Risk factors and outcomes associated with diabetes mellitus in COVID-19 patients: a meta-analytic synthesis of observational studies

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Abstract

Purpose We carried out a meta-analytic synthesis to evaluate the association between diabetes mellitus (DM) and related clinical outcomes, co-morbidities, their risk factors and resource utilization in patients with COVID-19.

Methods The MEDLINE and Web of Science databases were reviewed for identification of eligible studies. Meta-analysis was carried out using Review Manager 5.3. The random- effects model was used to compute the pooled estimates of odds ratio (OR)/mean difference and 95% confidence interval (CI).

Results A total of 14 studies including 3,644 individuals without DM and 1,428 with DM were included in the meta-analysis. Cardiovascular diseases (CVDs) [OR 2.91, 95% CI 2.34, 3.63], hypertension [OR 2.19, 95% CI 1.39, 3.46], acute kidney injury (AKI) [OR 3.59, 95% CI 1.46, 8.84], cerebrovascular disease [OR 2.09, 95% CI 1.22, 3.61], and acute respiratory distress syndrome (ARDS) [OR 3.40, 95% CI 2.09, 5.55] were significantly associated with DM in COVID-19 patients compared with non-DM patients ($p < 0.05$ for all instances). Mortality was significantly higher among COVID-19 patients with DM [OR 2.46, 95% CI 1.68, 3.58]. Intensive Care Unit (ICU) admission and use of mechanical ventilation were significantly associated with COVID-19 patients with DM [OR 2.79, 95% CI 1.79, 4.34], and [OR 3.33, 95% CI 2.05, 5.42], respectively. No significant difference was observed in the length of stay (LOS) and hospitalization.

Conclusions This meta-analysis shows that CVDs, hypertension, AKI, cerebrovascular disease, and ARDS are significantly higher among DM patients with COVID-19 compared with non-DM patients. Mortality, ICU admission and the use of mechanical ventilation were significantly associated with COVID-19 patients with DM. Further long-term, multinational and large sample size clinical studies are warranted to justify the current findings.

Keywords COVID-19 · Diabetes Mellitus · Mortality · Comorbidities · Resource utilization

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Introduction

The emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2, earlier known as 2019-nCoV) caused the outbreak of coronavirus disease (COVID-19) [1] which precipitated a global health crisis [1, 2]. The World Health Organization declared COVID-19 as a pandemic causing a wide array of signs and symptoms ranging from moderate to severe. Following SARS-CoV-2 exposure, symptoms can manifest up to 14 days, characterized by fatigue, pain in the muscles and body, headache, nausea, and loss of taste or smell, sore throat, sneezing, stuffy nose, diarrhea, and vomiting [3]. Patients with underlying health conditions, such as diabetes mellitus (DM) or hypertension are at high risk for COVID-19 [4].

DM is one of the most frequent comorbidities reported in patients with COVID-19 [5]. In general, DM increases the susceptibility to infection, and subsequently adversely affects the prognosis of diabetic patients infected with viral diseases compared to non-diabetics [6]. Few observational studies have shown that DM is associated with an increased risk for disease severity, poor prognosis, and high mortality among patients with COVID-19. A cohort study conducted in China among 258 consecutive hospitalized COVID-19 patients with or without DM reported that DM was associated with increased disease severity and a higher risk of mortality in patients with COVID-19 [7]. In another study, impaired fasting glucose and DM at hospital admission were significantly associated with increased risks of adverse outcomes among COVID-19 patients [8]. Similarly, a retrospective observational multi-centre study in Greece reported that Type 2 DM contributed to disease severity and mortality in COVID-19 critically ill patients [9]. Yet, another retrospective cross-sectional study conducted in the United Kingdom reported that hospitalized COVID-19 patients with DM had a longer length of stay (LOS) in the hospital than patients without DM. The same study also documented that older COVID-19 patients with DM and patients without diabetic ketoacidosis were less likely to survive compared to younger patients and patients with diabetic ketoacidosis, respectively [10]. DM has been linked to an increased risk of composite adverse endpoints (death, intensive care unit admission, and mechanical ventilation) [8].

