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REVIEW ARTICLE

Diabetes prevalence and mortality in COVID-19 patients: a systematic review, meta-analysis, and meta-regression

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Abstract

Background The coronavirus disease 2019 (COVID-19) patients with diabetes mellitus (DM) are at high risk of fatal outcomes. This meta-analysis quantifies the prevalence of mortality among (1) diabetic and (2) non-diabetic, and (3) the prevalence of DM, in hospitalized COVID-19 patients.

Methods Published studies were retrieved from four electronic databases (PubMed, Embase, Scopus, and medRxiv) and appraised critically utilizing the National Heart, Lung, and Blood Institute's tool. Meta-analyses were performed using the random-effects model. The measures of heterogeneity were ascertained by I- squared (I^2) and Chi-squared (Chi^2) tests statistics. Predictors of heterogeneity were quantified using meta-regression models.

Results Of the reviewed 475 publications, 22 studies (chiefly case series (59.09 %)), sourcing data of 45,775 hospitalized COVID-19 patients, were deemed eligible. The weighted prevalence of mortality in hospitlized COVID-19 patients with DM (20.0 %, 95 % CI: 15.0–26.0; I^2, 96.8 %) was 82 % (1.82-time) higher than that in non-DM patients (11.0 %, 95 % CI: 5.0–16.0; I^2, 99.3 %). The prevalence of mortality among DM patients was highest in Europe (28.0 %; 95 % CI: 14.0–44.0) followed by the United States (20.0 %, 95 % CI: 11.0–32.0) and Asia (17.0 %, 95 % CI: 8.0–28.0). Sample size and severity of the COVID-19 were associated ($p < 0.05$) with variability in the prevalence of mortality. The weighted prevalence of DM among hospitalized COVID-19 patients was 20 % (95 % confidence interval [CI]: 15–25, I^2, 99.3 %). Overall, the quality of the studies was fair.

Conclusions Hospitalized COVID-19 patients were appreciably burdened with a high prevalence of DM. DM contributed to the increased risk of mortality among hospitalized COVID-19 patients compared to non-DM patients, particularly among critically ill patients. **Registration**: PROSPERO (registration no. CRD42020196589).

Keywords Coronavirus infection · Diabetes mellitus · Diabetes mellitus, type 1 · Diabetes mellitus, type 2

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Introduction

In December 2019, the Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2) emerged in Wuhan, Hubei Province, China, and the disease it caused is called coronavirus disease-2019 (COVID-19) [1–3]. The COVID-19 spread rapidly across continents, and by March 2020, World Health Organization declared the epidemic as a pandemic [4]. By October 04, 2020, the cumulative total COVID-19 cases and deaths reported worldwide exceeded 34.8 million and 1 million, respectively [5].

Diabetes mellitus (DM) is one of the most frequently reported comorbidities in COVID-19 patients that determine their risk of morbidity and mortality. The prevalence of DM in hospitalized COVID-19 patients in China and the United States (US) was 9.7 and 28.3 %, respectively [6, 7]. An Italian

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study depicted that the prevalence of DM in severe COVID-19 patients admitted in intensive care units (ICU) was 17 % [8]. Previously also, in the 2009-H1N1 pandemic influenza and the Middle East respiratory syndrome, DM was a crucial determinant of mortality [9, 10]. Existing studies have consistently reported increased mortality among COVID-19 patients with DM [11–15].

Research shows, mortality risk among hospitalized COVID-19 patients with DM has an independent association with clinical and biological predictors including age, micro- and macro-vascular complications of DM, shortness of breath, and decreased platelet count [16]. It's hypothesized that the worse outcomes of COVID-19 patients with DM are attributable to the angiotensin-converting enzyme-2 receptor-mediated entry of the SARS-CoV-2 virus in the host cell, which damages the insulin-producing pancreatic islet cells [17–19].

Given this mortality risk in the SARS-CoV-2 infected DM patients, in the ongoing COVID-19 pandemic situation, it's vital to estimate the epidemiological burden of mortality among hospitalized COVID-19 patients to ensure the implementation of evidence-based public health initiatives. Therefore, we systemically reviewed published literature and quantified the overall and subgroup weighted prevalence of mortality among diabetic (primary outcome) and non-diabetic (secondary outcome) and the weighted prevalence of DM (secondary outcome), in hospitalized COVID-19 patients.

Methods

This review was reported according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2009 guidelines [20]. The PRISMA checklist is provided in the supplementary information (Supplementary Table: Table S1). The protocol for this review is available in the PROSPERO (registration no. CRD42020196589) [21].

Inclusion criteria

Published research articles reporting quantified or quantifiable estimates on the prevalence of mortality in diabetic hospitalized COVID-19 patients were deemed eligible to be included in this systematic review, considering the following additional eligibility criteria:

Study design: observational, experimental, or case-series studies.
Setting and population: hospitalized COVID-19 patients with confirmed disease regardless of age or gender.
Ascertainment of COVID-19: reverse transcription-polymerase chain reaction (RT-PCR) testing, computer tomography (CT) imaging, clinical, or all.
Ascertainment of DM: accepted as per the study authors ascertainment.
Geographic origin: global.
Language: English only.

