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 (I2) and Chi-squared (Chi2) 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 hospitalized COVID-19 patients with DM (20.0 %, 95 % CI: 15.0–26.0; I2, 96.8 %) was 82 % (1.82-time) higher than that in non-DM patients (11.0 %, 95 % CI: 5.0–16.0; I2, 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, I2, 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

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
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 systematically 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 (medRxiv). 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 %)
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 heterogeneity

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 (hospitalized COVID-19 patients) | DM type (diagnosis criteria) | Outcome COVID-19 patients with DM n (%) | Outcome DM n (%) | Outcome 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 11 (4.7) | T2DM 76 (32.8) | Mixed DM – | Unclear 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 69.8 years ± 13 | RT-PCR and/or clinically-/radiologically by chest CT | 1317 | T1DM 39 (3.0) | T2DM 1166 (88.5) | Mixed DM – | Unclear 2 (5.1) |
| Bhandari et al. 2020 [36]   | India 01/03/2020-unlear | 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 112 (8.5) |
| 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) |
| 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 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 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 8 (2) | T2DM 61 (14.9) | Mixed DM – | Unclear 1469 (29.7) |
| 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 – | Mixed DM – | Unclear 37 (2.5) |
| 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 (%) |
|----------------------|---------------|-----------------------------------|--------------|--------------------------------------|--------------------|-------------------|---------------------------------------------|-----------------------------|----------|-------------------------------|--------------------------------------------------|-------------|
| Lee et al. 2020      | 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                                          | Mixed DM                                     | 130 (8.2) | 13 (10)                      | 9 (12.7)                                           |             |
|                      |               |                                   |              |                                      |                     |                   | T1DM -                                      |                             |                       |                               |                                     |             |
|                      |               |                                   |              |                                      |                     |                   | T2DM -                                      |                             |                       |                               |                                     |             |
|                      |               |                                   |              |                                      |                     |                   | Mixed DM -                                   |                             |                       |                               |                                     |             |
|                      |               |                                   |              |                                      |                     |                   | Unclear -                                    |                             |                       |                               |                                     |             |
| Zhao et al. 2020     | 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 -                                      |                             |                       |                               |                                     |             |
|                      |               |                                   |              |                                      |                     |                   | Mixed DM -                                   |                             |                       |                               |                                     |             |
|                      |               |                                   |              |                                      |                     |                   | Unclear -                                    |                             |                       |                               |                                     |             |
| Khamis et al. 2020   | 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 -                                    |                             |                       |                               |                                     |             |
| Marcello et al. 2020 | 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 -                                    |                             |                       |                               |                                     |             |
| Zhang et al. 2020    | 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 -                                    |                             |                       |                               |                                     |             |
| Nikpouraghdam et al. 2020 | 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 -                                    |                             |                       |                               |                                     |             |
| Richardson et al. 2020 | 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 -                                      |                             |                       |                               |                                     |             |
|                      |               |                                   |              |                                      |                     |                   | Mixed DM -                                   |                             |                       |                               |                                     |             |
|                      |               |                                   |              |                                      |                     |                   | Unclear -                                    |                             |                       |                               |                                     |             |
| Rosenberg et al. 2020 | 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 -                                    |                             |                       |                               |                                     |             |
| Shi et al. 2020      | 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 -                                    |                             |                       |                               |                                     |             |

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| 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 (%) | Outcome COVID-19 patients with No-DM n (%) | Outcome Death among hospitalized COVID-19 patients with DM n (%) | Outcome Death among hospitalized COVID-19 patients with No-DM n (%) |
|-------------------|---------------|-------------------|-----------------------|---------------------------------------|-------------------------------------------------------------------------------------|---------------------|-----------------------------------------------|----------------------------------------|----------------------------------------|------------------------------------------|------------------------------------------------|------------------------------------------|
| Wang et al. 2020  | 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 -                                  | 0 (0.0)                                |                                          |                                              |                                          |
| Cen et al. 2020   | 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 -                                  | 31 (3.5)                               |                                          |                                              |                                          |
| Zhang et al. 2020 | 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 -                                  | 8 (4.1)                                |                                          |                                              |                                          |
| Yan et al. 2020   | 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 -                                  | 69 (47.6)                              |                                          |                                              |                                          |
| Jang et al. 2020  | 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 -                                  | 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
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
| Subgroup          | Category                          | Number of Studies | Number of admitted COVID-19 patients | Number of DM patients | Mean prevalence of DM % | 95% prediction interval | Heterogeneity measures |
|-------------------|-----------------------------------|-------------------|-------------------------------------|-----------------------|--------------------------|---------------------------|-------------------------|
| 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 1.0–30.0           | 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          | 0.0–0.50                  | 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

| Subgroup | Category | Number of studies | Number of DM patients | Number of non-DM patients | Number of deaths | Mean prevalence of deaths % | 95% prediction interval | Heterogeneity measures |
|----------|----------|-------------------|-----------------------|---------------------------|----------------|-----------------------------|------------------------|----------------------|
| 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 | 0.0–8.40 | 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 | 1,509 | 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 | 1,159 | 17.0 | 11.0–23.0 | 0.0–45.0 | 94.34 <0.01 |
| Diabetes diagnosis | Method specified | 5 | 6,496 | 1,681 | 30.0 | 16.0–46.0 | 0.0–89.0 | 98.80 <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 | 2,375 | 17.0 | 13.0–22.0 | 5.0–35.0 | 90.19 <0.01 |
| COVID-19 severity | Critically ill | 3 | 64 | 43 | 40.0 | 0.0–9.30 | Inestimable | - |
| Not Critically ill | 3 | 161 | 12 | 3.0 | 0.0–12.0 | Inestimable | - |
| Unclear | 16 | 11,586 | 21,25 | 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 | 2,840 | 20.0 | 15.0–26.0 | 2.0–48.0 | 96.75 <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.

Supplementary Information

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Author contribution

SS1 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. SS2, along with SS1, contributed to data abstraction and quality assessment of the reviewed studies. SS2 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.

Ethical approval

Since the study did not require any direct human participation, an ethical approval was not needed.

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