With both DM and COVID-19 on the rise, it is important to improve DM patients' treatment and care in order to reduce the risk of complications or death, and further research is needed to uncover the links between DM and COVID-19 outcomes.. The association between DM and COVID-19 was explored in the previously published systematic review and meta-analysis [11], but these studies considered limited studies and low sample size. Interestingly, no studies yet compared DM COVID-19 patients and non-DM COVID-19 patients. Furthermore, there is a lack of quantitative synthesis of observational data that has explored possible risk factors and healthcare resource utilization in COVID-19 patients with DM. A deeper understanding of clinical outcomes and their risk factors and resource utilization in patients could potentially improve understanding of comorbid conditions and improve the planning and organization of healthcare facilities to ensure better preparation and optimization of delivery of care during times of pandemic crisis. Thus, we aim to perform a systematic review and meta-analysis to evaluate the association between DM and related clinical outcomes, comorbidities and associated factors, as well as healthcare resource utilization in patients with COVID-19.

Materials and methods

This systematic literature review and meta-analysis were performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement [12]. This study was prospectively registered on the Prospective Register of Systematic Reviews (PROSPERO) (CRD42020213791).

Search strategy

A comprehensive literature search was conducted using databases of Medical Literature Analysis and Retrieval System Online (MEDLINE) or PubMed and Web of Science to identify eligible studies published in the English language from inception to January 2021.

Search terms used were "diabetes mellitus", "diabetes", "T1DM", "T2DM", "Coronavirus", "COVID-19", "SARS-CoV-2", "Wuhan virus", "novel coronavirus", "novel coronavirus 2019", "2019 nCoV" and "Wuhan coronavirus". Bibliographies of the retrieved articles, the previous systematic review [11], and Google Scholar were used to perform manual searches for additional studies and grey literature. Detailed search strategy provided in supplementary table S1.

Study selection and data extraction

Two reviewers independently performed the selection of study based on an initial screening of identified titles and abstracts followed by the second screening of full-text articles. Studies were considered eligible if they met the following criteria: (i) studied subjects were diabetic and non-diabetic exposed to COVID-19; (ii) outcome of interest reported comorbidities and clinical manifestations of COVID-19; and (iii) studies reporting observational study design (retrospective cohort, case-control, prospective cohort, and cross-sectional studies).

Two independent authors performed study screening and data extraction judiciously according to inclusion criteria. Any discrepancies were resolved through discussion of the third author until consent was achieved. A standard data extraction format was used to capture the study information, including the name of the first author, year of the publication, country, study design, age, gender, settings, country, the database used, study population, no. of comorbidities/symptoms reported, and other relevant information.
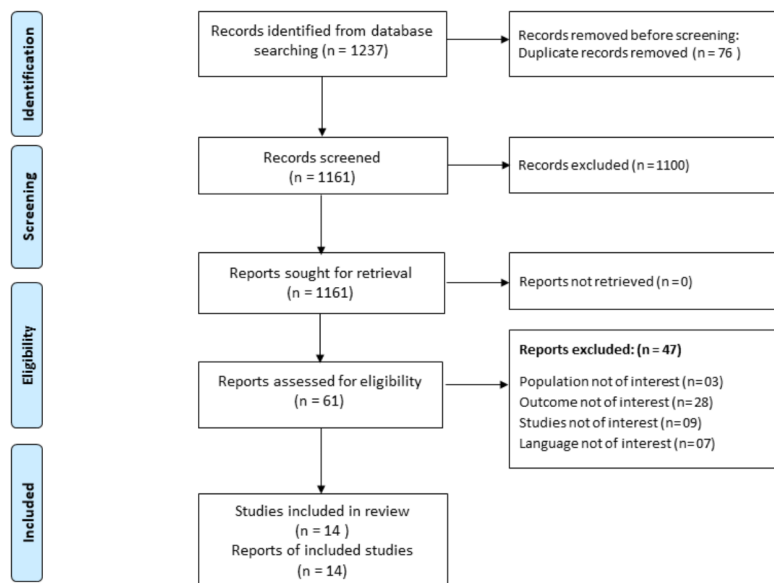
Fig. 1 PRISMA flow diagram of study selection process

Quality assessment

Two authors independently assessed the quality of the methodology for each study using the Newcastle-Ottawa Scale (NOS) [13]. The NOS comprised of three scales; selection (maximum of four stars), comparability (maximum of two stars), exposure/outcome (maximum of three stars) and graded out of 9 points (stars). This assessment critically appraised the internal (systematic error) and external validity of the studies. We consider studies with a score of 6 or greater as high quality. Any disagreement was resolved through consensus.