Exclusion criteria

We excluded published articles reporting suspected COVID-19 patients without further confirmatory testing (e.g., RT-PCR, CT imaging) or including COVID-19 patients with gestational DM. Editorials, letters, commentaries, and abstracts with no enough data or without full-text did not comprise the inclusion criteria.

Data source

Peer-reviewed publications were retrieved from three main electronic databases (PubMed, Embase, and Scopus). The last date of the search was June 30, 2020. The following strategy was used to search the PubMed database - "SARS-CoV-2" OR "Coronavirus" OR "COVID-19" AND "diabetes" NOT "MERS" NOT "Middle East respiratory syndrome." Following MeSH Terms were also used in the search: "coronavirus infection," "diabetes mellitus," "diabetes mellitus, type 1," "diabetes mellitus, type 2."

The literature search was also extended to a pre-print database (med*R*xiv). Bibliographies of the eligible publications were hand-searched for eligible studies that might have been missed.

Study selection, data abstraction, and risk of bias (RoB) assessment

After uploading the retrieved citations in the Rayyan systematic reviews software [22], the duplicates were removed. Then two reviewers (SS1 and SS2) independently skimmed the titles and abstracts of the remaining papers to assess their eligibility. A full-text reading ensued when the citations seemed to match fully or partially against the pre-stated eligibility criteria.

From the deemed-eligible publications, independently, two reviewers (SS1 and SS2) abstracted the necessary information and data. The abstracted information covered author name, year of publication, study design, study population, number of COVID-19 hospitalized patients with DM, number of deaths among COVID-19 hospitalized patients by the DM status, COVID-19 and DM diagnostic method, and the severity of the COVID-19. From same abstracted publications, whenever reported, additional data on the prevalence of DM and on the prevalence of mortality among non-DM hospitalized COVID-19 patients was also abstracted. Data abstraction was performed into a pre-defined data-extraction sheet. For

each included publication, the quality and risk of bias (RoB) was determined, independently, by SS1 and SS2 using the study design-specific quality assessment tool of the National Heart, Lung, and Blood Institute [23].

For particular study types, we eliminated RoB components not applicable to those study designs. RoB components that were adequately addressed by the studies (i.e., the 'yes' responses) were scored as one and otherwise 0 (zero). Then, we determined the study design-wise and the overall percentage of scores. Out of the maximum possible 'yes' response scores, we categorized the achieved score by the studies as poor, fair, and good when it was between 0–25, 25–76, and 76–100 %, respectively. Disagreements in opinion among the review authors were resolved by discourse.

Evidence synthesis: meta-analysis

In the meta-analysis, estimation of the weighted prevalence and its 95 % confidence interval (CI) was performed utilizing the DerSimonian and Laird random-effects model. The stabilization of variances in the prevalence estimates was determined by the exact binomial procedure and Freeman-Tukey double arcsine transformation, respectively [24]. Heterogeneity was estimated by I-squared (I^2) (categorized as low, moderate, and high based on its values of 25 %, 50 %, and 75 %, respectively) and Chi-squared (Chi^2) test statistics (statistically significant at $p < 0.1$). The predictive intervals estimated the prevalence of future studies.

Subgroup analysis

Subgroup wise weighted prevalence was determined for the country and continent, COVID-19 (RT-PCR only or multiple methods) and DM (specified or unclear) diagnostic method, DM type (type 1 or type 2), the severity of the COVID-19 infection (critically ill or not critically ill), and the sample size (< 100 versus ≥ 100).

Publication bias and heterogeneity assessment

Publication bias was assessed visually by generating funnel plots depicting prevalence against its standard error and statistically by Egger's test. Heterogeneity was explored statistically by univariate and multivariate meta-regression (random-effects model). The statistical significance of univariate meta-regression analyses was determined at $p < 0.1$ and was performed for the following potential predictors – country, continent, study design, COVID-19 diagnosis method, COVID-19 severity, diagnostic method, and type of DM, and sample size. Statistically significant predictors from univariate models were included in the multivariate meta-regression model, and the statistical significance was determined at $p < 0.05$.

Sensitivity analysis

The overall pooled prevalence of the respective outcomes was re-estimated by dropping a study each time. STATA statistical software (version 16; StataCorp, College Station, Texas, USA) was used for all analyses.

Results

Scope of the review

Out of the 607 retrieved citations from the four databases, 22 published articles [16, 25–45] were deemed eligible and included in this review (Fig. 1). The eligible articles reporting on inpatient COVID-19 patients between December 2019 and May 2020 from nine countries (China, India, Iran, Korea, Oman, France, Italy, UK, and the US) dispersed over three continents. Most of these were case series (59.09 %), and the remaining constituted of cross-sectional, case-control, and retrospective cohort studies, attributing to 14 % each.

A total of 45,775 COVID-19 patients hospitalized in 995 hospitals were reported. Of them, 46.3 % were from the European nations, followed by 31.7 % from the US, while the remaining 20.0 % were from five Asian countries. RT-PCR was used solely in 45.4 % of the COVID-19 patients, whereas for the rest, a combination of lab-based, radiological, and clinical interpretation was used. Although 11,811 COVID-19 patients had DM, the type of it was specified in 14.5 % of these cases. Among the 225 DM patients with available COVID-19 severity information, 28.44 % were critically ill.

Salient features of the reviewed studies are presented in Table 1.

