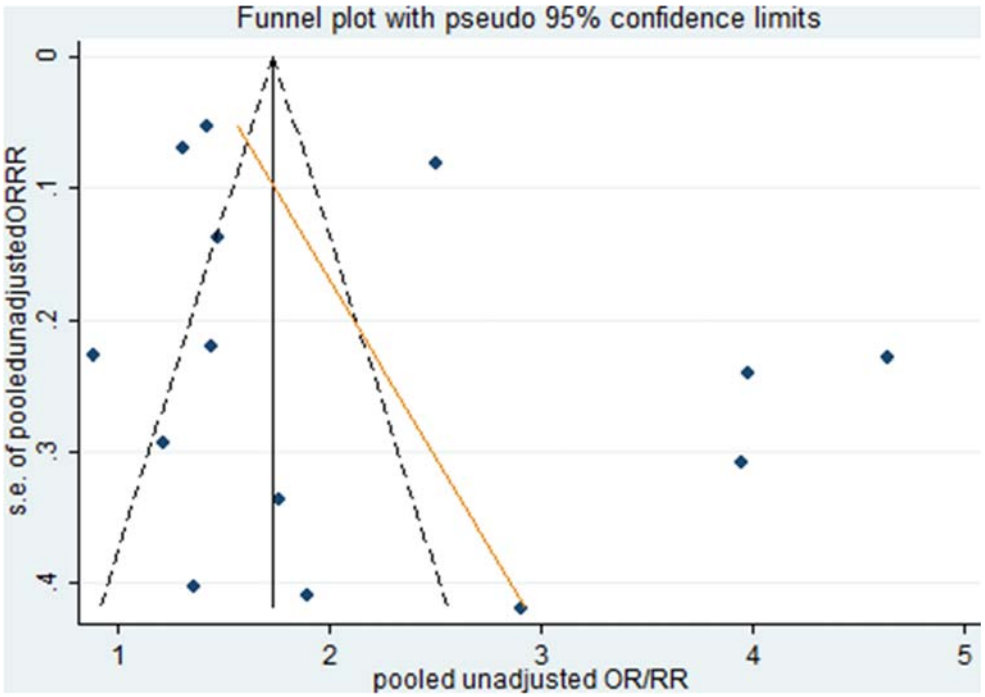

Fig. 5 Funnel plot for assessment of publication bias. Funnel plot is asymmetric among smaller studies suggesting possible publication bias. However, Egger's test was non-significant, thus, it was not suggestive of publication bias ($p = 0.255$)

Table 3 Results of the meta-regression analysis

Variables	Coefficient	Standard error	*p* value
Age	− 0.019	0.026	0.474
Female	− 0.003	0.010	0.766
HTN	− 0.005	0.007	0.524
CAD	0.594	0.361	0.808
HF	0.026	0.019	0.263
CKD	− 0.003	0.018	0.875
CVA	− 0.078	0.058	0.252
Smoking	− 0.012	0.024	0.639
COPD	− 0.022	0.043	0.620
Malignancy	0.025	0.024	0.329

Abbreviations: *HTN* hypertension, *CAD* coronary artery disease, *HF* heart failure, *CKD* chronic kidney disease, *CVA* cerebrovascular accident, *COPD* chronic obstructive pulmonary disease

per 1000 patients/year) [32]. In the 2009 H1N1 pandemic, it was noted that diabetes tripled the risk of hospitalization and quadrupled the risk of admission to intensive care units [33].

Reduced T lymphocyte response, decreased neutrophil function, impaired humoral immunity, increased adherence of microorganisms to diabetic cells, and increased virulence of some microorganisms in patients with hyperglycemia are some of the pathogenetic mechanisms that likely make diabetics more susceptible to infectious diseases [4, 34]. In addition, diabetes is a major cause of endothelial dysfunction [35]. The increasing evidence of endothelial involvement in severe COVID-19 [36, 37], which potentially contributes to COVID-19-associated coagulopathy [38], could raise the hypothesis that dysfunctional endothelium is more susceptible to further damage related to COVID-19.

The main strengths of our study are the strict methodology, robust analysis, and relatively large number of included studies and overall patient sample. Notably, three continents and most of the countries that had high COVID-19 incidence were represented. Sensitivity, subgroup, and meta-regression analyses were performed as needed.

The main limitation of our study is the lack of data on glycemic control prior to infection with COVID-19 or during hospitalization. Therefore, we could not estimate the associations of controlled and uncontrolled diabetes with in-hospital mortality and we recognize that the association could likely be stronger in patients with uncontrolled diabetes and weaker in patients with controlled diabetes. A patient-level meta-analysis would be needed to assess this very important parameter. Second, the estimated association is not adjusted for other important covariates. Unfortunately, only three of the included studies provided adjusted effect estimates with a total of only 977 patients. Pooling the adjusted estimates from these three studies did not show an independent association between diabetes and higher in-hospital mortality, likely because of low statistical power. However, a trend towards significance was observed (OR 1.29; 95% CI 0.87–1.71; I^2 0.00%; Supplementary Figure 1). We tried to solve this methodological issue by performing a meta-regression analysis, which demonstrated that the different rates of the other major comorbidities across different studies did not have an impact on the results. Similarly, a patient-level meta-analysis would be the ideal way to adjust for other significant covariates. Third, our meta-analysis was limited by significant heterogeneity, which we tried to assess by using a random effects model, performing subgroups and sensitivity, and meta-regression analysis. Fourth, we followed the PRISMA guidelines instead of the MOOSE guidelines [39]. The latter would be more appropriate given the fact that only observational studies were included in this systematic review and meta-analysis.

In conclusion, the present systematic review and meta-analysis revealed that the likelihood of death seems to be higher in diabetic hospitalized patients with COVID-19 compared with non-diabetics. Although the heterogeneity was substantial, meta-regression analysis did not reveal any significant confounders. Further studies are needed to assess whether this association is independent or not as well as to investigate the role of optimal glycemic control prior to or during the disease. The findings of our study also highlight the importance of preventing and controlling diabetes and its complications to protect this vulnerable population from COVID-19 given the increased risk for adverse outcomes. In addition, attention should be paid to the importance of controlling hyperglycemia in diabetic patients diagnosed with COVID-19 given the possible higher risk for adverse outcomes. While we recognize the limitations, we hope that our study will compliment further research of the effect of diabetes in COVID-19.

Data availability Yes, upon request to the first author.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethics approval Not applicable.

Consent to participate Not applicable.

Consent for publication All authors approved this manuscript.

Code availability Yes, upon request to the first author

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