Data analysis

We carried out a meta-analysis to calculate the pooled estimates of odds ratio/mean difference (OR)/(MD) and 95% confidence intervals (CI). The random effects model (DerSimonian and Laird) was used for the overall pooled estimate meta-analysis.

To provide a quantitative estimate of the association of the symptoms/complication of interest with severity outcomes (ICU admission, LOS or need for mechanical ventilation) or deaths were calculated from the crude frequency of exposed and non-exposed cases.

Heterogeneity among studies was assessed with the Cochran chi-square (χ^2) and quantified with the I^2 and tau-square (τ^2). Statistical heterogeneity was reported using the I^2 statistic, with results ranging from 0 to 100% and values of 25, 50 and 75% representing low, moderate and high levels of heterogeneity, respectively. The potential publication bias was assessed by inspecting funnel plots for signs of asymmetry using Egger's regression test [14, 15] if ten or more studies were included in the analysis [16]. All the statistical analysis was conducted using Review Manager 5.3 (Nordic Cochrane Centre, Cochrane Collaboration, 2014). A p-value of < 0.05 was considered statistically significant.

Results

Literature search and study inclusion.

The PRISMA flow diagram summarizing the process of study selection is shown in Fig. 1. The electronic search initially identified 1,237 potentially relevant records. After duplicates were removed (n = 76), a total of 1,161 articles were screened, of which 1,100 were excluded after screening the title and abstract. The remaining 61 full-text articles were assessed for eligibility and 47 were further excluded due to lack of information on COVID-19 non-DM patients, mortality, resource utilization, and study design. A total of 14 articles were included in the systematic review and meta-analysis.

Study characteristics and quality assessment

The general characteristics of included studies are reported in Table 1. Among included 14 studies, 12 were conducted in China, one in the USA, and one in the UK . This meta-analysis involved 5,697 patients (DM = 1,428 and non-DM = 3,644).

The quality assessment of the included studies is shown in supplementary Table S2. The NOS results showed that the average score was 7.2 (range 6–9) for all included studies. Accordingly, the quality of the included studies was good [17].

Symptoms associated with DM and COVID-19

Out of 14 included studies, a total of 11 studies reported symptoms, including fatigue, fever, headache, myalgia, nausea/vomiting, anorexia, cough, diarrhea, dyspnoea, palpitation, pharyngalgia, shortness of breath, polypnea, sore throat, sputum, chest pain and expectoration. Fever and cough followed by fatigue and diarrhea were the most commonly reported symptoms across the included studies. Results from the pooled meta-analysis found non-significant symptoms trends in DM patients with COVID-19 compared to non-DM patients with COVID-19. However, dyspnoea was significantly associated with DM [2.30 (1.37, 3.84); p value = 0.001; I^2 = 72%; p value = 0.003] compared with non-DM patients with COVID-19 (Table 2). There was no publication bias detected for cough, and fever with Egger's test (p = 0.81 and p = 0.94), respectively (Supplementary Figure S2).