Weighted prevalence of DM

The weighted prevalence of DM among hospitalized COVID-19 patients was 20.0 % (95 % CI: 15.0–25.0; $I^2 = 99.3$ %) (Table 2). The joint prevalence of DM in Italy and the UK was similar to that in the US (26 %) but higher than that in five Asian countries (17.0 %). Of the hospitalized COVID-19 patients, 29 %, 24 %, and 18 % were with type 2 DM, type 1DM, or the type of DM was unclear (presumably type 2 DM). The prevalence of DM in critically ill COVID-19 patients was 2.75-time higher than those not critically ill (Table 2).

Weighted prevalence of mortality in diabetic and non-diabetic patients

The weighted prevalence of mortality was 1.82-time higher in DM (20.0 %, 95 % CI: 15.0–26.0; I^2, 96.8 %) (Fig. 2) than non-DM (11.0 %, 95 % CI: 6.0–16.0; I^2, 99.32 %)

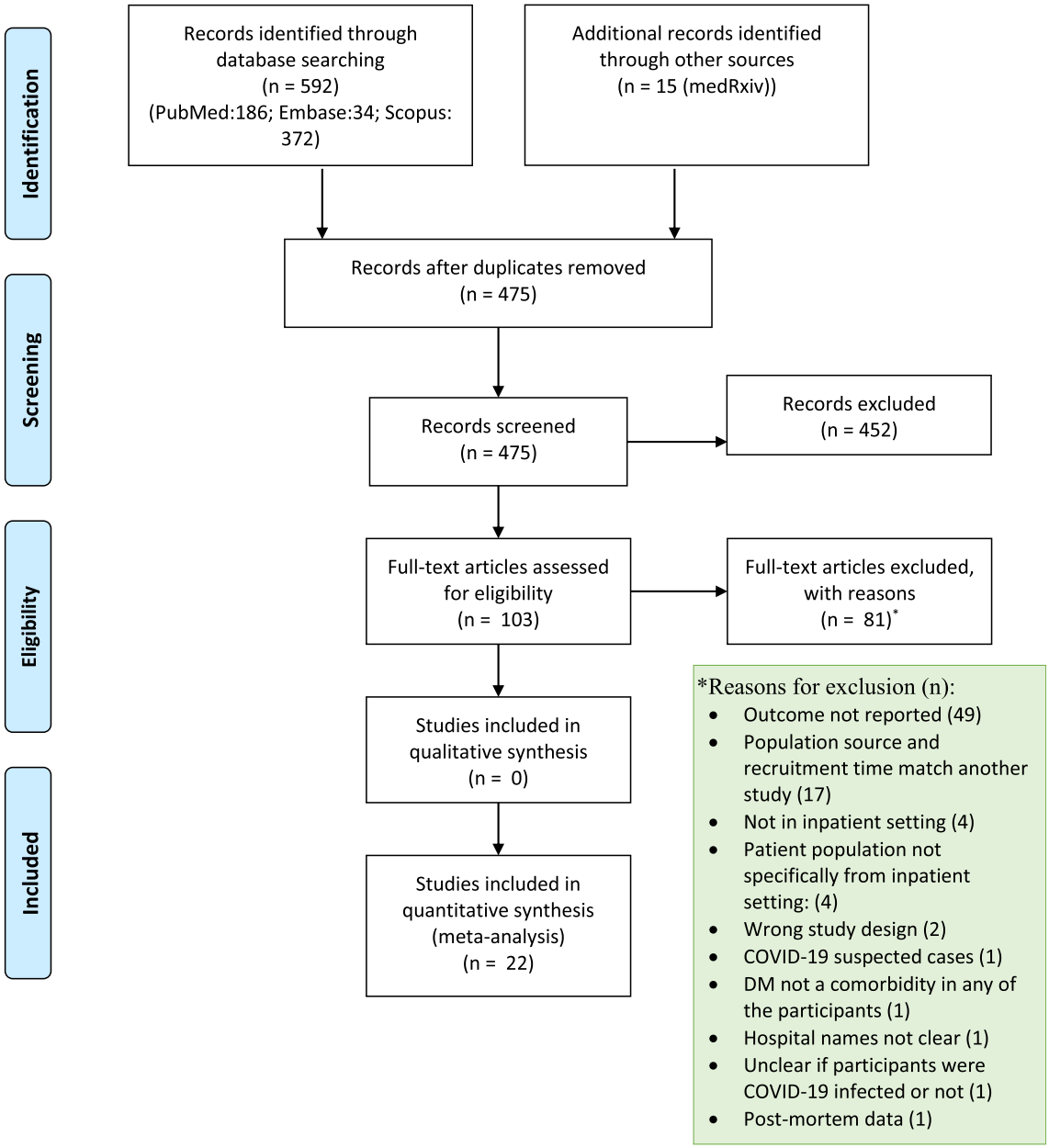

Fig. 1 Prisma flow diagram [20]

hospitalized COVID-19 patients (Table 3). The prevalence of mortality in COVID-19 patients with DM in France, Italy, and UK was higher (28 %; 95 % CI: 14.0–44.0) than the US (20.0 %, 95 % CI: 11.0–32.0) and the Asian countries (17.0 %, 95 % CI: 8.0–28.0) (Table 3).