Comorbidities associated with DM and COVID-19

A total of 11 studies reported comorbidities/complications including hypertension, chronic liver disease (CLD), chronic obstructive pulmonary disease (COPD), thyroid disease, acute kidney injury (AKI), cancer, cerebrovascular disease, chronic kidney disease (CKD), digestive disease, septic shock, and acute respiratory distress syndrome (ARDS). COPD, cardiovascular diseases (CVDs), and hypertension followed by cerebrovascular disease, cancer and CKD were most commonly reported co-morbidities/complications across the included studies. From reported co-morbidities, CVD, hypertension, AKI, cerebrovascular disease, acute cardiac injury (ACI) and acute respiratory distress syndrome (ARDS) were significantly associated with DM in COVID-19 patients compared to non-DM patients with COVID-19 (OR = 2.91 [95% CI 2.34, 3.63], p < 0.00001, I^2: 0%; p = 0.57); 2.19 [1.39, 3.46], p = 0.0008, I^2: 80%; p < 0.00001; 3.59 [1.46, 8.84], p = 0.005, I^2: 0%; p = 0.64; 2.09 [1.22, 3.61], p = 0.008, I^2: 41%; p = 0.09; 3.01

[1.63, 5.58], p = 0.0005, I^2: 2%; p = 0.36; and 3.40 [2.09, 5.55], p < 0.00001, I^2: 0%; p = 0.48; respectively). However, no significant association was observed with CLD, COPD, thyroid disease, cancer, CKD, digestive disease, and septic shock in DM patients with COVID-19 compared to non-DM patients (Table 3. and supplementary Figure S1). Visual inspection of funnel plots and quantified using Egger's test showed no significant asymmetry for CVD (p = 0.89), hypertension (p = 0.67), and COPD (p = 0.72) (Supplementary Figure S2).

DM and outcome

It includes mortality, recovery, LOS, mechanical ventilation, need for ICU, discharge from hospital, and hospitalization (Fig. 2. and supplementary Table S3).

Association between mortality and recovery with DM in COVID-19 patients

There were 12 studies reporting on mortality [7, 10, 18–27] and 5 studies reporting on recovery (being alive or discharged from the hospital) [10, 18, 21, 23, 24]. Pooled results from meta-analysis found significant association between mortality and DM compared to non-DM patients with COVID-19 (2.46 [1.68, 3.58], p < 0.00001; I^2: 62%; p = 0.002). No significant association was found between recovery with DM compared to non-DM COVID-19 patients (0.48 [0.21, 1.07], p = 0.07; I^2: 85%; p < 0.00001) (Fig. 2). Visual inspection of funnel plots and Egger's test showed no significant asymmetry (p = 0.75) (Supplementary Figure S2).

Association between healthcare utilization and DM in COVID-19 patients

LOS and hospitalization were not significantly differing between DM and non-DM patients with COVID-19 (1.91 [-1.12, 4.94], p = 0.22; I^2: 91%, p < 0.00001 and 1.45 [0.51, 4.08], p = 0.49; I^2: 59%, p = 0.12 respectively) (Fig. 2). However, discharge from hospital was significantly higher in non-DM patients with COVID-19 compared to DM patients (0.52 [0.34, 0.81], p = 0.004; I^2: 6%, p = 0.35). On the other hand, ICU admission and use of mechanical ventilation were significantly associated with DM and COVID-19 patients compared to the non-DM patients (2.79 [1.79, 4.34], p < 0.00001; I^2: 0%, p = 0.53 and 3.33 [2.05, 5.42], p < 0.00001; I^2: 48%, p = 0.09, respectively) (Fig. 2).

Table 1 Characteristics of included studies

Author, Year	Country	Study design	Sample size (N)	Diabetes/Non-diabetes	Age	Comorbidities/ Complications	Symptoms	Mortality, Alive/recovered	Resource utilization
Zhang, 2020 [7]	China	Retrospective Cohort Study	258	63/195	Median (IQR): 64 (56–70)	Hypertension, CVD, Cerebrovascular disease, COPD, CKD, CLD, Cancer/ Malignancies, ACI, Acute respiratory distress syndrome(ARDS), Acute kidney injury(AKI)	Fever, Cough, Fatigue, Diarrhoea, Myalgia, Nausea, Vomiting, Polypnea, Expectoration, Headache	Mortality	Mechanical ventilation, Discharge from hospital
Zhang, 2020a [27]	China	Retrospective observational study	145	61/84	Mean: 62.7	Hypertension, CVD, Cerebrovascular disease, COPD, CKD, Thyroid Cancer/ Malignancies, Digestive system disease	Fever, Cough, Fatigue, Diarrhoea, Nausea, Vomiting, Expectoration, Chest Pain, Headache, Anorexia, Dyspnoea, Sore throat, Palpitation	Mortality	Length of stay(LOS) (days), Mechanical ventilation, Hospitalization, Discharge from hospital, Intensive care unit (ICU)
Xu, 2020 [25]	China	Observational study	364	114/250	Mean (IQR): 65 (55–73)	-	-	Mortality	-
Shang, 2020 [23]	China	Retrospective cohort study	584	84/500	-	Hypertension, CVD, ARDS, COPD, CKD, CLD, Cancer/ Malignancies, ACI, AKI,	Fever, Cough, Fatigue, Diarrhoea, Nausea, Vomiting, Myalgia, Expectoration, Chest Pain, Headache, Anorexia, Dyspnoea, Sore throat, Palpitation	Mortality, Alive/recovered	Mechanical ventilation, ICU
Chung, 2020 [45]	China	Retrospective cohort study	110	29/81	Mean: 56.9	Hypertension, CVD, Cerebrovascular Disease, COPD, Cancer/ Malignancies	Fever, Cough, Diarrhoea, Myalgia, Headache, Dyspnoea, Sputum	-	ICU
Alkundi, 2020 [10]	England	Retrospective cross-sectional study	232	87/145	Mean: 71.4	Hypertension, CVD, COPD, Cancer/ Malignancies	-	Mortality, Alive/ recovered	-

Discussion

This meta-analysis of 14 studies aimed to evaluate the

Table 1 (continued)

Author, Year	Country	Study design	Sample size (N)	Diabetes/Non-diabetes	Age	Comorbidities/ Complications	Symptoms	Mortality, Alive/recovered	Resource utilization
Chen, 2020 [20]	China	Retrospective study	904	49/292	-	Hypertension, CVD, Cerebrovascular Disease, COPD, CKD, Cancer/ Malignancies	Fever, Cough, Fatigue	Mortality	LOS (days)
Yan, 2020 [26]	China	Retrospective, observational study	193	48/145	Mean (IQR): 64 (49–73)	Hypertension, CVD, Cerebrovascular Disease, COPD, CKD, CLD,	Fever, Cough, Fatigue, Diarrhoea, Nausea, Vomiting, Headache, Anorexia, Dyspnoea	Mortality	LOS (days), Mechanical ventilation, ICU
Bode, 2020 [18]	USA	Retrospective observational study	1122	451/671	Median (IQR): 65 (24–95)	-	-	Mortality, Alive/ recovered	LOS (days)
Wang, 2020 [24]	China	Retrospective study	132	47/85	Median (IQR): 60 (56–72)	Hypertension, CVD, Cerebrovascular Disease, COPD, CKD, Thyroid	Fever, Fatigue, Diarrhoea, Myalgia, Shortness of breathing	Mortality, Alive/ recovered	Time from onset to admission (days)
Zhang, 2020b [8]	China	Retrospective cohort study	312	84/166	Median (IQR): 57 (38–66)	Hypertension, CVD, Cerebrovascular Disease, COPD, CKD, CLD, Cancer/ Malignancies, ACI, ADRS, AKI, Septic Shock	Fever, Cough, Fatigue, Diarrhoea, Nausea or Vomiting, Myalgia, Polypnea, Headache, Dyspnoea, Palpitation, Sputum, Shortness of breathing	-	Mechanical ventilation
Chen, 2020a [19]	China	Retrospective study	208	96/112	Median (IQR): 64 (55–69)	Hypertension, CVD, Cerebrovascular Disease, COPD, CKD, Cancer/Malignancies, AKI, Septic Shock, ARDS,	Fever, Cough, Fatigue, Diarrhoea, Nausea or Vomiting, Myalgia, Sore throat, Shortness of breathing, Headache, Sputum	Mortality	Mechanical ventilation, Hospitalization time (days), Hospitalization, Discharge from hospital,

Table 1 (continued)