Juxtaposed to less severe COVID-19 infection, DM and non-DM patients with severe COVID-19 infection had 37 and 19 % higher prevalence of mortality, respectively, (Table 3). Table S2 presents more weighted estimates on the prevalence of mortality grouped by continents.

The DM patients with COVID-19 who were admitted to ICU had a seven-percentage point higher prevalence of death (26.0 %) compared with those who were not admitted to the ICU (19.0 %) (Table S3). The DM patients who died in the ICU setting were primarily suffering from severe COVID-19 infection (81 %; 95 % CI: 67.0–91.0).

Sources of heterogenity

DM among COVID-19 patients

The univariate meta-regression analyses suggested that COVID-19 severity as the determinant of heterogeneity (Table S4).

Table 1 Salient features of the reviewed studies

Author, year	Country, city	Study time period	Design	Follow up from day of hospitalization	Studied population	COVID-19 diagnosis	Sample size (hospitalized COVID-19 patients)	DM type (diagnosis criteria)	Outcome		
									COVID-19 patients with DM n (%)	Death among hospitalized COVID-19 patients with	
										DM n (%)	No-DM n (%)
Alkundi et al. 2020 [25]	UK	10/03 – 10/05, 2020	Cross-sectional	NA	COVID-19 patients with a mean age of 70.5 years ±15.	RT-PCR	232	T1DM T2DM Mixed DM Unclear	11 (4.7) 76 (32.8) – –	6 (54.5) 34 (44.7) – –	49 (33.8)
Cariou et al. 2020 [16]	France	10/03 – 10/04, 2020	Case series	7 days	Hospitalized COVID-19 patients with diabetes of Mean age of 69.8 years + 13	RT-PCR and/or clinically/-radiologically by chest CT	1317	T1DM T2DM Mixed DM Unclear	39 (3.0) 1166 (88.5) 112 (8.5)	2 (5.1) 127(10.9) 11 (9.8)	-
Bhandari et al. 2020 [36]	India	01/03/2020-unlcear	Case series	Unclear (until submission date of the manuscript)	Unclear with a median (range) age 43.5 (2-85) years	RT-PCR	21	T1DM T2DM Mixed DM Unclear	- - - 2 (9.5)	- - - 0 (0.0)	19 (0)
Bode et al. 2020 [39]	US	01/03 – 06/04, 2020	Retrospective cohort	In DM patients: 3885 patient days; in non-DM patients: 3793 patient days	Unclear with age of DM and/or uncontrolled hyperglycemia: median (range): 65 (24-95); patients without DM and/or uncontrolled hyperglycemia: Median (range): 61 (18-101)	RT-PCR	1122	T1DM T2DM Mixed DM Unclear	- - - 88 (7.8)	- - - 13 (14.8)	64 (6.2)
Yu et al. 2020 [40]	China	14/01 – 26/03, 2020	Case control	NA	Dead and recovered hospitalized COVID-19 positive patients with median (IQR) age 64.0 (51.0–71.0) years	RT-PCR	1464	T1DM T2DM Mixed DM Unclear	- - - 211 (14.4)	- - - 69 (32.7)	143 (11.4)
Docherty et al. 2020 [41]	UK	06/02 – 03/05, 2020	Case series	>2 weeks	Inpatient COVID-19 cases with median age (IQR) 72.9 (58.0-82.0) years	RT-PCR and clinical	20133	T1DM T2DM Mixed DM Unclear	- - - 4949 (24.6)	- - - 1469 (29.7)	3696 (24.3)
Ciceri et al. 2020 [42]	Italy	25/02 – 01/05, 2020	Case series	>1 month	All adult COVID-19 cases admitted to the emergency department with median (IQR) age 65 (56-75) years	One or more: RT-PCR, clinically, and radiological findings suggesting COVID-19 pneumonia	410	T1DM T2DM Mixed DM Unclear	8 (2) 61 (14.9) - -	2 (25) 20 (32.8) - -	73 (21.4)
Guan et al. 2020 [43]	China	11/12 – 31/01, 2020	Cross-sectional	NA	Unclear with Mean age 48.9±16.3 years	RT-PCR	1590	T1DM T2DM	- -	- -	37 (2.5)

Table 1 (continued)