Author, Year	Country	Study design	Sample size (N)	Diabetes/Non-diabetes	Age	Comorbidities/ Complications	Symptoms	Mortality, Alive/recovered	Resource utilization
Li, 2020 [21]	China	Retrospective study	199	76/123	Median (IQR): 63 (50–75)	-	Fever, Cough, Anorexia, Fatigue, Dyspnoea, Diarrhoea, Nausea, Vomiting, Headache	Mortality, Alive/recovered	LOS (days), ICU
Liu, 2020 [22]	China	Retrospective study	934	139/795	Mean: 64.5	CVD, Cerebrovascular Disease, COPD, Digestive System Disorder, Cancer/ Malignancies'	Fever	Mortality	-

Data presented as Median (IQR)

Abbreviation: IQR: Interquartile range; **CVD**: Cardiovascular disease; **COPD**: Chronic obstructive pulmonary disease; **CKD**: Chronic kidney disease; **CLD**: Chronic liver disease; **ACI**: Acute cardiac injury; **ICU**: Intensive care unit; **LOS**: Length of stay; **AKI**: Acute kidney injury

association between DM and related clinical outcomes, co-morbidities, their risk factors and resource utilization in patients with COVID-19. Results from the current study showed that mortality, ICU admission, ARDS, mechanical ventilation, discharge from hospital, and co-morbidities (CVD, hypertension, AKI, cerebrovascular disease, ACI) were significantly associated with DM in COVID-19 patients.

DM was one of the most common comorbid conditions reported in patients with COVID-19, and the prevalence of DM varied across the studies.There are studies on Chinese patients that have reported prevalence rates of 5.3% [28] and 8.2% [29], and a recent study of 5,700 patients from New York City Areafound that 33.8% had DM [30]. Several studies have reported that DM and uncontrolled glycemia were significant predictors of severity and mortality in patients infected with lower respiratory tract infections [6, 8]. Previous studies found increased severity of COVID-19, caused by the infection with SARS-CoV-2 in patients with DM [6, 11]. Interacting with other risk factors; hyperglycaemia

Table 2 Results summary from meta-analysis for symptoms

Outcomes	Number of studies	Diabetic population		Non diabetic population		OR (95% CI)	P value	Heterogeneity	
		Total	Events	Total	Events			I^2	*P*value
Fatigue	9	608	277	1658	622	1.22 [0.79, 1.88]	0.37	76%	< 0.00001
Fever	11	776	535	2534	1836	0.84 [0.61, 1.16]	0.3	59%	0.006
Headache	7	457	46	906	133	0.66 [0.41, 1.05]	0.08	28%	0.21
Myalgia	6	403	71	1095	162	1.08 [0.78, 1.49]	0.65	0%	0.58
Nausea and vomiting	7	512	76	1325	185	0.98 [0.71, 1.35]	0.92	0%	0.42
Anorexia	4	269	92	852	290	1.10 [0.77, 1.59]	0.6	24%	0.27
Cough	10	637	449	1739	1100	1.19 [0.96, 1.47]	0.1	0%	0.51
Diaarhea	9	588	112	1447	234	1.15 [0.72, 1.84]	0.55	55%	0.02
Dyspnea	6	382	214	1099	390	2.30 [1.37, 3.84]	0.001	72%	0.003
Palipitation	2	145	22	250	38	0.91 [0.51, 1.64]	0.76	0%	0.87
Pharyngalgia	2	147	12	695	60	1.44 [0.39, 5.30]	0.59	63%	0.1
Shortness of breath	2	143	73	153	70	1.13 [0.68, 1.87]	0.63	0%	0.68
Polypnea	2	147	44	361	102	1.74 [0.60, 5.09]	0.31	76%	0.04
Sore throat	2	157	15	196	18	1.21 [0.42, 3.48]	0.72	41%	0.19
Sputum	2	125	38	193	59	0.92 [0.34, 2.49]	0.87	68%	0.08
Chest pain	2	124	13	279	22	1.06 [0.35, 3.24]	0.92	41%	0.19
Expectoration	2	124	58	279	94	1.42 [0.90, 2.23]	0.13	0%	0.18

$P < 0.05$ considered significant

Abbreviation: OR: Odds ratio; **CI**: Confidence interval; **I^2**: Heterogeneity