Author, year	Country, city	Study time period	Design	Follow up from day of hospitalization	Studied population	COVID-19 diagnosis	Sample size (hospitalized COVID-19 patients)	DM type (diagnosis criteria)	Outcome		
									COVID-19 patients with DM n (%)	Death among hospitalized COVID-19 patients with	
										DM n (%)	No-DM n (%)
								Mixed DM	-	-	
								Unclear	130 (8.2)	13 (10)	
Lee et al. 2020 [44]	Korea	18/02 – 04/03, 2020	Case series	≥2 weeks	≥65 years older hospitalized COVID-19 patients with median (IQR) age 72 (68.0–79.0) years	RT-PCR	98	T1DM	-	-	9 (12.7)
								T2DM	-	-	
								Mixed DM	-	-	
								Unclear	27 (27.6)	11 (40.7)	
Zhao et al. 2020 [45]	China	27/01 – 01/04, 2020	Case series	Until 01-Apr-2020	First 29 severe COVID-19 cases admitted for treatment with median (IQR) age 56.0 (31.5–66.0) years	RT-PCR	29	T1DM	-	-	1 (4.5)
								T2DM	7 (24.1)	0 (0.0)	
								Mixed DM	-	-	
								Unclear	-	-	
Khamis et al. 2020 [26]	Oman	24/02 – 24/04, 2020	Case series	Until 24-Apr-2020	RT-PCR confirmed cases admitted to the hospital with mean age 48±16 years	RT-PCR	63	T1DM	-	-	1 (2.3)
								T2DM	-	-	
								Mixed DM	-	-	
								Unclear	20 (31.7)	4 (20.0)	
Marcello et al. 2020 [27]	US	05/03 – 16/04, 2020	Case series	Until 16-Apr-2020	RT-PCR confirmed cases with median (IQR) age 61 (49.7-72.9) years	RT-PCR	6248	T1DM	-	-	1145 (27.2)
								T2DM	-	-	
								Mixed DM	-	-	
								Unclear	2045 (32.7)	597 (29.2)	
Zhang et al. 2020 [28]	China	09/01 – 19/02, 2020	Case control	NA	Critically ill COVID-19 pneumonia patients with mean age 64.4 ± 11.0 years	RT-PCR	60	T1DM	-	-	6 (11.8)
								T2DM	-	-	
								Mixed DM	-	-	
								Unclear	9 (15.0)	4 (44.4)	
Nikpouraghdam et al. 2020 [29]	Iran	19/02 – 15/04, 2020	Cross-sectional	NA	Unclear with mean age 55.5±15.15 years	One or more: RT-PCR or clinically by CT-scan	2964	T1DM	-	-	228 (8.0)
								T2DM	-	-	
								Mixed DM	-	-	
								Unclear	113 (3.8)	11 (9.7)	
Richardson et al. 2020 [30]	US	01/03 – 04/04, 2020	Case series	Until 04-Apr-2020	COVID-19 cases admitted to the hospital with median (range) age 63 (0-107) years	RT-PCR	5700	T1DM	-	-	329 (8.5)
								T2DM	1808 (31.7)	224 (12.4)	
								Mixed DM	-	-	
								Unclear	-	-	
Rosenberg et al. 2020 [31]	US	15/03 – 24/04, 2020	Case series	Until 24-Apr-2020	COVID-19 cases admitted to the hospital with median age 63 years	RT-PCR	1438	T1DM	-	-	158 (16.9)
								T2DM	-	-	
								Mixed DM	-	-	
								Unclear	504 (35.0)	134 (26.6)	
Shi et al. 2020 [32]	China	01/01 – 08/03, 2020	Case control	NA	COVID-19 cases with DM who were discharged or admitted to the hospital.	RT-PCR	306	T1DM	-	-	16 (10.5)
								T2DM	-	-	
								Mixed DM	-	-	
								Unclear	153 (50.0)	31 (20.3)	

Table 1 (continued)

Author, year	Country, city	Study time period	Design	Follow up from day of hospitalization	Studied population	COVID-19 diagnosis	Sample size (hospitalized COVID-19 patients)	DM type (diagnosis criteria)	Outcome		
									COVID-19 patients with DM n (%)	Death among hospitalized COVID-19 patients with	
										DM n (%)	No-DM n (%)
					Patients with DM: median (IQR) age 64.0 (56.0–72.0) years; Patients without DM median (IQR) age 65.0 (56.0–72.0) years						
Wang et al. 2020 [33]	China	07/02 – 22/02, 2020	Case series	Until 22-Feb-2020	Non-critically ill admitted COVID-19 cases with median (IQR) age 50 (39-58) years	RT-PCR	1012	T1DM T2DM Mixed DM Unclear	- - - 27 (2.7)	= = - 0 (0.0)	0 (0.0)
Cen et al. 2020 [34]	China	10/02 – 08/03, 2020	Case series	28 days	Mild or moderately ill admitted COVID-19 cases with median (IQR) age 61 (49-68) years	RT-PCR	1007	T1DM T2DM Mixed DM Unclear	- - - 119 (11.8)	- - - 12 (10.1)	31 (3.5)
Zhang et al. 2020 [35]	China	29-Jan	Retrospective cohort	Until 12-Mar-2020	All COVID-19 patients admitted with median (IQR) age 64 (56-70) years	RT-PCR	258	T1DM T2DM Mixed DM Unclear	- - - 63 (24.4)	- - - 7 (11.1)	8 (4.1)
Yan et al. 2020 [37]	China	10/01 – 24/02, 2020	Retrospective cohort	Unclear	Hospital admitted severe COVID-19 cases with median (IQR) age 64 (49-73) years	RT-PCR and chest CT	193	T1DM T2DM Mixed DM Unclear	- 48 (24.9) - -	- 39 (81.3) - -	69 (47.6)
Jang et al. 2020 [38]	Korea	19/02 – 15/04, 2020	Case series	Until 15-Apr-2020	>18 years COVID-19 cases admitted via emergency room or outpatient department with mean age 56.9±17.0 years.	RT-PCR	110	T1DM T2DM Mixed DM Unclear	- - - 15* (13.6)	- - - 0 (0.0)	CD

* only for those diabetes mellitus cases with available mortality data

Abbreviations: CD: cannot determine; DM: diabetes mellitus; NA: not applicable; RT-PCR: reverse transcriptase-polymerase chain reaction