Table 3 Results summary from meta-analysis for comorbidities

Outcomes	Number of studies	Diabetic population		Non diabetic population		OR (95% CI)	P value	Heterogeneity	
		Total	Events	Total	Events			I²	Pvalue
Chronic kidney disease (CKD)	8	532	29	1535	46	1.79 [0.77, 4.17]	0.18	53%	0.04
Chronic liver disease (CLD)	4	279	9	1006	31	1.63 [0.76, 3.50]	0.21	0%	0.54
Acute respiratory distress syndrome (ARDS)	4	272	45	554	49	3.40 [2.09, 5.55]	<0.00001	0%	0.48
Cardiovascular disease (CVD)	11	787	222	2556	439	2.91 [2.34, 3.63]	<0.00001	0%	0.57
Chronic obstructive pulmonary disease (COPD)	11	787	42	2556	189	0.96 [0.59, 1.56]	0.87	31%	0.15
Thyroid disease	2	108	1	125	3	0.50 [0.07, 3.46]	0.48	0%	0.67
Acute kidney injury (AKI)	4	272	14	554	9	3.59 [1.46, 8.84]	0.005	0%	0.64
Hypertension	10	648	315	1761	519	2.19 [1.39, 3.46]	0.0008	80%	<0.00001
Acute cardiac injury	3	176	24	442	23	3.01 [1.63, 5.58]	0.0005	2%	0.36
Cerebrovascular disease	9	616	52	1911	96	2.09 [1.22, 3.61]	0.008	41%	0.09
Digestive disease	2	200	9	879	41	1.07 [0.50, 2.30]	0.85	0%	0.78
Cancer	9	692	32	2370	114	1.16 [0.76, 1.77]	0.5	0%	0.69
Septic shock	2	180	16	278	4	5.25 [0.60, 45.68]	0.13	54%	0.14

$P < 0.05$ considered significant

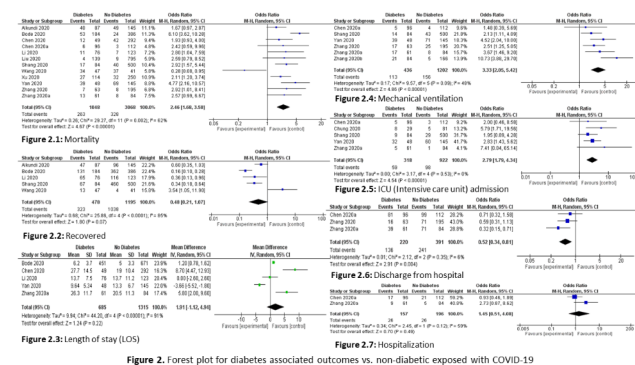**Abbreviation: OR**: Odds ratio; **CI**: Confidence interval; **I²**: Heterogeneity

Fig. 2 Forest plot for diabetes associated outcomes vs. non-diabetic exposed to COVID-19

Blue squares and horizontal lines represent study-specific estimates and 95% CI. The size of the square is proportional to the weights of the individual studies. Black diamond represents pooled estimates (center) and 95% CI (width)

Outcomes comprised of; Mortality, Recovered, Hospitalization, Mechanical ventilation, Intensive care unit (ICU) admission, length of stay (LOS), Discharge from hospital

2.1: Mortality; **2.2**: Recovered; **2.3**: LOS; **2.4**: Mechanical ventilation; **2.5**: ICU (Intensive care unit) admission; **2.6**: Discharge from hospital; **2.7**: Hospitalization

might modulate immune and inflammatory responses, thus predisposing patients to severe COVID-19 and possible lethal outcomes. Potential pathogenetic links between COVID-19 and DM include effects on glucose homeostasis, inflammation, altered immune status and activation of the renin-angiotensin-aldosterone system [5].

The presence of DM and the individual degree of hyperglycaemia seem to be independently associated with COVID-19 severity and increased mortality [11, 31]. Furthermore, the presence of typical complications of DM (CVD, heart failure and CKD) also increases COVID-19

mortality [32, 33]. In the current meta-analysis, we found a higher mortality rate in DM COVID-19 patients compared to non-DM COVID-19 patients.