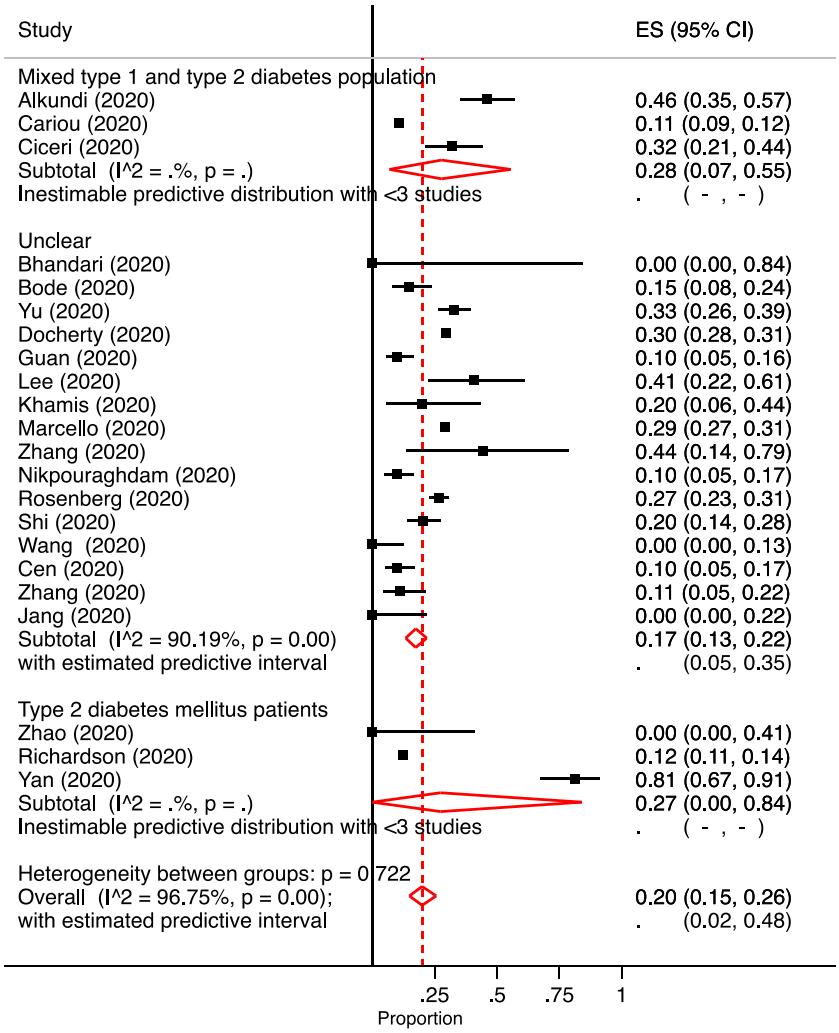

Fig. 2 Forest plot depicting the overall and diabetes mellitus (DM) type-wise prevalence of mortality in hospitalized COVID-19 patients with DM. The diamond is centred on the summary of the prevalence estimate, and the width indicates the corresponding 95 % CI

Mortality among diabetic COVID-19 patients

An adjusted meta-regression model including sample size and COVID-19 severity as predictors depicted a 452 % (p = 0.014) increased risk of mortality in DM patients with severe COVID-19 infection compared to the reference group (Table S5).

Mortality among non-diabetic COVID-19 patients

For the prevalence of mortality among non-DM hospitalized COVID-19 patients, nation, continent, and COVID-19 diagnostic methods were the plausible predictors of heterogeneity; however, none was statistically significant in the multivariate models (Table S6).

Publication bias

For all outcomes, the visual inspection of funnel plots (Supplementary Figure: S1-S3) and Egger's test findings did not suggest any small study effect.

Sensitivity analysis

Upon sensitivity analysis, the overall pooled prevalences of the respective outcomes obtained in each iteration closely resembled the preliminary estimates.

Risk of bias assessment

Overall, the quality of the studies was fair. The average study score was 6.4 out of a maximum possible average score of 9.4. The most common study type, case series, was of good quality (average score 6.5 out of a maximum possible score of 8) (Table S7).

Discussion

Overall, 22 observational studies with a total of 45,775 hospitalized COVID-19 patients were reviewed. The prevalence of DM was appreciably high among hospitalized COVID-19

Table 2 Overall and subgroup wise prevalence of diabetes mellitus in hospitalized COVID-19 patients