COVID-19 can progress to ARDS, which requires positive pressure oxygen and intensive care therapy [10]. A previous systematic review and meta-analysis conducted by Huang et al. [6] showed that ARDS and disease progression were significantly associated with DM in COVID-19 patients. In addition, a retrospective case study conducted by Chen et al. reported that SARS-CoV-2 can cause both pulmonary and systemic inflammation, leading to multiorgan dysfunction in patients at high risk [34]. ARDS, respiratory failure, sepsis, acute cardiac injury, and heart failure were the most common critical complications during exacerbation of COVID-19 [34]. In line with the previous finding, our meta-analysis also found a significant association between DM and ARDS and other co-morbidities in COVID-19 patients compared to non-DM COVID-19 patients. In addition, various studies reported that patients with DM are more likely than healthy people to develop COVID-19 disease and complications such as ARDS and even death [32, 35–37].

According to published studies, COVID-19 patients usually suffer from sore throat, fever, dry cough, fatigue, and diarrhea [38–40]. In support of our observations, the International Diabetes Federation (IDF) reported that symptoms in DM patients were similar to those in COVID-19 patients [41]. In general, though, patients show more severe symptoms [21, 42]. Another study conducted in Greece reported that type 2 diabetes and obesity may have contributed to disease severity and mortality in COVID-19 critically ill patients [8]. HbA1c was associated with inflammation,

hypercoagulability, and low SaO2 in COVID-19 patients, and the mortality rate (27%) is higher in DM patients [24].

In a study on a patient with both COVID-19 and DM, the patient was discharged from the hospital after 15 days [43]. The survival term of the non-survivors was likely to be within 1–2 weeks after ICU admission. The severity of SARS-CoV-2 pneumonia poses a great strain to hospital critical care resources, especially if they are not adequately staffed or resourced [44].

In a retrospective study of 312 patients with COVID-19, DM was associated with higher risks of composite adverse endpoints (mechanical ventilation, admission to ICU, or death) and mortality, and impaired fasting glucose was also associated with a higher risk of mortality. Similarly, in the current meta-analysis, we also observed that ICU admission, mechanical ventilation, discharge from the hospital and hospitalizations were significantly associated with DM among patients with COVID-19 compared to non-DM patients. This finding could help in decision-making process and improve the planning and organization of healthcare facilities to ensure better preparation and optimization of delivery of care during the COVID-19 pandemic.

To the best of our knowledge, this is the only largest meta-analysis to evaluate risk factors and resource utilization associated with DM COVID-19 patients compared to non-DM COVID-19 patients. This study has the following limitations. First, the causal relationship between DM and adverse outcomes in patients with COVID-19 cannot be confirmed on account of the inherent limitation of the retrospective cohort studies. Second, only articles written in English were included and this may have resulted in the missing of relevant studies. Third, the majority of the included studies were from China, so the generalizability of findings at a global level should be taken with caution. Lastly, we did not assess the sensitivity analysis to reduce the heterogeneity (I^2).

Implication andrecommendation.

This meta-analysis suggests a strong association between clinical outcomes, co-morbidities, their risk factors, mortality and resource utilization in diabetic COVID-19 patients. The poor outcomes of patients with DM and COVID-19 indicated that these patients need more supervision. To reduce the risk of disease progression, preventive measures should be considered by DM patients. Proper management of blood glucose levels during the COVID-19 pandemic might help DM patients to avoid humanistic and economic burdens which may arise due to ICU admission, frequent hospital visits, hospitalization and mechanical ventilation requirement.

Conclusions

This meta-analysis shows that CVDs, hypertension, AKI, cerebrovascular disease, and ARDS are significantly higher among DM patients with COVID-19 compared with non-DM patients. Mortality, ICU admission and the use of mechanical ventilation were significantly associated with COVID-19 patients with DM. More prospective, long-term, multinational studies, especially clinical studies with large sample sizes are needed to justify the current findings.

Declarations

Conflict of interest The authors declare no conflict of interests associated with this publication.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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