Subgroup	Category	Number of Studies	Number of admitted COVID-19 patients	Number of DM patients	Mean prevalence of DM		95% prediction interval	Heterogeneity measures	
					%	95% CI		I^2 (%)	Q (p-value)
Continent	Asia	14	9,175	944	17.0	11.0–24.0	0.0–48.0	98.13	<0.01
	Europe	3	20,775	5105	26.0	18.0–34.0	-	-	-
	North America	4	14,508	4445	26.0	17.0–35.0	0.0–75.0	99.31	<0.01
Country	China	9	5,919	767	18.0	10.0–26.0	0.0–54.0	98.26	<0.01
	India	1	21	2	10.0	1.0–30.00	Inestimable	-	-
	Iran	1	2,964	113	4.0	3.0–5.0	Inestimable	-	-
	Italy	1	410	69	17.0	13.0–21.0	Inestimable	-	-
	Korea	2	208	42*	20.0	15.0–25.0	Inestimable	-	-
	Oman	1	63	20	32.0	21.0–45.0	Inestimable	-	-
	UK	2	20,365	5036	25.0	24.0–25.0	Inestimable	-	-
	US	4	14,508	4445	26.0	17.0–35.0	0.0–75.0	99.31	<0.01
COVID-19 diagnosis	RT-PCR	17	20,758	5315	21.0	15.0–28.0	1.0–55.0	99.13	<0.01
	Multiple modes	4	23,700	5179	16.0	4.0–34.0	0.0–98.0	99.72	<0.01
DM diagnosis	Method specified	4	1,918	391	28.0	9.0–53.0	0.0–100	99.02	<0.01
	Unclear	17	42,540	10,103	18.0	13.0–24.0	1.0–48.0	99.40	<0.01
DM types	Mixed T1DM patients and T2DM	2	642	156	24.0	20.0–27.0	Inestimable	-	-
	Type 2	3	5,922	1863	29.0	23.0–34.0	Inestimable	-	-
	Unclear	16	37,894	8475	18.0	12.0–25.0	0.0–51.0	99.44	<0.01
COVID-19 severity	Critically ill	3	282	64	22.0	16.0–28.0	Inestimable	-	-
	Not Critically ill	3	2,129	161	8.0	2.0–18.0	Inestimable	-	-
	Unclear	15	42,047	10,269	22.0	17.0–29.0	3.0–53.0	99.42	<0.01
Sample size	<100	12	3,608	462	18.0	11.0–27.0	0.0–56.0	96.80	<0.01
	≥100	9	40,850	10,032	22.0	15.0–30.0	2.0–55.0	99.65	<0.01
Overall	NA	21	44,458	10,494	20.0	15.0–25.0	0.02–0.50	99.33	<0.01

*only diabetes patients for whom mortality data was available were included

Table 3 Overall and subgroup wise prevalence of mortality among hospitalized COVID-19 patients with and without diabetes mellitus

Hospitalized COVID-19 patients with diabetes mellitus									
Subgroup	Category	Number of studies	Number of DM patients	Number of deaths	Mean prevalence of deaths		95% prediction interval	Heterogeneity measures	
					%	95% CI		I^2 (%)	Q (p-value)
Continent	Asia	14	944	201	17.0	8.0–28.0	0.0–66.0	92.10	<0.01
	Europe	4	6,422	1671	28	14.0-44.0	0.0–96.0	98.87	<0.01
	North America	4	4,445	968	20.0	11.0-32.0	0.0–79.0	98.35	<0.01
Country	China	9	767	175	20.0	8.0–34.0	0.0–76.0	94.35	<0.01
	France	1	1,317	140	11.0	9.0–12.0	Inestimable	-	-
	India	1	2	0	0.0	0.0–84.0	Inestimable	-	-
	Iran	1	113	11	10.0	5.0–17.0	Inestimable	-	-
	Italy	1	69	22	32.0	21.0–44.0	Inestimable	-	-
	Korea	2	42	11	21.0	9.0–35.0	Inestimable	-	-
	Oman	1	20	4	20.0	6.0–44.0	Inestimable	-	-
	UK	2	5,036	1509	30.0	29.0–31.0	Inestimable	-	-
	US	4	4,445	968	20.0	11.0–32.0	0.0–79.0	98.35	<0.01
COVID-19 diagnosis	RT-PCR	17	5,315	1159	17.0	11.0-23.0	0.0-45.0	94.34	<0.01
	Multiple modes	5	6,496	1681	30.0	16.0–46.0	0.0–89.0	98.80	<0.01
Diabetes diagnosis	Method specified	5	1,708	231	19.0	10.0–31.0	0.0–69.0	93.67	<0.01
	Unclear	17	10,103	2609	21.0	15.0-27.0	2.0–48.0	96.35	<0.01
DM type	Mixed T1 and T2 DM	3	1,473	202	28.0	7.0–55.0	Inestimable	-	-
	T2DM	3	1,863	263	27.0	0.0–84.0	Inestimable	-	-
	Unclear	16	8,475	2375	17.0	13.0-22.0	5.0–35.0	90.19	<0.01
COVID-19 severity	Critically ill	3	64	43	40.0	0.0–93.0	Inestimable	-	-
	Not Critically ill	3	161	12	3.0	0.0–12.0	Inestimable	-	-
	Unclear	16	11,586	2785	21.0	15.0-27.0	3.0–47.0	97.15	<0.01
Sample size	<100	12	462	140	21.0	8.0-38.0	0.0–86.0	91.96	<0.01
	≥100	10	11,349	2700	19.0	13.0–25.0	2.0–46.0	98.21	<0.01
Overall		22	11,811	2840	20.0	15.0–26.0	2.0–48.0	96.75	<0.01
Hospitalized COVID-19 patients without diabetes mellitus*									
Subgroup	Category	Number of studies	Number of non-DM patients	Number of deaths	Mean prevalence of deaths		95% prediction interval	Heterogeneity measures	
					%	95% CI		I^2 (%)	Q (p-value)
Continent	Asia	13	8,136	549	7.0	3.0–12.0	0.0–0.31	97.59	<0.01
	Europe	3	15,670	3,818	25.0	21.0-30.0	Inestimable	-	-
	North America	4	10,063	1,696	14.0	5.0–26.0	0.0–0.81	99.53	<0.01
Country	China	9	5,152	311	8.0	3.0–15.0	0.0–0.41	98.21	<0.01
	India	1	19	0	0.0	0.0–18.0	Inestimable	-	-
	Iran	1	2,851	228	8.0	7.0–9.0	Inestimable	-	-
	Italy	1	341	73	21.0	17.0–26.0	Inestimable	-	-
	Korea	1	71	9	13.0	6.0–23.0	Inestimable	-	-
	Oman	1	43	1	2.0	0.0–12.0	Inestimable	-	-
	UK	2	15,329	3,745	24.0	24.0–25.0	Inestimable	-	-
	US	4	10,063	1,696	14.0	5.0–26.0	0.0–0.81	99.53	<0.01
COVID-19 diagnosis	RT-PCR	16	15,348	1997	8.0	4.0-14.0	0.0–40.0	99.05	<0.01
	Multiple modes	4	18,521	4,066	24.0	12.0–38.0	0.0–0.91	99.45	<0.01
COVID-19 severity	Critically ill	3	218	76	20.0	1.0–52.0	Inestimable	-	-
	Not Critically ill	2	1,873	31	1.0	1.0–1.0	Inestimable	-	-
	Unclear	15	31,778	5,956	11.0	7.0-17.0	0.0–38.0	99.26	<0.01
Sample size	<100	11	3,051	280	10.0	3.0-21.0	0.0–61.0	98.12	<0.01
	≥100	9	30818	5,783	11.0	6.0–18.0	0.0–0.42	99.57	<0.01
Overall		20	33,869	6063	11.0	6.0-16.0	0.0–0.41	99.32	<0.01

* The study from France and Korea was not included in the analysis as all patients had diabetes and accurate number of deaths in non-diabetes patients could not be determined, respectively. [16, 38]

patients. Compared to inpatient COVID-19 patients with no DM, those with DM had a higher prevalence of death, particularly in those with critically ill SARS-CoV-2 infection.

In comparison to the existing systematic reviews and meta-analysis studies, similar to our study, Zheng et al. (2020) also depicted a high preponderance of diabetes in COVID-19 patients with severe disease compared to non-severe cases [46] ext, Kumar et al. (2020) found that DM patients with COVID-19 have about a twofold increased risk of mortality contrasted to COVID-19 patients without diabetes, [47] supporting our findings. However, the findings of this study were chiefly based on data extracted from case-control studies retrieved from the PubMed database only. Another prevalence meta-analysis study of hospitalized COVID-19 patients reported a DM prevalence of nearly 8 % [48]. In contrast, this estimate was much higher in our study, which might have happened because we included studies that reported mortality information on COVID-19 patients. However, our meta-analysis models included a larger number of studies.

The inclusion of studies irrespective of their study design and geographical origin allowed us to make a comprehensive prevalence estimation of the inpatient deaths in COVID-19 infected DM patients. Additionally, as we did not exclude from meta-analysis the studies with zero numerators, our estimates plausibly did not compromise with the sample size and power. Furthermore, the substantial sample size and the relative geographic diversity of the origin of the study population might ensure better generalizability of our study.

Despite these strengths, our study has certain limitations. First, due to the incorporation of publications in the English language only, the obtained estimates might biased given not searching for studies published in other languages. However, this is could be unlikely the case, and if so the bias would be very minimal, as due to the nature of the ongoing pandemic and the aim to reach a broader range of readers, the primary publication language was the English. Additionally, we could not account for the mortality of those DM patients who remained hospitalized at the end of the follow-up period of the studies. Third, the obtained weighted prevalence estimates need cautious interpretation since these estimates were based on studies including only hospitalized COVID-19 patients. Finally, the cautious interpretation also should be exercised with regard to the generalizability of the findings as producing estimates from studies reported from a limited number of countries should not be generalized to the whole region, sub-region, or global level.

The chief implication of this study is that it provides an estimate on the burden of mortality in hospitalized COVID-19 patients with and without comorbidity diabetes. These estimates are likely to be useful for health authorities to make better hospital management protocols for such patients like, reviewing the existing management paradigm in a hospital, using efficient triaging, close monitoring, and determining the need for specialist care. Additionally, the substantial mortality burden among ICU admitted COVID-19 infected diabetes patients highlights the urgent need for additional research to ascertain its determinants.

Conclusions

Hospitalized COVID-19 patients with DM were at nearly twice the risk of mortality compared with their non-diabetic counterparts. The risk of mortality frequented when DM patients with SARS-CoV-2 infection required ICU support. It is warranted to review and strengthen the existing management protocols of the hospitals treating COVID-19 patients with diabetes with the implementation of an effective triaging system to ensure prompt and effective care of these patients during the ongoing pandemic.

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Author contribution SS^1 conceptualized and designed the manuscript, analyzed, drafted, and edited all versions of the manuscript. RHA critically reviewed, opined, drafted the 'introduction' part, and edited the manuscript. SS^2, along with SS^1, contributed to data abstraction and quality assessment of the reviewed studies. SS^2 also hard edited the manuscript. All authors agree with the final content of the manuscript.

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Declarations

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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